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Single Port Access (SPA) Surgery—a 24-Month Experience

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Abstract
Introduction In April 2007, we performed our first single port access (SPA) surgical procedure. Beginning with simple procedures, we progressed to more complex procedures employing modifications of the initial technique.
Methods Maintaining our abdominal entry technique through a single incision, typically umbilical, we have now successfully performed cholecystectomies, colon resections, small bowel procedures, liver biopsy, splenectomy, adrenalectomy, and surgery of the gastroesophageal junction.
Results Two procedures have required additional port sites, none has employed transabdominal sutures, and <5% of all procedures have required articulation. Immediate follow-up demonstrates safe completion of multiple procedures with acceptable outcomes of blood loss and hospital stay. Although initial operative times are extended, a decrease is seen following a learning curve. At 2-year follow-up, two hernias developed at the extended incision for colon extraction.
Discussion and Conclusion With initial procedures performed in April 2007, we now report 24-month follow-up of a novel laparoscopic approach utilizing standard instrumentation. We demonstrate that SPA surgery is an alternative to multiport procedures with proposed initial benefits of decreased number of incisions and improved cosmesis for the patient. Long-term prospective randomized large case series will be necessary to assess pain, recovery, and hernia formation proving advantages, if any, over multiport laparoscopy.

Keywords Single port access · SPA surgery · LESS · Laparoscopy · Alimentary tract · Minimal access surgery · Single incision laparoscopy

Introduction

The benefits of surgical treatment of disease have always been viewed as being obtained with a certain acceptable level of pain and trauma to the patient. Minimizing this untoward effect of any surgical procedure has been a driving force of laparoscopy since its inception in the early 1900s.[1,2] Our desire to offer our patients the benefit of our craft with less iatrogenic harm has inspired us to expand laparoscopy from simple explorative procedures to the most advanced general surgical procedures. Even with the clear benefits of laparoscopy over open surgery,[3] we have continue to see a trend toward less invasion in the quest for "scarless" surgery. In the case of cholecystectomy, successful reports of decreased number of port sites have been published.[4,5] Ultimately, in 1997, Navarra published a transumbilical cholecystectomy technique utilizing suture retraction as an assist technique to limit the incision to the umbilicus.[6] Even he questioned the validity of the approach in terms of safety, efficacy, and operative time patient selection.[7] In addition, application to procedures other than cholecystectomy did not seem possible.

The turn of the century saw the emergence of advanced endoscopy as a possible replacement for open surgery. Ponsky et al. revolutionized feeding access, as well as

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demonstrating a new approach to surgery with the introduction of the percutaneous gastrostomy tube.[8] Kalloo et al. demonstrated the ability to push endoscopic principles to a new level, performing intra-abdominal procedures transgastrically.[9] NOTES™ has now emerged as perhaps one path to the further minimization of the necessary trauma we inflict upon our patients.[10] Techniques and series of transvaginal cholecystectomy performed in humans are now emerging.[11–13]

Also inspired by this quest to continue to improve, we began the elimination of port sites with ventriculoperitoneal shunt placements in the 1990s, as well as performing two port site ventral hernia repairs in 2002.[14] In the fall of 2006, we began a stepwise approach of reduction of port sites and consolidation of trocars resulting in one umbilical incision for laparoscopic cholecystectomy. Initially eliminating the subxyphoid port and then abandoning the lateral retraction port sites in a stepwise fashion, we ultimately performed our first transumbilical single port access (SPA) cholecystectomy in April 2007.[15–17] In addition, we were able to apply this technique to basic laparoscopic procedures such as appendectomy and gastrostomy tube placement.[18] Since then, through a number of simple modifications, we have applied the single port access technique to multiple abdominal and pelvic procedures. Additionally, we have progressed to only use standard rigid instruments and standard trocars widely available to any laparoscopic surgeon. The versatility of standard instruments and individual trocars has provided "independence of movement" allowing us to perform multiple procedures or multiquadrant procedures on the same patient during one visit to the operating room.

Over the past year, there has been an emergence of SPA-based, or "reduced port", procedures demonstrating interest in pursuing this old, yet revitalized, path toward the ultimate goal of decreased pain and trauma to our patients. As we begin this journey, we need to do so with a cautious eye so as to ensure that we maintain basic tenets of surgery, without increasing the potential risks. Safety, costs, and the ability to train and develop the technique will all have to be demonstrated.

With this in mind, we present our first 2-year experience with this new technique as we have adapted SPA surgery into standard practice. We propose that SPA is a feasible alternative to multiport laparoscopy.

Methods

Technique

The technique of SPA surgery has been described in prior publications.[17,19] The standard schematic (Figs. 1 and 2) demonstrates the basic arrangement of the multiple trocars placed within the single port of entry. The initial 1.8-cm incision is made within a skin fold within the umbilicus (in most cases), and accessed is obtained via surgeon preference (Veress needle, bladeless, or open). An initial 5-mm clear trocar is utilized for insertion via direct visualization and subsequent visualization of accessory trocars through its side in order to maintain safety. Once the abdomen is explored and deemed appropriate for a SPA procedure, the *very* low profile trocars are placed. The abdomen is partially desufflated to allow better mobilization of the skin and soft tissue flaps off the underlying fascia. Flaps are raised along the fascia for a distance of approximately 2 to 3 cm in both directions from the central trocar. This exposure of the fascia yields an approximately 5-cm area into which separate trocars can now be placed through this single port of entry. In addition, if additional retraction is necessary (i.e., the fundus of the gallbladder, caudal retraction of the stomach in gastroesophageal (GE) junction procedures, or upward retraction of the colon) a separate fascial incision can be made at the apex of the triangle for insertion of an instrument without a trocar.

The standard SPA technique was developed for cholecystectomy. Modifications of this technique offer the ability to perform other procedures. Changing the position of the trocars within the incision provides access to other quadrants of the abdomen. Enlarging the initial incision in those cases in which specimen extraction will be required (i.e., colon, spleen) is another modification of the SPA technique. This also increases the diameter of the circle of exposed fascia expanding the distance possible between trocars. When larger 12-mm trocars are placed to accommodate the stapler, this provides more space for independent movement without clashing of instruments. Once the trocars are placed, the dissection is then performed in the standard fashion of multiport laparoscopy, most times with standard instruments.

Upon completion of the procedure, the multiple trocar fascial sites are closed. If the fascial incision was enlarged (i.e., the facial sites connected) for specimen extraction, then the wound is closed in a standard fashion. If the fascial sites do not need to be extended or connected, each is closed separately. Although they are only 5-mm fascial defects, the close proximity to one another prompts us to close them routinely. After the development of widened skin flaps, we began approximating the subcutaneous adipose tissue to prevent seroma formation. The skin is then approximated in a standard fashion with suture.

Chart Review

Under our institutional review board protocol, we retrospectively reviewed the charts of patients undergoing SPA

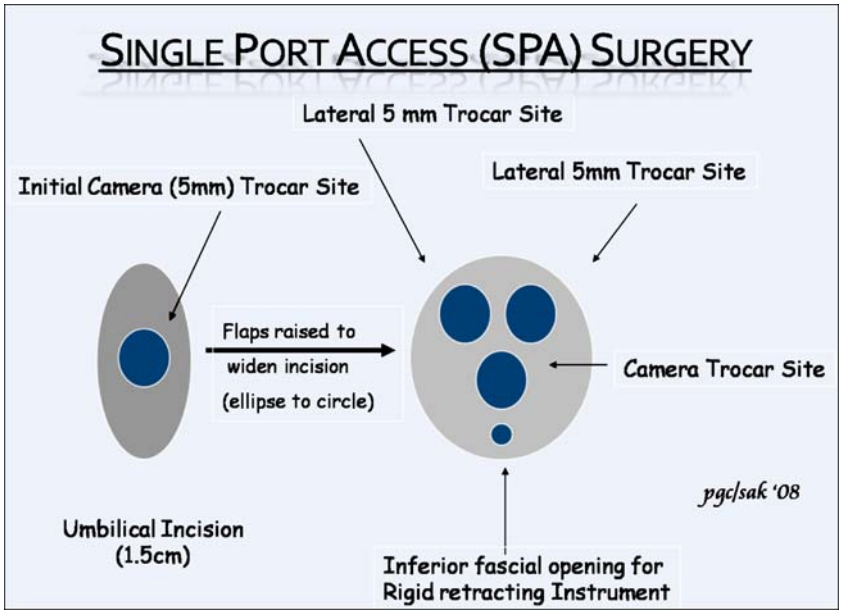

Figure 1 Schematic of SPA technique.

procedures. Specific patient identifiers were discarded from the data sheet in order to protect patient identity.

Demographics (age, sex, body mass index) as well as presenting diagnoses were recorded. Operative information was also recorded (initial skin incision operative time, estimated blood loss, intraoperative complications, addition of port sites or conversion to open, and final skin incision). We also recorded whether articulating instrumentation was used. Finally, outcomes (length of stay (LOS), wound infections, seromas, hernia formation) were collected from both the hospital chart and office charts.

Results

Cholecystectomy

Table 1 lists the various procedures performed to date utilizing the SPA technique. The largest series cases is of cholecystectomy. Diagnoses varied from acute to chronic disease. There was no patient selection "bias", including a 306-lb female patient with acute cholecystitis and an 85-year-old male who developed choledocholithiasis while admitted to the hospital with a congestive heart failure exacerbation. Table 2 demonstrates the operative times, blood loss, and LOS of this initial series, demonstrating an extended mean operative time but acceptable blood loss and length of stay. The initial ten cholecystectomies were performed with two articulating instruments. A third transfascial retractor was then added. Finally, the transition to all rigid instruments was made. Initially, two articulating instruments were used creating a steep learning curve (Table 3). After modifying the technique to two rigid dissecting instruments with one retracting instrument, better

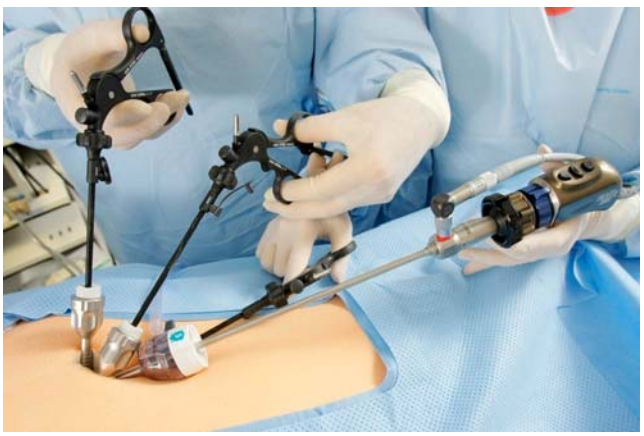

Figure 2 External trocar arrangement.

Table 1 List of Procedures

List of procedures	Number
Cholecystectomy	45
Colon	13
Right	3
Left	1
Sigmoid	8
Total proctocolectomy with j-pouch	1
Appendectomy	2
Small bowel	35
Gastric/GE junction	9
Splenectomy	2
Adrenalectomy	1
Omental resection	1
Liver biopsy	1

Table 2 Results of Procedures

Procedure	Number	Operative time (average min)	EBL	LOS (days)	Incision (initial, cm)	Incision (final, cm)
Ventral hernia	15	61	Min	0–2	1.5	1.5
Cholecystectomy	45	92	Min	0–4*	1.5–1.8	1.5–1.8
G tube	5	44	Min	2–*	1.5	1.5
Nissen	2	128	Min	2–3	1.8	1.8–2.0
Appendectomy	2	42*	Min	0–*		
Splenectomy	2	191	250	2–4	1.8–2.5	4.5
Adrenalectomy (Pheo)	1	180	150	4*	2.0	2.8
Omental resection	1	*	Min	5	1.8	2.2

EBL estimated blood loss

exposing the critical view, the operative times decreased as the number of cases performed increased. Also, in the initial cases using two articulating instruments, additional port sites were added in two cases due to inadequate retraction and exposure of the common/cystic duct relation. Of note, intraoperative cholangiogram was not routinely performed as we typically use preoperative endoscopic retrograde cholangiopancreatography (ERCP). In one patient, a cholangiogram was performed via the umbilicus. In a subsequent cholangiogram, the catheter was inserted directly through the skin in the right upper quadrant providing easier cannulation of the duct. Patients who traveled from out of state were offered extended stays of 2 days if desired. This in combination with patients admitted for other comorbidities extended our mean LOS. All gallbladders were delivered through the initial incision without need for extension. In some cases, the fascial defects were combined to accommodate a larger organ or stone. One patient had spontaneous drainage and minimal erythema at the umbilical incision not requiring further intervention.

Small Bowel Procedures

Our small bowel procedures were for a combination of procedures including ventral herniorrhaphy, adhesiolysis, and omental mass resection (Tables 1 and 2). These procedures were some of the first we performed along with the cholecystectomy. Given the wide range of operative times required for adhesiolysis, reduction of hernia, and the inclusion of omental resection as part of the small bowel procedure list, these times are not reported. Ventral hernias were all repaired with mesh using laparoscopic tackers to secure to the abdominal wall. No enterotomies occurred.

Table 3 Results 2 Versus 3 Instrument Cholecystectomy

Number of instruments	Operative time (min)	Addition of accessory port	EBL (cc)
2	104.9	2	Min
3	77.3	0	Min

EBL estimated blood loss

Colonic Procedures

Colon procedures were performed beginning with appendectomy (Tables 1 and 4). These setups included exchanging a 5-mm trocar for a 12-mm trocar to accommodate the stapler. Two appendectomies were performed with one appendiceal stump being secured with a suture loop device and the other with a laparoscopic stapling device. Next, we advanced to colon mobilizations starting with right colons. Initial incisions were extended as a larger incision would be necessary at the conclusion for specimen extraction. This afforded a larger operative area, allowing further spacing of trocars widening the triangulation at the abdominal wall. These procedures were performed for a combination of benign and malignant disease. Colon surgeries were performed with anastomosis being performed extracoporeally for right colons and a combination of extra- and intracorporeal anastomoses for the sigmoid and left colons. The splenic flexure was not mobilized in every sigmoid resection if an adequate specimen with negative margins could be obtained. Finally, a total proctocolectomy with j-pouch was performed in a patient with ulcerative colitis. The mean operative time reflects the combination of all of these cases. The shortest time of 112 min was in a sigmoid resection for adenocarcinoma yielding negative margins and 16 nodes. At the conclusion of the operations, the incisions were often enlarged for specimen removal. One wound infection was observed in follow-up, resulting in spontaneous opening of the skin and not requiring further exploration or intervention. Two patients have developed access site hernias (ASH) at the site of specimen extraction in the final extended umbilical incision.

Table 4 Results of Colon Resections

Segment resected	Previous surgery	Benign	Malignant	Mean operative time (min)	EBL (cc)	Nodes	LOS
Right	TAH		3	155	Min–150	12–18	6–7
Left	TAH		1	179	Min	14	5
Sigmoid		4	4	169	Min–350	13–16	5–8
Total colon (j-pouch)	Umbilical hernia	1		300	100	na	5

EBL estimated blood loss, *na* not applicable, *TAH* total abdominal hysterectomy

Splenectomy

Two patients underwent splenectomy (Tables 1 and 2). These procedures both required a 12-mm trocar to accommodate the stapler. Both also used a combination of articulating instruments and camera. Splenectomy was performed using the laparoscopic stapling device for the hilum and a tissue sealing device for the short gastrics. In one patient, the spleen was mobilized successfully using the SPA entry technique in 1.5 h. The operation was then completed as open as she had a pancreatic mass adherent to the retroperitoneum. The second patient underwent splenectomy for staging. The entire procedure was done using the SPA technique via the umbilicus. The operative time was 3 h with minimal blood loss. The umbilical incision was extended to allow for organ removal. This patient was tolerating oral intake on day 1 and discharged home on day 2. Follow-up at 1 year reveals a well-healed incision without herniation.

Gastric and Gastroesophageal Junction Procedures

Various GE junction procedures were also performed. Our first cases were insertion of gastrostomy tubes in patients unable to undergo percutaneous endoscopic placement due to cancer. Five patients underwent successful placement with a mean operative time of 43 min. Gastroesophageal junction cases included Nissen fundoplication. In one patient at 1-year follow-up, the wrap is in place with complete resolution of symptoms.

One gastrointestinal stromal tumor (GIST) was done in coordination with our gastroenterologists performing endoscopy in order to identify the site of the tumor intraoperatively, assist in delivery of the tumor through our SPA gastrostomy, and ultimately evaluate our gastric stapled closure line at completion.

Seroma formation has occurred in eight patients in this initial series of SPA procedures.

Discussion

Our initial reports with our early experience demonstrated that SPA surgery is possible for basic laparoscopic procedures.[17–20] However, as we move forward, we need to constantly assess the safety and efficacy as compared to multiport procedures. The benefits at this point in its development, we suspect, may be negligible at best. Patients' desire for the cosmetic benefit is important, but the price cannot be increased risk or complication. In this light, we present our *very* preliminary data and a *very* short-term experience and demonstrate that SPA surgery can be performed safely as an alternative laparoscopic approach to abdominal access. In addition, it is not limited to basic laparoscopic procedures but can be applied to more advanced procedures as well.

The initial goals of the development of SPA surgery were to develop a technique that fit within what we believed to be the important criteria to maintain current standards. Availability to surgeons and patients, an eye to costs, a focus on safety, and a commitment to developing a technique that would not be prohibitive from a training standpoint were all primary goals.

First, we focused on reproducibility to ensure feasibility and availability. The SPA technique is based on standard exposure and dissection of multiport laparoscopy, starting with cholecystectomy. This requires the surgeon to learn a new method of access and then become comfortable performing the familiar dissection techniques with a new arrangement of standard, familiar instruments but in close proximity. In addition, the "stepwise down" approach to SPA surgery (Fig. 3) allows the surgeon to work his way toward the goal of single port access surgery. We began with a series of cholecystectomies, gradually improving the technique and comfort level before applying the access technique to more difficult procedures. Once adept with the common procedures, more advanced procedures can be performed (of note, from both a safety and medicolegal standpoint, the authors do believe a training program is in order, rather than a simple "see one, do one" technique, and we are currently evaluating our method of training in this respect).

Over the 2 years, we found areas for improvement and subsequently altered the technique accordingly. Initially, we utilized articulating instrumentation. These instruments were not widely available, not completely reliable, expensive, and associated with a learning curve. In the initial ten

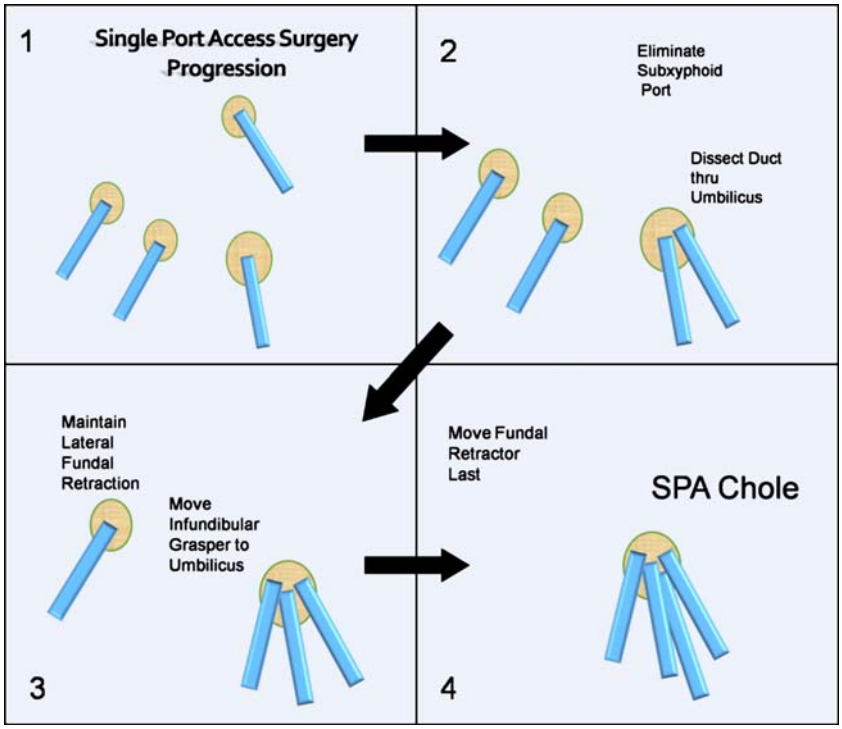

Figure 3 SPA progression.

cholecystectomies, we used two articulating instruments resulting in longer operative times. After the addition of a rigid retractor and the transition to all rigid instruments, our operative time decreased (Fig. 4). Overall, our time trend has been down approximately 20%.

Safety must be the leading focus of any new procedure. This is why SPA surgery had become more of a philosophy than just a technique. First, the SPA cholecystectomy was developed around maintenance of the critical view of the cystic duct/common bile duct relationship.[21] Once we realized the difficulty in obtaining this with only two instruments for dissection, we added the third "trocarless" instruments and had been able to maintain the critical view in every subsequent gallbladder surgery we perform. This also maintains the same instrument number as traditional multiport cholecystectomy and allows dynamic fundal retraction and infundibular manipulation. The addition of the third instrument then allowed us to apply the same technique to caudal retraction of the stomach for GE junction procedures, additional retraction for occasional colon procedures, and an additional instrument for some ventral hernia procedures. It also is the rationale behind the concept of "single port rescue". The importance of adding an additional port site to maintain safety is prerequisite of single port access surgery.

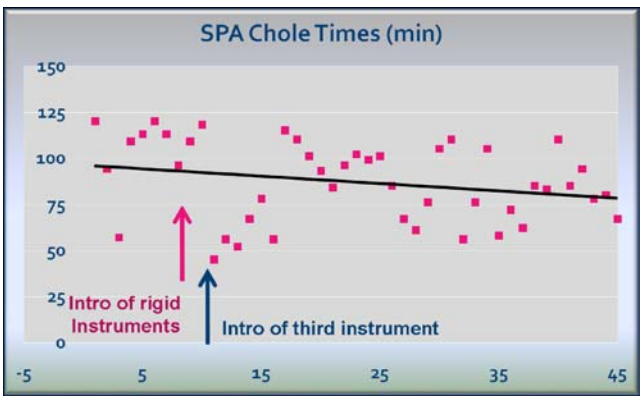

Figure 4 Operative times in SPA cholecystectomy (with addition of third rigid instruments).

Although we report operative times, it must be understood that this is only to provide reference for comparison, demonstrating that we are comparable to standard multiport times. The ability to perform a "fast" cholecystectomy is not a goal we strive to obtain at the expense of a "safe" cholecystectomy.

Also, as we refined the access technique by widening larger skin flaps, we were able to space trocars further apart. This increased SPA circle of entry permitted larger triangulation at the abdominal wall, enabling us to move to straight instruments. We have found this to be an improvement in terms of maintaining a better view of the entire instrument as we are now visualizing "in-line", as well as eliminating most of the instrument collision of hand pieces outside the body. After extending the initial incision for colon surgery, as this would be required at the conclusion to permit specimen extraction, more spacing of trocars further widened the triangulation at the abdominal wall. This also further decreases the "chopstick effect".

Using these standard instruments provided better exposure and eliminated the extended time associated with the learning curve providing a more efficient operation. This transition to straight, reusable instruments has also contained our costs. In addition, we have been able to eliminate the need for an access device and have been able to move to *very low profile* trocars. In cholecystectomy we eliminated one trocar, thus reducing our costs further. Needless to say, this also is an ecological advantage in terms of waste and progressing toward a more "green" approach.

Despite these improvements to the technique over the first 2-year experience, a learning curve exists. This is anticipated with any novel advancement.

Although our outcomes are acceptable and prove that this technique is feasible, parameters such as length of stay, postoperative recovery, pain assessment, and patient satisfaction will need to be determined on a large scale as we move forward. Again, given the success and excellent outcomes we obtain with multiport procedures, we may see no significant benefit.

Single port access provides an alternative approach to minimally invasive surgery. While the immediate draw appears to be cosmetic, potential benefits or disadvantages require further evaluation. This technique may offer a more ergonomic operation with the ability for easier access to the entire abdomen with one setup. Conversely, if the initial access is not obtained properly, gas leak and instrument collision may prohibit a successful operation. It will be difficult to prove advantages in term of short-term outcomes as there is not great room for improvement compared to multiport. The decrease in incisions may decrease the development of infection or hernia sites and the formation of intra-abdominal adhesions. On the other hand, a larger incision may increase the rate of seroma and umbilical hernia. Seromas are not a routine development in standard multiport procedures, and these will have to be followed. The concern will clearly be increased risk of infection and ultimately potential for increased hernia formation at the access site. We will have to continue to follow ASH as we progress. We will also have to compare the ASH incidence in this technique versus the techniques utilizing the single port devices with multiple lumens.

We offer this laparoscopic access technique to all patients. During consent, we not only discuss the potential but not proven risks and benefits but also discuss the possibility of addition of ports or conversion to an open procedure. All procedures begin with an umbilical trocar. Next, the abdomen is inspected and the decision to continue with SPA or convert is made.

With the initial insertion of a celioscope for evaluation of the peritnoneum,[1] the stage was set for us to continue to perform procedures with minimal insults to the patient. Over the past century, we have seen this field grow from simple laparoscopic explorations to the performance of some of the most advanced surgical procedures.[22] One of the main benefits of the current instrumentation and techniques has been the versatility and applicability to a multitude of procedures. We have been able to offer all surgeons training in laparoscopy, and subsequently, the availability to patients has grown. As we continue down this road to the next phase of minimal access surgery, we need to ensure that we can develop procedures, techniques, and instruments that are available and applicable to the large volume of surgery being performed. In Navarra's communication, he indicates the concern that his technique was only applicable to selected patients and may not be worth the additional operative time and expense.[7] The addition of new equipment, reliance on disposable instrumentation, may all increase the costs of our current practices. In addition, training of surgeons and adoption into practice will be a limiting factor in the acceptance and application of new procedures. In the early 1990s, the tradeoff for this was the transition from large incisions for open surgeries to the minimally invasive procedures we currently do today. Although preceded by extreme skepticism, improvements in outcomes of recovery, pain, length of stay, and cosmesis resulted in acceptance.[3] As we move toward NOTES™, the concerns of costs and availability are certainly coming into question. Further and of paramount importance is the attention to maintenance of the basic principles of safety. All of these factors need to be considered as we move toward a new technique or procedure.

Interestingly, NOTES™ almost has a built in safety net. Given its extreme variance from standard and current operative techniques of laparoscopy, although interest has grown and development is progressing, it cannot be routinely performed in most situations. It has an almost inherent property of protection against rapid adoption. This may be one of the biggest strengths of NOTES™-based procedures. On the other hand, single port procedures, as well as the entire realm of reduced port surgical procedures, are being adopted in a much more rapid and broad reaching sweeping motion. These procedures are being performed from university settings to community hospitals. At SAGES 2009, there were nearly 500 cases reported in one session of the most common procedure, laparoscopic cholecystectomy, in its first 2 years of development.[23–25] It is in this light that we need to truly evaluate the advancement into the reduced port surgery arena now and with strict adherence to safety and efficacy of adoption.

Finally, the training of a new procedure needs to be an issue to attend to early in its development. The provision of adequate training and skill development of surgeons on a new technique will ensure its safe adoption into our surgical

community's realm of safe procedures. If we do not address this early on, then "early" adopters with no resource to train may not obtain the benefits of learning from the process the developers of the technique experienced. In the SPA technique, we progressed from four to three to two to one port in cholecystectomy. A similar approach to SPA colon procedures allowed us to be successful in our early development as well. This process, combined with a training program in the lab, will yield a better overview than simply observing a procedure, watching one on the internet, or attempting one "cold".

As new techniques develop, their versatility is important. If each and every minimal access procedure we perform requires a new set of instruments or tools, a different access device or technique, or a different approach, then again we could see learning curves and costs grow exponentially.

Progression and application must proceed with caution and without compromise of the basic tenets of surgery. Physicians should be the motivating force for application and instrument development. While media attention may persuade patients to seek out this procedure for an enhanced cosmetic result, we must ensure a safe result. Although industry will be liked to the development of new procedures and instrumentation, surgeons should be the driving force in development of necessary technology and not vice versa.

With all these "obstacles" and such a limited potential for any "real" benefit, the obvious question is why to proceed down this path of reduced port surgery. Aside from the desire to improve upon our current successes and offer our patients a dedication to improving care, we need to not only look to the future but also plan and develop the steps that will lead us there. Just as single port access surgery developed in a stepwise progression, reduced port surgery offers us a more systematic and perhaps safer approach to the ultimate goal of scarless surgery.

References

1. Schollmeyer T, Soyinka AS, Schollmeyer M et al. Georg Kelling (1866–1945): the root of modern day minimal invasive surgery. A forgotten legend? Arch Gynecol Obstet. 2007;276:505–509.
2. Vecchio R, MacFayden BV, Palazzo F. History of laparoscopic surgery. Panminerva Med. 2000;42:87–90.
3. Casillas RA, Yegiyants S, Collins C. Early laparoscopic cholecystectomy is the preferred management of acute cholecystitis. Arch Surg. 2008;143(6):533–537.
4. Kumar M, Agrawal CS, Gupta RK. Three-port versus standard four-port laparoscopic cholecystectomy: a randomized controlled clinical trial in a community-based teaching hospital in eastern Nepal. JSLS. 2007;11(3):358–362.
5. Slim K, Pezet D, Stencl J Jr, Lechner C, Le Roux S, Lointier P, Chipponi J. Laparoscopic cholecystectomy: an original three-trocar technique. World J Surg. 1995;19(3):394–397.
6. Navarra G, Pozza E, Occhionorelli S et al. One-wound laparoscopic cholecystectomy. Br J Surg. 1997;84:695.
7. Navarra G, La Malfa G, Bartoletta G, Curro G. The invisible cholecystectomy: a different way. Surg Endoscopy. 2003;22:2103.
8. Ponsky JL, Gauderer MW, Stellato TA. Percutaneous endoscopic gastrostomy. Review of 150 cases. Arch Surg. 1983;118(8):913–914.
9. Kalloo AN, Singh VK, Jagannath SB et al. Flexible transgastric peritoneoscopy: a novel approach to diagnostic and therapeutic interventions in the peritoneal cavity. Gastrointest Endosc. 2004;60:114–117.
10. de la Fuente SG, Demaria EJ, Reynolds JD et al. New developments in surgery: Natural Orifice Transluminal Endoscopic Surgery (NOTES). Arch Surg. 2007;142:295–297.
11. Box GN, Bessler M, Clayman RV. Transvaginal access: current experience and potential implications for urologic applications. J Endourol. 2009;23(5):753–757.
12. Horgan S, Mintz Y, Jacobsen GR, Sandler BJ, Cullen JP, Spivack A, Easter DW, Chock A, Savu MK, Ramamoorthy S, Bosia J, Agarwal S, Lukacz E, Whitcomb E, Savides T, Talamini MA. NOTES: transvaginal cholecystectomy with assisting articulating instruments. Surg Endosc 2009;23:1900.
13. Bessler M, Stevens PD, Milone L, et al. Transvaginal laparoscopic cholecystectomy: laparoscopically assisted. SAGES Meeting; 2006.
14. Curcillo PG (2002) Laparoscopic ventral hernia repair with self expanding mesh—a "one stitch, two port" technique. American Hernia Society Annual Meeting, Tuscon, AZ.
15. Podolsky ER, Rottman SJ, Curcillo PG. Single port access (SPA Surgery™); single port access cholecystectomy (SPA surgery), Society of Laparoendoscopic Surgeons (SLS): Asian American Summit III; Honolulu, Hawaii; February 6–9, 2008.
16. Curcillo PG,Wu A, Podolsky E, Rottman, Drahota L, Dunham RH, Katz L, Kharod A. Single port access (SPA) cholecystectomy—initial validation of a single incision approach—SAGES April 2008, Philadelphia, PA.
17. Podolsky ER, Rottman SJ, Poblete H, King SA, Curcillo PG II. Single port access (SPA Surgery™) cholecystectomy: a completely transumbilical approach. J Laparoendosc Adv Surg Tech. 2009;19(2):219–222.
18. Podolsky ER, Rottman SJ, King SA, Curcillo PG. Single port access surgery (SPA) gastrostomy tube in patients unable to receive percutaneous endoscopic gastrostomy placement. Surg Endosc. 2009;23(5):1142–1145.
19. King SA, Atogho A, Podolsky ER, Curcillo PG. Single port access (SPA) bilateral oopherectomy and hysterectomy. Laparoscopy Today, The Green Issue, 7;2,26.
20. Curcillo PG, Podolsky ER. Featured video presentation; single port access (SPA Surgery™) technique; 49th Annual Meeting—Society for Surgery of the Alimentary Tract (SSAT), San Diego, CA; May 17–21, 2008
21. Strasberg SM, Hertl M, Soper NJ. Analysis of the problem of biliary injury during laparoscopic cholecystectomy. J Am Coll Surg. 1995;180:101–105.
22. Gagner M, Pomp A. Laparoscopic pylorus-preserving pancreaticoduodenectomy. Surg Endosc 1994;8:408–410.
23. Wu AS, Podolsky ER, Curcillo PG, Bessler M, Cohen L, Copper C, Dunham R, Fendley S, Graybeal C, Gumbs A, Iannelli A, Katkhouda N, Kelley W, Mason R, Neff M, Norton M, Single port access (SPA) cholecystectomies: multi-institutional report of the first 100 cases. SAGES, scientific session and panel, single incision/single port laparoscopy, Phoenix, AZ; April 24, 2009.
24. Rivas H, Varela E, Scott D. Single incision laparoscopic cholecystectomy, initial evaluation of a large series of patients. SAGES, scientific session and panel, single incision/single port laparoscopy, Phoenix, AZ; April 24, 2009.

25. Edwards CA, Bradshaw A, Ahearne P, Mauterer D, Soosaar P, Johnson R, Humble T, Dematos P. Single incision laparoscopic cholecystectomy is safe and feasible. SAGES, scientific session and panel, single incision/single port laparoscopy, Phoenix, AZ; April 24, 2009.
26. Curcillo PG, King SA, Podolsky ER, Rottman SJ. Single port access (SPA™), minimal access surgery through a single incision. Surgical Technology International, Vol. XVIII, chapter 241.

Discussant

Dr. Mark A. Talamini (San Diego, California): Drs. Podolsky and Curcillo report a retrospective series of 113 patients over a two-year period who underwent single incision minimally invasive procedures. This has to be one of if not the largest experiences reported in this evolving field. The manuscript, which I appreciated receiving before the meeting, is primarily a description of the technique and some of the issues surrounding the development of the technique. Obviously the manuscript, the experience it describes, and this field in general is controversial and raises many questions. I have four that I would like to pose to you. First, can you share with us two unexpected outcomes either positive or negative that you all have discovered in following these patients up, things that surprised you?

Second, what aspects of your experience related in this manuscript might convince you that in a decade we'll be doing operations this way? Third, what are the arguments for or against needing IRB approval, review board approval, for taking up this kind of work for surgeons? Finally, I would be remiss if I didn't mention one case in your manuscript that looked like one of the colon cases had a 1500 cc blood loss, which would bring up the issue of conversion. If you need to consider conversion, would that be a laparoscopic approach or an incision?

Closing Discussant

Dr. Erica R. Podolsky (Philadelphia, Pennsylvania): At this point I think one of the most surprising things is how well we have been able to apply this technique and how well it's been received. Initially, it was something that was experimental, performing it in porcine models. I think that extending to human patients and really seeing good initial outcomes and being able to apply it to multiple procedures has really been something a little bit surprising and very exciting.

I think SPA is an alternative. I think that we need long-term follow-up, because I'm not sure that it's going to result in improved outcomes. And if we do see more hernias or complications, it may be a technique that isn't something we'll see in ten years. But I think with the push for NOTES, it provides an alternative, and maybe it can be a stepping stone to help perform those procedures. Maybe we can start this way and combine this umbilical access with NOTES and then transition to pure NOTES.

As far as IRB approval, we did have an IRB approval for review of this and recommend it for using the technique as it is a new novel approach. A thorough patient consent should also be included – this technique versus other techniques, and the possibility of conversion to multiple trocars and/or incisions.

If we do need to convert, there's really no holding back on adding another trocar or converting to open surgery. And all of our patients are consented that way.

Your question regarding the large blood loss and conversion to open is a very important point. This is a patient that was converted to open after placing the first two trocars and exploring and identifying a large tumor into the abdominal wall. An open approach was decided to be best and indicates a clear need to advance slowly. Included in error in our presentation of SPA cases, we will fix this in our manuscript.

Discussant

Dr. L. Michael Brunt (St. Louis, Missouri): I would like to congratulate you on this large series of single-port access cases and this impressive variety of numbers that you have accomplished has really helped develop and push forward this technique. I have a specific question about the lap-choles. In how many cases did you do cholangiography? And what was your cholangiography technique?

Closing Discussant

Dr. Erica R. Podolsky (Philadelphia, Pennsylvania): We don't routinely perform cholangiography. We use ERCP. We did perform cholangiography in two patients. In the first patient we tried to do a trans-umbilical cholangiography, which we found technically difficult. And then we thought about it and found that it would be easier to just insert a cholangiography catheter into the right upper quadrant and get the right angle and just directly place it within the duct. In surgeons that are performing cholangiography with this technique, I think that's the technique that they are using as another site to insert the catheter.

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2009 SSAT POSTER PRESENTATION

Not Just for Trauma Patients: Damage Control Laparotomy in Pancreatic Surgery

Katherine Morgan · Deanna Mansker · David B. Adams

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Abstract
Background Damage control laparotomy (DCL) has been a major advance in modern trauma care. The principles of damage control which include truncation of operation to correct acidosis, hypothermia, and coagulopathy with subsequent planned definitive repair are applicable in managing patients undergoing abdominal operations. In order to define indications, technique, and outcome, we undertook a retrospective review and analysis of pancreatic surgery patients in whom DCL was utilized.
Methods In a cohort of 835 patients who underwent elective pancreatic operations at the Medical University of South Carolina from 2001 to 2007, eight patients were identified who required DCL. Under Institutional Review Board approval, records were reviewed to define intraoperative blood loss, acidosis, hypothermia, coagulopathy, operative techniques, timing of definitive operation, and hospital outcome.
Results There were five men and three women with a mean age of 51 years. The diagnosis was chronic pancreatitis in seven patients and cancer in one. The index operation was pancreatoduodenectomy in four patients, distal pancreatectomy in three, and total pancreatectomy in one. In four patients undergoing elective pancreatic resection intraoperative portal vein hemorrhage initiated damage control laparotomy. Four patients had damage control utilized at reoperation for abdominal sepsis (two) and hemorrhage (two). DCL techniques included external tube drainage (eight), abdominal packing (seven), staple closure of open bowel (four), and rapid abdominal closure (four). Operative blood loss ranged from 300 to 12,000 cc. Operative transfusions ranged from 0 to 44 U of packed red cells. Intraoperative INR was greater than 1.5 in four patients, pH ranged from 7.08 to 7.45, and temperature ranged from 34.8 to 38.8°C. Laparotomy for pack removal and intestinal reconstruction was undertaken 1 to 7 days after DCL. Length of hospital stay ranged from 7 to 80 days. Hospital mortality was zero.
Conclusions Patients with exsanguinating hemorrhage and severe sepsis related to pancreatic surgery can be successfully managed with principles of DCL. Truncation of operation with abdominal packing, bowel closure, external drainage of bile and pancreatic ducts, and rapid abdominal closure with planned subsequent completion laparotomy should be considered in pancreatic operations when patients risk intraoperative acidosis, hypothermia, and coagulopathy due to sepsis or hemorrhage.

Keywords Pancreas · Surgery · Complications · Damage control

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Introduction

Damage control laparotomy (DCL) has entered the mainstream surgical lexicon in modern trauma care. It represents one of the major advances in the surgical management of the severely injured patient. Stone described in 1983 the survival advantage of the early truncation of laparotomy when encountering exsanguinating traumatic hemorrhage to

allow for physiologic resuscitation prior to definitive operative repairs [1]. Rotondo applied the term "damage control laparotomy" to this approach as applied to the severely injured trauma patient, borrowing the vocabulary of the Naval service and the shipboard principle of maintaining the vital capacities of the ship and containing damage in the case of attack in order to maintain mission integrity and stay afloat.[2] DCL can be a lifesaver for the trauma patient in the operating room who develops hypothermia, acidosis, and coagulopathy. Operative time is minimized, with attention to control of hemorrhage and containment of gastrointestinal contamination, employing stapled bowel closure, external tube drainage, abdominal packing, and rapid abdominal closure.[1–4] This strategy, which has evolved in major trauma centers over the past two decades, is as applicable to patients who suffer operating room trauma as to those who suffer trauma on the streets.

It is alarming when patients undergoing elective and urgent abdominal surgery develop severe physiologic disturbances secondary to operative hemorrhage or sepsis. The accompanying intraoperative hypothermia, acidosis, and coagulopathy are harbingers of high morbidity and mortality. DCL principles are utilized successfully in general surgery patients in many situations. Elective and urgent pancreatic operations in particular have occasional need for utilization of DCL to salvage patients who are unexpectedly severely injured with operative trauma. In order to review and describe the use of DCL in operations on the pancreas, a retrospective review and analysis was undertaken of patients undergoing pancreatic surgery over a 6-year period.

Methods

An inpatient hospital database identified a cohort of 835 patients who underwent elective and urgent pancreatic operations at the Medical University of South Carolina from 2001 to 2007. Eight patients were identified who required DCL. With the approval of the Institutional Review Board for the evaluation of human subjects, the electronic medical records of these eight patients were reviewed. Data collected and analyzed included patient demographics, indications for surgery, operative conduct, intraoperative blood loss, pH, patient temperature and INR, damage control techniques, timing of definitive operation, and hospital outcome.

Results

There were five men and three women with a mean age of 51 years (range 37 to 65 years) who underwent an elective pancreas operation and subsequently required DCL during the study time period. The indication for surgery was chronic pancreatitis in six patients, chronic pancreatitis and intrapapillary mucinous neoplasm in one, and ampullary cancer in one. The index operation was pancreatoduodenectomy in four patients, distal pancreatectomy in three, and total pancreatectomy in one (Table 1).

In four patients undergoing elective pancreatic resection intraoperative portal vein hemorrhage initiated damage control laparotomy. The site of portal vein injury was at the portosplenic confluence in two patients undergoing distal pancreatectomy, anteriorly under the neck of the pancreas in one patient undergoing total pancreatectomy, and laterally behind the common bile duct in one patient undergoing pancreatoduodenectomy.

While the injuries encountered were in variable locations, several common techniques were employed in the management of portal venous hemorrhage. Initial venous compression for temporary control was undertaken to facilitate identification of injury site and extent, as well as to allow for preparation of the operative team, including anesthesiologist and surgeon. Compression was accomplished via a Kocher maneuver for manual pressure in all cases. Spongesticks were also used for means of venous compression. Next adequate exposure of the injury was obtained via division of the pancreas and expeditious removal of the specimen.

In all patients primary repair of the identified portal venous injury was attempted. In two patients primary repair was successful. In one patient with a portosplenic confluence injury, temporary vascular control was obtained with vascular clamps. Due to the size of the injury, primary repair risked venous compromise and he therefore underwent venous repair using a patch of native splenic vein (harvested from the specimen). The final patient with portal injury had his portal vein ligated during attempts at hemostasis. The small bowel became immediately severely engorged and ischemic appearing. Due to concerns for bowel viability, an interposition graft of cadaver iliac vein was utilized at this primary operation. While classic DCL principles would entail temporizing measures such as vascular shunting with planned staged definitive repair, these latter two patients were managed well with revascularization at the primary operation (Table 2).

Four patients had damage control utilized at reoperation for abdominal sepsis (two) and hemorrhage (two). Abdominal sepsis was due to a leak at the choledochojejunostomy in one patient. She presented with fever, hypotension, and extraluminal fluid and air on CT scan postoperative day 9, and on exploration was found to have anastomotic dehiscence. Another patient presented 53 months after pancreatoduodenectomy with obstructive symptoms and hemodynamic instability and was found to have an internal

Table 1 Demographics

Pt #	Age, gender	Diagnosis	Operation
1	53, M	Chronic pancreatitis	Pancreaticoduodenectomy
2	50, F	Chronic pancreatitis	Pancreaticoduodenectomy
3	62, M	Chronic pancreatitis, intrapapillary mucinous neoplasm	Total pancreatectomy
4	65, F	Chronic pancreatitis	Distal pancreatectomy
5	37, M	Chronic pancreatitis	Distal pancreatectomy
6	57, M	Chronic pancreatitis	Distal pancreatectomy
7	40, F	Ampullary cancer	Pancreaticoduodenectomy
8	37, M	Chronic pancreatitis	Pancreaticoduodenectomy

hernia with bowel infarction. As this patient demonstrates, the altered anatomy of the post pancreatectomy patient can lend to catastrophic complication. One patient developed hypotension, tachycardia, and profound anemia on postoperative day 1; bleeding was found in the bed of the resected pancreatic head on re-exploration. Another patient, on postoperative day 3, similarly became hemodynamically unstable and anemic and was found at reoperation to have bleeding from the splenic artery stump after distal pancreatectomy (Table 2).

DCL techniques included external tube drainage of biliary, pancreatic, or enteric contents (five), staple closure of open bowel (four), abdominal packing (seven), and rapid abdominal closure (seven; Table 2). External tube drainage consisted of the use of a red rubber catheter for control of biliary contents and a pediatric feeding tube for diversion of pancreatic exocrine secretions. Closed suction drains were placed in the operative bed and octreotide infusion was employed to decrease pancreatic exocrine output. Rapid abdominal closure employed a protective covering over the bowel with the application of a negative pressure dressing.

Operative blood loss ranged from 300 to 12,000 cc. Operative transfusions ranged from 0 to 44 U of packed red cells (mean 14.1 U). Intraoperative INR was a mean of 2.19 (range 1.43–3.3) and was greater than 1.5 in seven out of eight patients. Intraoperative pH ranged from 7.08 to 7.45 (mean 7.27), and temperature ranged from 34.8 to 38.8°C (mean 36.1; Table 3).

Laparotomy for pack removal and intestinal reconstruction was undertaken 1 to 3 days after DCL in seven of the patients. Three patients underwent more than one additional reoperation (range 0 to 6). One patient underwent external tube drainage of her bile duct with suture closure of the adjacent jejunum after complete dehiscence of her choledochojejunostomy. Reoperation for anastomotic revision was planned, but a fistula developed between the bile duct and jejunum, which was subsequently able to be dilated by the percutaneous transhepatic route in interventional radiology and she therefore avoided reoperation.

Six patients achieved fascial closure, while two underwent vicryl mesh closure. Perioperative morbidity was substantial, including intra-abdominal abscess (six), respiratory failure (five), pneumonia (two), acute renal failure (two), venous thromboembolism (two), cardiac arrhythmia (one), pancreatic fistula (one), and enterocutaneous fistula (one). Three patients developed ventral hernias requiring delayed reconstruction. Length of hospital stay ranged from 7 to 80 days. Five patients required hospital readmission. Hospital mortality and long-term mortality (median follow-up 58 months) were zero. Hospital charges averaged $275,627 per patient (range from $32,363 to $931,723)

Table 2 Intraoperative Data

Pt #	Complication	Techniques employed to truncate laparotomy
1	Bleeding	External tube drainage, packs, stapled bowel closure, rapid abdominal closure
2	Bleeding	Packs, rapid abdominal closure
3	Bleeding	External tube drainage, packs, stapled bowel closure, rapid abdominal closure
4	Bleeding	Packs, rapid abdominal closure
5	Bleeding	External tube drainage, packs, rapid abdominal closure
6	Bleeding	Packs, stapled bowel closure, rapid abdominal closure
7	Sepsis	External tube drainage
8	Sepsis	External tube drainage, stapled bowel closure, rapid abdominal closure

Table 3 Intraoperative Data Continued

Pt #	EBL (ml)	Intraop transfusion (units pRBCs)	Intraop pH	Intraop temp (C)	Intraop INR
1	5,800	12	7.29	34.8	1.84
2	4,500	6	7.28	35.9	3.12
3	5,000	27	7.27	36.6	2.16
4	1,800	1	7.45	35.6	1.43
5	12,000	22	7.17	35.0	1.71
6	6,000	44	7.08	35.8	3.30
7	400	0	7.37	38.8	1.72
8	300	1	7.22	36.1	2.24

Discussion

Elective pancreas surgery in the modern era is safe and effective when performed at high-volume centers. Despite the advantages which specialized centers offer, when surgeons work in and around the pancreas, the potential for catastrophic complication persists. Pancreatic cancer and chronic pancreatitis patients are often chronically malnourished, and may have resultant poor healing capabilities and limited physiologic reserve related to age and chronic illness.

The dense inflammatory fibrosis associated with chronic pancreatitis obliterates planes and distorts anatomy increasing risk for vascular injury. Pancreatic cancer can involve nearby major vascular structures requiring complex vascular reconstruction. Exsanguinating hemorrhage can quickly develop, particularly in the event of portal venous injury, which was the most common complication encountered in this series.

Postoperative pancreatic and biliary anastomotic leaks can lead to a noxious broth of pancreatic exocrine secretions and bile with consequent pancreatic enzyme activation with attendant autolysis of surrounding soft tissues. Activation of pancreatic enzymes is a potent stimulus for cytokine release and the vicious cascade of a severe systemic inflammatory response can result. This postoperative occurrence leads directly to renal, pulmonary, cardiovascular, hepatic, and central nervous system failure escalating the severity of illness. Additionally, severe hemorrhagic complications can occur as a result of enzymatic vessel destruction. The anastomotic leak after pancreatic surgery can be catastrophic.

Patients that have undergone pancreatic surgery with altered foregut anatomy are at risk for the development of small bowel obstruction and internal herniation. Afferent limb obstruction after pancreatoduodenectomy, efferent limb obstruction due to jejunal fixation for feeding tubes, and internal herniation of proximal jejunum at the base of the transverse mesocolon are potential causes of small bowel obstruction. These proximal obstructions are difficult to differentiate from postoperative pain and pain related to chronic pancreatitis, and history and physical examination will need to be supplemented by CT imaging.

In trauma, lag time leads to loss of physiologic reserve due to hemorrhage and visceral contamination. Time delay from injury to treatment is a large determinant of survival. In the 1980s, the recognition of the role of physiologic reserve in outcomes in critically injured trauma patients led to the emergence of damage control surgery. Once the deadly combination of hypothermia, acidosis, and coagulopathy has been incited in the setting of trauma, these factors become the priority and must be corrected, often delaying definitive operative injury repair.

In patients undergoing elective pancreas surgery, the physiologic disadvantage is usually not due to delay in time to operation. These patients are physiologically disadvantaged due to their underlying disease process and limited reserve. Portal venous hemorrhage and pancreatobiliary leak are significant physiologic stressors that can quickly lead to hypothermia, acidosis, and coagulopathy. As in trauma, damage control principles, with truncated laparotomy, stapled closure of bowel, external tube drainage, abdominal packing, and rapid abdominal closure with planned re-exploration after physiologic resuscitation are no different than principles used in trauma surgery.

All patients in the study group developed hypothermia, acidosis, and/or coagulopathy during or following pancreas surgery. Damage control techniques were successfully utilized with attention to controlling hemorrhage, maintaining intravascular volume, and draining pancreatobiliary secretions. Truncated laparotomy was employed to allow for correction of abnormal physiology with planned delayed definitive repair. While significant resource utilization was involved with multiple reoperations, intensive care therapy, and long hospital stay, there was no mortality.

Conclusions

Operations on the pancreas are known to be a risky undertaking with infrequent but well-known intraoperative and postoperative catastrophic complications. When pancreatic operations result in hemorrhage and sepsis with hypothermia, acidosis, and coagulopathy, DCL principles should

be utilized. DCL can be life saving and should be an essential tool in the armamentarium of the modern pancreas surgeon.

References

1. Stone HH, Strom PR, Mullins RJ. Management of the Major coagulopathy with onset during laparotomy. Ann Surg 1983;197:532–535.
2. Rotondo MF, Schwab CW, McGonigal MD, et al. "Damage control": an approach for improved survival in exsanguinating penetrating abdominal injury. J Trauma 1993;35:375–383.
3. Burch JM, Ortiz VB, Richardson RJ, et al. Abbreviated laparotomy and planned reoperation for critically injured patients. Ann Surg 1992;215:476–484.
4. Cosgriff N, Moore EE, Sanaia A, et al. Predicting the life threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidosis revisited. J Trauma 1997;42:857–862.

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2009 SSAT PLENARY PRESENTATION

Conservative and Surgical Treatment of Chronic Anal Fissure: Prospective Longer Term Results

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Abstract
Introduction The aim of this prospective study was to assess the efficacy of different medical treatments and surgery in the treatment of chronic anal fissure (CAF).
Patients and Methods From January 2004 to March 2009, 311 patients with typical CAF completed the study. All patients were initially treated with 0.2% nitroglycerin ointment (GTN) or anal dilators (DIL) for 8 weeks. If no improvement was observed after 8 weeks, the patients were assigned to the other treatment or a combination of the two. Persisting symptoms after 12 weeks or recurrence were indications for either botulinum toxin injection into the internal sphincter and fissurectomy or lateral internal sphincterotomy (LIS). During the follow-up (29±16 months), healing rates, symptoms, incontinence scores, and therapy adverse effects were prospectively recorded.
Results Overall healing rates were 64.6% and 94% after GTN/DIL or BTX/LIS. Healing rate after GTN or DIL after 12 weeks course were 54.5% and 61.5%, respectively. Fifty-four patients (17.4%) responded to further medical therapy. One hundred two patients (32.8%) underwent BTX or LIS. Healing rate after BTX was 83.3% and overall healing after LIS group was 98.7% with no definitive incontinence.
Conclusion In conclusion, although LIS is far more effective than medical treatments, BTX injection/fissurectomy as first line treatment may significantly increase the healing rate while avoiding any risk of incontinence.

Keywords Chronic anal fissure · Surgery · Botulinum

Introduction

The treatment of chronic anal fissure (CAF) has changed greatly during the past two decades with ongoing research on medical approaches directed at lowering the internal anal sphincter tone and avoiding the risk of fecal continence disturbance. Glycerin trinitrate (GTN), topical calcium channel blockers and anal dilators and botulinum toxin injection alone are all known to be able to lower the IAS tone but results have been disappointing in curing CAF, often marginally better than to placebo.

In a recent meta-analysis of randomized clinical trials comparing medical treatments to placebo or surgery,[1] Nelson et al. have shown that GNT, botulinum toxin injection, and surgery have overall response rates of about 55%, 65%, and 85%, respectively, whereas the placebo healing rate is about 35% across all the studies. This evidence led Nicholls in a recent editorial to point out that surgery in the form of sphincterotomy is markedly superior to any form of chemical sphincterotomy and is the most effective treatment for fissure at present.[2]

Lateral internal sphincterotomy (LIS) allows prompt healing in more than 90% of the patients with a low recurrence risk of 3%. However, it may cause minor but permanent incontinence.[3–10] According to a systematic review of randomized surgical trials,[11] the overall risk of

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continence disturbance after surgery is about 10% but can be as high as 35% from nonprospective uncontrolled data.

Obviously these findings augment the fear of incontinence and reluctance toward surgery for both the patient and the surgeon with the continuing call for changes to safer medical alternatives. Medical treatment seems therefore a reasonable first line therapy for most patients with CAF.

Second line use of botulinum toxin seems to heal only 50% of fissures resistant to GTN.[12] It is likely that the fibrotic nature of chronic fissures resistant to GTN is not resolved by chemical sphincterotomy alone. Fissurectomy alone is not currently used in adults, but its combination with botulinum toxin injection has been recently used with success to treat fissures resistant to medical treatment,[13–15] with healing rates higher than 90% (not far from LIS), and with negligible risk of incontinence.

We have previously demonstrated that surgical treatment either with fissurectomy and botulinum toxin injection and LIS is safe and associated with the highest likelihood of CAF healing compared to common medical treatments. In this prospective study, we present longer term results in a larger cohort of patients with CAF assessing the efficacy of different conservative treatments (including GTN and anal dilators or a combination of the two) and surgery.

Patients and Methods

Between January 2004 and March 2009, 311 consecutive patients with CAF were enrolled in the study. Diagnosis was made according to history and physical exam. CAF was defined by duration of symptoms longer than 3 months and the presence of a skin tag, a sentinel pile or fibrosis at the margins of the fissure. Exclusion criteria included atypical CAF associated with grade III/IV hemorrhoids, previous anal surgery, incontinence, inflammatory bowel disease, infection, or cancer. Patients with coexisting medical conditions requiring calcium channel blockers and oral, sublingual, or transdermal nitrates were also considered ineligible for this study. Patients with incomplete follow-up were also excluded.

During the outpatient visit, a complete explanation of the disease as well as the medical treatment options, benefits, and side effects was given to the patient.

After this, each patient was assigned to an 8-week course of medical therapy with either 0.2% GTN or DIL according to his/her preference. Patients in the GTN group were instructed to apply the ointment twice a day to the edge and just inside the anal canal (morning and evening) after a warm Sitz bath. The amount of *crème* to be applied was shown during the outpatient visit. If patients experienced side effects, he/she was instructed to use a finger glove for application or to reduce the amount to be applied.

DIL group patients were instructed to use an anal dilators set (Dilatan, Sapi-Med, Alessandria, Italy) as follows: heating the DIL for 15 min in water, lubricating it with a preparation gel (Dilatan crema, Sapi-Med, Alessandria, Italy), introducing it fully into the anal canal, and maintaining the position for 10 min twice a day (morning and evening).

Patients were invited to repeat this procedure for 3 weeks starting with small diameter dilators (20–23 mm), followed by medium size dilators (23–27 mm), and ending with the large ones (30 mm). An illustrated brochure containing practical suggestions was given to the patients.

The primary end-point was fissure healing at last follow-up. Secondary end-points were symptomatic improvement, need for surgery, side effects and surgical complications, and patients' satisfaction.

Improvement was defined as absence of pain or bleeding. Healing was defined as complete epithelialization of the fissure base. Those patients in which no improvement in symptoms was observed after 8 weeks were crossed to the other treatment (either GTN or DIL) or switched to a combination of the two for additional 4 weeks according to his/her preference. Botulinum toxin injection in the IAS associated to fissurectomy (BTX-F) or LIS were offered to patients who did not benefit from the 12 weeks treatment course with GTN, DIL, or DIL/GTN combined, after full explanation about the risks and benefits of either procedure. Patients with nonhealed or recurrent CAF who refused surgery were offered a further medical treatment. Anorectal manometry was performed before either one of the procedures.

Either fissurectomy/Botox injection or LIS were performed in a day-surgery setting under sedation and local anesthesia in lithotomy position. Before surgery, all patients had a limited bowel preparation with one Sorbiclis (Sofar S.p.a, Milan, Italy). An Eisenhammer speculum was gently inserted, avoiding excessive sphincter dilatation. Fissurectomy was always performed by minimal excision of the fibrotic edges of the fissure and curettage of its base just back to fresh, normal, nonfibrotic tissue. If present, the sentinel pile was excised with cutting diathermy. Once fissurectomy was performed, 25 units of botulinum toxin (Botox, Allergan, Milan, Italy) were injected as follows: A volume of 1.6 ml of saline solution was mixed into a 100-unit vial of botulinum toxin and 0.4 ml aliquot (equal to 25 units) was drawn up into a 1 ml syringe with a 27 Gauge needle and equally injected into the IAS at 3 and 9 o'clock.

An open LIS was performed with patient in lithotomy position under local anesthesia and/or deep sedation when necessary. A circumanal incision of 1 cm was made just distal to the intersphincteric grove in the lateral position

with subsequent partial division of the internal anal sphincter using coagulation diathermy. The distal internal sphincter was divided under direct vision for a length up to the fissure apex. In all cases fissurectomy was performed as previously described.[14]

Patients in both groups were discharged home on the same day and stayed on a high residue diet and stool softener for 7 days. A nonnarcotic analgesic was also prescribed as needed and patients were advised to take regular warm Sitz baths. Patients were seen in outpatient clinic after 1 week and therefore at a 1-, 2-, 3-, and 12-month intervals. Patients were then contacted by phone. Independently of these scheduled appointments, patients were seen on request. Information about fissure healing, symptoms, complications, and adverse effects were prospectively collected. Wexner incontinence score was used to assess continence after the procedures.

Differences between treatment groups were evaluated by *chi-square* test

Results

Patients' demographics, fissure characteristics, and treatment failures are shown in Table 1. Median follow-up was 29±16 months ranging from 3 to 63 months.

Healing after 12 weeks was observed in 54.5% (103/189) of patients for the GTN only group and in 61.5% (75/122) of patients for the DIL only group without significant differences (p=0.2). Overall fissure healing after medical treatment with either GTN or DIL alone was observed in a total of 178 (57.2%) patients.

Recurrence rates after 12 weeks treatment were 23.3% for GTN only group and 9.3% for DIL only group, respectively (p=0.02), reducing the overall healing rate of single medical treatment to 47.3% (147 patients).

In particular, healing with no recurrence was observed in 79 out of 189 patients (41.8%) treated with GTN alone and in 68 out of 122 patients (55.7%) who underwent DIL only. This difference was statistically significant (p=0.01). In most of the patients, healing time ranged from 8 to 12 weeks after treatment course. No significant difference was noted between the two groups in terms of healing time (p=0.4).

One hundred thirty-three patients (42.8%) experienced nonhealing or sudden recurring disease within the first 8 weeks observation period. Of those, 46 patients (previously treated with GTN) were switched to DIL, 38 (previously treated with DIL) to GTN for additional 4 weeks. The remaining 49 patients accepted combined GTN/DIL treatment.

A total of 54 patients (17.4%) responded to this further medical therapy and overall definitive healing rate rose significantly from 47.3% to 64.6% (p=0.001). In particular, at the end of this additional 4 weeks treatment, GTN after DIL resulted effective in 60.5% of the treated patients (23 out 38) and DIL after GTN in 45.7% (21 out of 46; p=0.4). Of the 49 patients treated with combined DIL/GTN, 20 responded with healing (40.8%; p=0.6 vs DIL and p=0.08 vs GTN). During the follow-up, recurrence rates were 14.3% for DIL after GTN, 13% for GTN after DIL, and 20% for combined GTN/DIL, with no significant differences among groups.

Definitive healing was observed in 18 out of 46 patients treated with DIL after GTN (39.1%), in 20 out of 38

Table 1 Patients' Demographics, Fissure Characteristics and Treatment Failures

	GTN	DIL	GTN/DIL	Botox/fissurectomy	LIS
Number (N)	189	122	49	30	72
Mean age (years)	49	44	47	38	45
Sex M/F	88/101	53/69	17/32	11/19	28/34
Fissure position					
Posterior	164	100	31	27	51
Anterior	20	18	13	2	9
Both/other	5	4	5	1	2
Sentinel pile N/%	117/62%	87/71%	33/67%	22/73%	51/71%
Single treatment (12 weeks) success N/(%)	103/189 (54.5%)	75/122 (61.5%)	NA	NA	NA
Recurrence	24/103 (23.3%)	7/75 (9.3%)	NA	NA	NA
After crossover healing N/%	21/46 (45.7%)	23/38 (60.5%)	20/49 (40.8%)	NA	NA
Recurrence	3/21 (14.3%)	3/23 (13%)	4/20 (20%)	NA	NA
Overall Success N/%	97/189 (51.3%)	88/122 (72.1%)	16/49 (32.6%)	25/30 (83.3%)	71/72 (98.6%)
Overall Success N/% (DIL/GTN combined included)	109/189 (57.7%)	92/122 (75.4%)	NA	NA	76/77 (98.7%)

GTN nitroglycerin ointment, *DIL* anal dilators, *BTX* botulinum, *LIS* lateral internal sphincterotomy, *NA* not applicable

patients treated with GTN after DIL (52.6%), and in 16 out of 49 patients treated with combined GTN/DIL (32.6%). DIL after GTN and combined GTN/DIL treatments were similar in terms of definitive healing but worse compared GTN after DIL treatment although differences were not significant (p=0.07).

At the end of the study, overall medical treatment (including the crossover) success was 57.7% (109 out of 189 patients) and 75.4% (92 out of 122 patients), respectively, for patients initially treated with GTN or DIL. This difference between the two groups was statistically significant (p=0.01). At the end of the study, 64.6% of the patients resulted cured by medical approach alone. Overall incidence of GTN side effects was 9.7% (23 out of 236 patients), mostly mild headache (15 patients) and *pruritus ani* (eight patients). Seven patients (3.7%) discontinued therapy and were switched to DIL.

A total of 208 patients were treated with DIL (122 patients as initial treatment and 86 patients after GTN treatment) and 10.1% interrupted the DIL course because of severe discomfort. After nonhealing or recurrence, surgery was offered to 110 patients (35.4%). At the end of follow-up, eight patients refused either botulinum treatment or surgery and further medical treatment was offered with minimal beneficial effect. Of the remaining 102 patients, 30 underwent fissurectomy/Botox injection and 72 to LIS. Manometry results between these two groups are shown in Table 2. Healing was reported in 25 out of 30 (83.3%) patients after fissurectomy/Botox injection. This percentage was significantly higher compared to GTN alone course (p=0.001), to DIL alone treatment (p=0.004), or to overall combined/crossover groups (p=0.001). One patient (3.3%) experienced transitory flatus incontinence. Nonhealing was observed in two patients (6.7%) and recurrence in three (10%). Despite reluctance to further surgery after failed fissurectomy/Botox by two patients, all five patients underwent LIS had complete healing. No perioperative complications were observed in this group.

All but one patient treated with LIS showed complete healing with no postoperative incontinence. Overall morbidity after LIS was 9.7%. Three patients experienced urinary retention after surgery (all males) and needed catheterization. Two patients experienced perianal ecchymosis and one perianal abscess with submucosal fistula that required surgery 7 months later. One patient experienced recurrence 10 months after surgery.

Comparing the different treatment groups, there were no significant differences in terms of healing rates between males and females, presence or absence of sentinel pile or previous GTN or/and DIL treatment.

Overall patient's satisfaction with the outcome of surgery including the LIS after BTX failures was 93.5% (72/77).

Discussion

The most recent theories on etiopathogenesis of anal fissures have focused on increased tonicity of the IAS, which induces ischemia of the anodermis mainly of the posterior commissure.[16–22] Since the introduction of the posterior internal sphincterotomy by Eisenhammer in 1951, CAF has been managed with surgery once conservative measures failed.[23] The more safe lateral sphincterotomy popularized by Notaras in 1969 has, until recently, been the mainstay of treatment.[24] Despite surgery is highly efficacious and succeeds in curing CAF in more than 90% of patients (often exceeds 95% with high patient satisfaction), postoperative impairment of continence is not uncommon.[1,17] The incidence varies between 0% and 35% for flatus incontinence, 0% and 21% for liquid, and

Table 2 Anorectal Manometry Results Between Patients Underwent LIS or BTX/Fissurectomy

Parameters	Mean LIS ± SD	Mean BTX/fissurectomy ± SD	*P* value
IAS resting length	4.96±1.34	5.08±1.10	0.8117
IAS contraction length	5.25±1.02	4.90±1.57	0.4398
IAS resting pressure	69.82±20.54	65.84±22.80	0.6271
IAS contraction pressure	94.60±27.65	97.53±30.36	0.7899
HPZ resting length	2.67±0.71	2.86±1.17	0.5567
HPZ contraction length	2.35±0.79	2.61±1.08	0.4454
HPZ resting pressure	90.98±30.50	85.06±22.70	0.5974
HPZ contraction pressure	131.45±28.13	140.34±37.40	0.4552
Resting P max	159.24±42.96	141.78±53.61	0.3281
Contraction P max	226.87±59.34	250.47±52.53	0.2964
Resting anal canal asymmetry	23.73±8.55	23.77±5.64	0.9897
Contraction anal canal asymmetry	21.86±8.71	20.64±5.77	0.7017
IAS resting asymmetry	17.57±6.56	16.14±5.09	0.5626
IAS contraction asymmetry	18.53±17.45	13.74±5.46	0.4299

LIS lateral internal sphincterotomy, *BTX* botulinum, *IAS* internal anal sphincter, *HPZ* high pressure zone

0% and 5% for solid stool.[25–28] As indicated by Nelson in a recent systematic review, the overall risk of incontinence is about 10%,[1,11,29] mostly to flatus. In 2005, Casillas et al. conducted a review of patients who had undergone LIS, comparing a postal survey response of these patients to hospital notes.[30] Chart review revealed incontinence to stool and gas of 2.8% and 4.4%, respectively, whereas the postal survey of the same group of patients revealed incidences of 28.7% and 31.5%.[30] Consequently, surgeons may significantly underestimate the scale of postoperative continence impairment after LIS.[31] Nonetheless, the normal weakening of the sphincters with age or other insults (anorectal surgeries, radiation, or obstetrical trauma) may influence the continence during the life. Besides endoanal ultrasound reports demonstrate extensive permanent sphincter defects after LIS even if patient remains continent.[27] Incontinent patients after LIS seem to have a thinner external sphincter than those who remain continent postoperatively.[32]

In order to minimize this risk, several authors have tried a more limited division of internal sphincter, a tailored or controlled sphincterotomy.[33,34]

Nonetheless, in addition to continence disturbance, general surgical complication rates range from 7% to 42% mostly related to hemorrhage, abscess, fistula, fecal impaction, and urinary retention.[35]

In the late 1990s, alternatives to surgery were sought because of risk of incontinence, complications, costs, and recovery time. These included nitroglycerin ointment, calcium channel blockers, and botulinum toxin injection.

GTN causes sphincter relaxation by acting as a nitric oxide donor and improves anodermal perfusion.[36] Topical calcium channel blockers (diltiazem and nifedipine) induce IAS by decreasing cytosolic calcium concentration.

Despite early trials (including both acute and chronic fissure) of conservative treatments that showed overall healing rates and pain relief close to surgery, usually results are only marginally better than placebo or conservative therapies alone (fibers, Sitz baths, topical lidocaine) with healing rates between 36% to 68% and relapse rates as high as 35%.[37,38] According to Nelson's meta-analysis, a marginal advantage in using GTN (55%) over placebo (35%) exists but no statistical differences were found comparing GTN to either botulinum toxin or calcium channel blockers. We used GTN ointment in addition to conservative approaches (fibers and Sitz bath) as first line treatment because of its safety, convenience, and cost. The dosage and number of applications previously reported ranges from 0.2% to 0.5% and from twice to four per day.[39–42] The principal side effect is headache and less commonly anal pruritus.[37,43–45] Compliance issues are observed in up to 72% of patients and about 20% of patients will discontinue therapy.[29,42,46] Our healing rate after GTN alone treatment was close to 42% increasing to only 51.3% after crossover to DIL and to 57.7% if DIL/GTN combined course is considered. We also observed a 23.3% recurrence rate, similar to combined GTN/DIL, but higher compared to DIL use only (9.3%, $p=0.01$), DIL after GTN (14.3%, $p=0.5$), and GTN after DIL (13%, $p=0.4$). These findings did not differ from our previous observations apart a significant lower success of DIL/GTN combined therapy.

In our series, the incidence of side effects associated with GTN application was lower (9.7%) than the commonly reported incidence of 20–30% (but up to 72%).[47] Almost 4% of the patients discontinued the therapy and were switched to DIL. GTN therapy was discontinued because of headache (four patients) and *pruritus ani* (three patients). As previously observed, we believe that our low incidence of side effects and good compliance to treatment program are the result of number of applications (twice a day) and the accuracy of given instructions.

The rationale for the use of DIL is the finding that they induce muscle relaxation with consequent reduction in sphincter hypertonia. Moreover blood flow is improved in the IAS thus favoring fissure healing. When the DIL is heated, the relaxing effect is enhanced.[45] Short-term healing rates are reported as high as 95% when used in combination with GTN,[46–49] with about 10% reduction after 2 years follow-up. Recently, Schiano et al. reported healing rates of 75% with DIL only and 93.7% with combined GTN/DIL treatment.[45] In our experience, the DIL-only treatment was associated with a 55.7% healing rate, significantly superior to GTN use only (41.8%). The significantly lower recurrence rate after DIL alone (9.3% vs 23.3%) may explain this result. It seems that DIL use allows a durable healing and the reduced recurrence rates observed when DIL is implemented may suggest this observation. This observation is confirmed by the observed success rates at the end of the study: 57.7% for initially treated with GTN vs 75.4% for initially treated with DIL. It may be argued that patients initially treated with dilatation experienced less pain as expression of less severe disease at the time of diagnosis thus more likely to agree for such treatment and with more chances to heal. As a matter of fact, patients who decided for DIL instead of GTN treatment presented a lower visual analogue scale score at presentation despite differences were not statistically significant.

When DIL group was switched to GTN because of nonhealing, the success rate increased to 52.6% higher, but not significantly, than the success rate of 39.1% observed when GTN course was followed by DIL. We explain this difference with a shorter healing time observed with GTN compared to DIL course that needs few weeks applications of different size dilators. A 4-week DIL course may not be sufficient to significantly increase the healing rate after

GTN thus reducing the likelihood of surgery. On the other hand, differently from our previous observation, patients treated with combined DIL/GTN showed a low definitive healing rate of 32.6% with a 20% recurrence rate. This result is far from the 93.5% healing rate, reported by Schiano et al. Our longer follow-up may temper this difference. In our experience DIL use is safe, healing rate are slightly better to GTN treatment, but compliance is lower. Overall 10.1% of the patients (vs 2.9% of GTN) interrupted the DIL course because of severe discomfort preferring "less invasive" approaches. Of those, 17 patients (81%) were patients from DIL/GTN combined group. The reluctance in using DIL after GTN failure (either as crossover or in combination) as well as the reduced compliance may explain the low healing rate observed in this group.

In the recent years, injection of botulinum toxin A into the internal sphincter has emerged as an alternative to surgery in the treatment of CAF. By a temporary chemical sphincterotomy, it allows fissure healing in approximately 50% of resistant CAF when used alone and as much as 93% in the short and medium term when combined to fissurectomy.[34,50] It reduces maximum resting pressure by a similar proportion to that of GTN (25–30%),[46] but muscle paralysis occurs within hours after injection and the effect remains over a 2–3 months period of time.[25,51] Botulinum injection is a simple procedure, easy to learn, and can be also done in the outpatient clinic without the need for sedation or local anesthesia. A single botulinum injection is well tolerated, with minor side effects thus eliminating noncompliance issues.

The most common side effect is transient incontinence to flatus (up to 10%) or feces (up to 5%),[48] which may persist until the toxin's effect have worn off by neuronal degeneration.[52] To date there is only one case of long-term fecal incontinence after botulinum injection.[53]

Recurrence are common, but may be easily retreated with a good rate of healing even if up to 20% of patients will need LIS.[29,49,54]

There is no consensus on dose, site, or number of injections.[55] However, a dosage between 20 and 25 units and anterior injection seems more effective and causes no additional side effects.[16,17,44,48,56,57] Despite healing rates as high as 90% for acute and chronic fissures shown by early trials, the enthusiasm was tempered by the disappointing results on CAF. Lindsey et al., in a prospective study of 40 patients with GTN-resistant fissures treated with 20 units of botulinum, reported a healing rate of only 43%.[12] Similarly, Minguez et al.[58] did not show healing rates as high as surgery after botulinum injection with a 42 months follow-up, while Arroyo and Mentes observed 1-year recurrence rates after botulinum injection approaching, respectively, 50% and 40%.[59,60] Higher healing rates are observed if botulinum is given early before the chronic fibrosis of the fissure is established.[46] Since botulinum injection treats only the internal sphincter spasm, Lindsey et al. have proposed to add fissurectomy to chemical sphincterotomy reporting a healing rate of 93% for medically resistant CAF.[25]

Fissurectomy enhances healing removing the fibrotic fissure edges, unhealthy granulation tissue at the base, and the sentinel pile when present.[25,61] Fissurectomy alone creates in essence an acute fissure with fresh wound edges, but does not address the underlying IAS spasm at the base of CAF pathogenesis. Few authors suggested that higher rates of fissure healing could be achieved if fissurectomy is combined with conservative pharmacological sphincterotomy.[31]

We adopted this novel sphincter-sparing procedure as second line treatment after failure of GTN and/or DIL course. We observed a long-term healing rate of 83.3%, significantly higher than all other medical approaches. Along with Lindsey et al., we believe that fissure healing is significantly higher with fissurectomy–botulinum toxin injection compared to medical treatment alone because with this treatment we are able to address both elements of chronic fissure, chronic fibrosis, and internal sphincter spasm. We observed a single case of transitory low grade incontinence (Wexner incontinence score=2). The main drawback of this approach is the need of an operating theater and the costs. Although five patients of this group experienced fissure recurrence or nonhealing with all requiring subsequent LIS at certain point, fissurectomy and botulinum injection reduces significantly the need of LIS. The paucity of minor side effects associated to the good healing rates indicate that botulinum injection/fissurectomy may be used as first line approach for selected CAF even without previous medical treatment. Our study confirms that medical treatment alone for chronic, well-established fissures might be inappropriate, merely delaying definitive fissure healing.[14] We believe that BTX/fissurectomy should be offered as first line treatment for patients with typical CAF even without previous medical/conservative treatments. Patients at high risk for anal incontinence, young female patients, and patients with previous anal surgery can also be treated with BTX/fissurectomy. Botulinum toxin injection associated to a gentle fissurectomy seems to be very safe, reducing greatly the likelihood of surgery and abolishing the risk of incontinence. The main drawback of BTX/fissurectomy is the need of surgery and the costs. However, we believe that with the prompt and excellent healing rates (close to LIS), the absence of severe side effects or complications might justify the costs.

Failure of BTX/fissurectomy or recurrence indicates the need of LIS.

Our study confirms that LIS represents the most effective approach to CAF with minor morbidity and minimal recurrence rate. Although transitory postoperative inconti-

nence can been observed in up to one third of patients, in our experience we did not incur in any. Nonetheless, we did not observe any permanent incontinence.

Our general complication rate after LIS was approximately 10% within the range reported from the literature.[35]

Although the proximal extent of the LIS continues to be a topic of debate, in our experience, by "tailoring" the amount of sphincter to be divided to the length of the fissure, the risk of incontinence is minimized as well as the fissure healing achieved.

The proximal extent of LIS up to the apex of fissure, although associated with a delayed healing and increased recurrences,[16,35,61] minimizes the risk of continence disturbance. Proximal extent of LIS is particularly important in female patients because of the shorter length of the internal sphincter and vaginal deliveries that have been found to a be a significant risk factor of incontinence after LIS.[30]

In conclusion, although LIS is far more effective than medical treatments, BTX injection/fissurectomy as first line treatment may significantly increase the healing rate compared to standard conservative treatment. Moreover, this approach as first line treatment allows a faster healing time compared to medical treatments while avoiding any risk of incontinence if compared to LIS.

References

1. Nelson R. Non surgical therapy for anal fissure. Cochrane Database Syst Rev 2006;(4):CD003431.
2. Nicholls J. Anal fissure; surgery is the most effective treatment. Colorectal Dis. 2008;10(6):529–530.
3. Marby M, Alexander-Williams J, Buchmann P, Arabi Y, Kappas A, Minervini S, Gatehouse D, Keighley MR. A randomized controlled trial to compare anal dilatation with lateral subcutaneous sphincterotomy for anal fissure. Dis Colon Rectum 1979;22:308–311.
4. Weaver RM, Ambrose NS, Alexander-Williams J, Keighley MR. Manual dilatation of the anus vs. lateral subcutaneous sphincterotomy in the treatment of chronic fissure-in-ano. Results of a prospective, randomized, clinical trial. Dis Colon Rectum 1987;30:420–423.
5. Boulos PB, Araujo JG. Adequate internal sphincterotomy for chronic anal fissure: subcutaneous or open technique? Br J Surg 1984;71:360–362.
6. Jensen SL, Lund F, Nielsen OV, Tange G. Lateral subcutaneous sphincterotomy versus anal dilatation in the treatment of fissure in ano in outpatients: a prospective randomised study. Br Med J (Clin Res Ed) 1984;289:528–530.
7. Kortbeek JB, Langevin JM, Khoo RE, Heine JA. Chronic fissure-in-ano: a randomized study comparing open and subcutaneous lateral internal sphincterotomy. Dis Colon Rectum 1992;35:835–837.
8. Wiley M, Day P, Rieger N, Stephens J, Moore J. Open vs. closed lateral internal sphincterotomy for idiopathic fissure-in-ano: a prospective, randomized, controlled trial. Dis Colon Rectum 2004;47:847–852.
9. Arroyo A, Perez F, Serrano P, Candela F, Calpena R. Open versus closed lateral sphincterotomy performed as an outpatient procedure under local anesthesia for chronic anal fissure: prospective randomized study of clinical and manometric longterm results. J Am Coll Surg 2004;199(3):361–367.
10. Aysan E, Aren A, Ayar E. A prospective, randomized, controlled trial of primary wound closure after lateral internal sphincterotomy. Am J Surg 2004;187:291–294.
11. Nelson R. Operative procedures for fissure in ano. Cochrane Database Syst Rev. 2005;(2):CD002199.
12. Lindsey I, Jones OM, Cunningham C, George BD, Mortensen NJ. Botulinum toxin as second-line therapy for chronic anal fissure failing 0.2 percent glyceryl trinitrate. Dis Colon Rectum 2003;46:361–366.
13. Scholz T, Hetzer FH, Dindo D, Demartines N, Clavien PA, Hahnloser D. Long-term follow-up after combined fissurectomy and Botox injection for chronic anal fissures. Int J Colorectal Dis. 2007 Jan 30; [Epub ahead of print].
14. Lindsey I, Cunningham C, Jones OM, Francis C, Mortensen NJ. Fissurectomy- botulinum toxin: a novel sphincter-sparing procedure for medically resistant chronic anal fissure. Dis Colon Rectum 2004;47:1947–1952.
15. Sileri P, Mele A, Stolfi VM, Grande M, Sega G, Gentileschi P, Di Carlo S, Gaspari AL. Medical and surgical treatment of chronic anal fissure: a prospective study. J Gastrointest Surg 2007;11(11):1541–1548.
16. Steele SR, Madoff RD. Systematic review: the treatment of anal fissure. Aliment Pharmacol Ther 2006;24(2):247–257.
17. Ayantunde AA, Debrah SA. Current concepts in anal fissures. World J Surg 2006;30(12):2246–2260.
18. Lund JN, Binch C, McGrath J, Sparrow RA, Scholefield JH. Topographical distribution of blood supply to the anal canal. Br J Surg 1999;86:496–498.
19. Klosterhalfen B, Vogel P, Roxen H, Mittermayer C. Topography of the inferior rectal artery: a possible cause of chronic primary anal fissure. Dis Colon Rectum 1999;32:43–52.
20. Lindsey I, Cunningham C, Jones OM, Francis C, Mortensen NJ. Fissurectomy-botulinum toxin: a novel sphincter-sparing procedure for medically resistant chronic anal fissure. Dis Colon Rectum 2004;47:1643–1649.
21. Hancock BD. The internal sphincter and anal fissure. Br J Surg 1977;64:216–220. Surg Gynecol Obstet. 1959;109:583.
22. Schouten WR, Briel JW, Auwerda JJ. Relationship between anal pressure and anodermal blood flow. The vascular pathogenesis of anal fissures. Dis Colon Rectum 1994;37(7):664–669.
23. Eisenhammer S. The evaluation of the internal anal sphincterotomy operation with special reference to anal fissure. Gynecol Obstet 1959;109:583.
24. Notaras MJ. Lateral subcutaneous sphincterotomy for anal fissure-a new technique. J R Soc Med 1969;62:713.
25. Lindsey I, Cunningham C, Jones OM, Francis C, Mortensen NJ. Fissurectomy-botulinum toxin: a novel sphincter-sparing procedure for medically resistant chronic anal fissure. Dis Colon Rectum 2004;47(11):1947–1952.
26. Nyam DC, Pemberton JH. Long-term results of lateral internal sphincterotomy for chronic anal fissure with particular reference to incidence of fecal incontinence. Dis Colon Rectum 1999;42:1306–1310.
27. Sultan AH, Kamm MA, Nicholls RJ, Bartram CI. Prospective study of the extent of internal anal sphincter division during lateral internal sphincterotomy. Dis Colon Rectum 1994;37:1291–1295.
28. Khubchandani IT, Reed JF. Sequelae of internal sphincterotomy for chronic fissure-in-ano. Br J Surg 1989;76:431–434.
29. Orsay C, Rakinic J, Perry WB, Hyman N, Buie D, et al. Practice parameters for the management of anal fissures (Revised). Dis Colon Rectum 2004;47(12):2003–2007.

30. Casillas S, Hull TL, Zutshi M, Trzcinski R, Bast JF, Xu M. Incontinence after a lateral internal sphincterotomy: are we underestimating it? Dis Colon Rectum 2005;48(6):1193–1199.
31. Collins EE, Lund JN. A review of chronic anal fissure management. Tech Coloproctol 2007;11(3):209–223.
32. García-Aguilar J, Belmonte Montes C, Perez JJ, Jensen L, Madoff RD, Wong WD. Incontinence after lateral internal sphincterotomy: anatomic and functional evaluation. Dis Colon Rectum 1998;41 (4):423–437.
33. Cho DY. Controlled lateral sphincterotomy for chronic anal fissure. Dis Colon Rectum 2005;48(5):1037–1041.
34. Jones OM, Brading AF, Mortensen NJ. Mechanism of action of botulinum toxin on the internal anal sphincter. Br J Surg 2004;91:224–228.
35. Kiyak G, Korukluoğlu B, Kuşdemir A, Sişman IC, Ergül E. Results of lateral internal sphincterotomy with open technique for chronic anal fissure: evaluation of complications, symptom relief, and incontinence with long-term follow-up. Dig Dis Sci 2009 Jan 1. (Epub ahead of print).
36. Littlejohn DR, Newstead GL. Tailored lateral sphincterotomy for anal fissure. Dis Colon Rectum 1997;40:1439–1442.
37. Fruehauf H, Fried M, Wegmueller B, Bauerfeind P, Thumshirn M. Efficacy and safety of botulinum toxin A injection compared with topical nitroglycerin ointment for the treatment of chronic anal fissure: a prospective randomized study. Am J Gastroenterol 2006;101(9):2107–2112.
38. Floyd DN, Kondylis L, Kondylis PD, Reilly JC. Chronic anal fissure: 1994 and a decade later- are we doing better? Am J Surg 2006(191);344–348
39. Utzig MJ, Kroesen AJ, Buhr HJ. Concepts in pathogenesis and treatment of chronic anal fissure. A review of the literature. Am J Gastroenterol 2003;98:968–974.
40. Lorder PB, Kamm MA, Nicholls RJ, Philips RK. Reversible chemical sphincterotomy by local application of glyceryl trinitrate. Br J Surg 1994;81:1386–1389.
41. Scholefield JH, Bock JU, Marla B, et al. A dose finding study with 0.1 percent,0.2 percent, and 0.4 percent glyceryl trinitrate ointment in patients with chronic anal fissures. Gut 2003;52:264–269.
42. Zuberi BF, Rajput MR, Abro H, et al. A randomized trial of glyceryl trinitrate ointment and nitroglycerin patch in healing of anal fissures. Int J Colorectal Dis 2000;15:243–245.
43. Altomare DF, Rinaldi M, Milito G, et al. Glyceryl trinitrate for chronic anal fissure-healing or headache? Results of a multicenter, randomized, placebo-controlled, double-blind trial. Dis Colon Rectum 2000;43:174–179.
44. De Naedi P, Ortolano E, Radaelli G, Staudacher C. Comparison of glycerine trinitrate and botulinum toxin-A for the treatment of chronic anal fissure: Long-term results. Dis Colon Rectum 2006;49(4):427–432.
45. Schiano di Visconte M, Di Bella R, Munegato G. Randomized. Prospective trial comparino 0.25 percent glycerin trinitrate ointment and anal cryothermal dialtors only with 0.25 percent glycerin trinitrate ointment and only with anal cryothermal dilators in the treatment of chronic anal fissure: a two-year follow-up. Dis Colon Rectum 2006;49:1822–1830.
46. Brisinda G, Maria G, Bentivoglio AR, Cassetta E, Gui D, Albanese A. A Comparison of injections of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure. N Engl J Med 1999;341:65–69.
47. Witte ME, Klaase JM. Botulinum toxin A injection in ISDN ointment-resistant chronic anal fissures. Dig Surg 2007;24 (3):197–201.
48. Jost WH. One hundred cases of anal fissure treated with botulin toxin: early and long-term results. Dis Colon Rectum 1997;40 (9):1029–1032.
49. Brisinda G, Maria G, Sganga G, Bentivoglio AR, Albanese A, Castagneto M. Effectiveness of higher doses of botulinum toxin to induce healing in patients with chronic anal fissures. Surgery 2002;131(2):179–184.
50. Baraza W, Boereboom C, Shorthouse A, Brown S. The long-term efficacy of fissurectomy and botulinum toxin injection for chronic anal fissure in females. Dis Colon Rectum 2008;51 (2):239–243.
51. Radwan MM, Ramdan K, Abu-Azab I, Abu-Zidan FM. Botulinum toxin treatment for anal fissure. Afr Health Sci 2007;7(1):14–17.
52. Arthur JD, Makin CA, El-Sayed TY, Walsh CJ. A pilot comparative study of fissurectomy/diltiazem and fissurectomy/botulinum toxin the treatment of chronic anal fissure. Tech Coloproctol 2008;12(4):331-336; discussion 336.
53. Smith M, Frizelle F. Long-term faecal incontinence following the use of botulinum toxin. Colorectal Dis 2004;6(6):526–527.
54. Jost WH, Schrank B. Repeat botulin toxin injections in anal fissure: in patients with relapse and after insufficient effect of first treatment. Dig Dis Sci 1999;44(8):1588–1589.
55. Jones OM, Ramalingam T, Merrie A, Cunningham C, George BD, Mortensen NJ, Lindsey I. Randomized clinical trial of botulinum toxin plus glyceryl trinitrate vs. botulinum toxin alone for medically resistant chronic anal fissure: overall poor healing rates. Dis Colon Rectum 2006;49(10):1574–1580.
56. Maria G, Brisinda G, Bentivoglio AR, Cassetta E, Gui D, Albanese A. Influence of botulinum toxin site of injections on healing rate in patients with chronic anal fissure. Am J Surg 2000;179(1):46–50.
57. Fernandez LF, Conde FR, Rios RA, Garcia Iglesias J, Cainzos FM, Potel LJ. Botulinum toxin for the treatment of anal fissure. Dig Surg 1999;16:515–518.
58. Minguez M, Herreros B, Espi A, Garcia-Granero E, Sanchiz V, Mora F, Lledo S, Benages A. Long-term follow-up (42 months) of chronic anal fissure after healing with botulinum toxin. Gastroenterology 2002;123:112–117.
59. Arroyo A, Perez F, Serrano P, Candela F, Lacueva J, Calpena R. Surgical versus chemical (botulinum toxin) sphincterotomy for chronic anal fissure: long-term results of a prospective randomized clinical and manometric study. Am J Surg 2005;189:429–434.
60. Mentes BB, Irkorucu O, Akin M, Leventoglu S, Tatlicioglu E. Comparison of botulinum toxin injection and lateral internal sphincterotomy for the treatment of chronic anal fissure. Dis Colon Rectum 2003;46:232–237.
61. Scholz T, Hetzer FH, Dindo D, Demartines N, Clavien PA, Hahnloser D. Long-term follow-up after combined fissurectomy and Botox injection for chronic anal fissures. Int J Colorectal Dis 2007.

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Comparison of Pre-treatment Clinical Prognostic Factors in Patients with Gastro-Oesophageal Cancer and Proposal of a New Staging System

Andrew B. C. Crumley · Robert C. Stuart · Margaret McKernan · James J. Going · Christopher J. Shearer · Donald C. McMillan

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Abstract
Background Clinical staging in patients with gastro-oesophageal cancer, is of crucial importance in determining the likely benefit of treatment. Despite recent advances in clinical staging, overall survival remains poor. The aim of the present study was to examine the relationship between pre-treatment clinical prognostic factors and cancer-specific survival.
Methods Two hundred and seventeen patients, undergoing staging investigations including host factors (Edinburgh Clinical Risk Score (ECRS)) and the systemic inflammatory response (Glasgow Prognostic score (mGPS)), in the upper GI surgical unit at Glasgow Royal Infirmary, were studied.
Results During the follow-up period, 188 (87%) patients died; 178 of these patients died from the disease. The minimum follow-up was 46 months, and the median follow-up of the survivors was 65 months. On multivariate survival analysis of the significant factors, only cTNM stage (HR 1.84, 95% CI 1.56–2.17, $p<0.001$), mGPS (HR 1.67, 95% CI 1.35–2.07, $p<0.001$) and treatment (HR 2.12, 95% CI 1.73–2.60, $p<0.001$) were independently associated with survival. An elevated mGPS was associated with advanced cTNM stage, poor performance status, an elevated ECRS and more conservative treatment.
Conclusions Pre-treatment mGPS improves clinical staging in patients with gastro-oesophageal cancer. Therefore, it is likely to aid clinical decision making for these difficult to treat patients.

Keywords Gastro-oesophageal cancer · Pre-operative clinical stage · C-reactive protein · Survival

Introduction

Gastro-oesophageal cancer is the third commonest cause of cancer death in the UK. Each year, there are approximately 16,500 new cases and over 13,000 deaths attributable to the disease. Overall survival is poor with the majority of patients presenting with advanced, inoperable disease.[1] Even in those who undergo potentially curative resection, less than 30% survive 5 years.[2,3]

The use of neoadjuvant chemo- and radiotherapy has increased the need for more accurate clinical staging methods. In particular, following neoadjuvant therapy pathologic staging of the tumour specimen is not as informative as in untreated patients. Therefore, clinical staging is of crucial importance in determining the likely benefit of treatment, in terms of subsequent quality of life and survival. Currently, clinical staging is based on measures of the burden of disease (CT, laparoscopy and Endoscopic Ultrasound) and the fitness of the patient (weight loss and performance status). However, neither weight loss or performance status are objectively defined,[4–6] and as a consequence do not accurately stratify patient outcomes and responses to the treatment. Clearly, more

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accurate assessment of patient fitness will improve the allocation of treatment and therefore outcomes for all patients with gastro-oesophageal cancer.

Recently, the pre-treatment clinical factors; clinical stage, weight loss, performance status and an elevated C-reactive protein concentration, have been shown to independently predict survival in patients undergoing clinical staging for gastro-oesophageal cancer.[7] However, this has not to date been prospectively validated.

Also, the selective combination of C-reactive protein and albumin (termed the Glasgow Prognostic score (GPS)) has been shown to be a prognostic factor, independent of tumour stage, in a variety of gastrointestinal cancers[8] including gastro-oesophageal cancer.[9–12]

The aim of the present study was to examine the relationship between pre-treatment clinical prognostic factors and cancer-specific survival in an unselected cohort of patients with gastro-oesophageal cancer.

Materials and Methods

Patients

Two hundred and seventeen patients, undergoing staging investigations for gastro-oesophageal cancer (between January 2002 and December 2004) in the upper GI surgical unit at Glasgow Royal Infirmary, were studied.

For gastric cancers, TNM stages I to III tumours were considered to be amenable to curative surgical resection. For oesophageal cancers, TNM stages I to III tumours, excluding T4, were considered to be amenable to curative surgical resection.

The study was approved by the Research Ethics Committee of Glasgow Royal Infirmary.

Methods

The extent of tumour spread was recorded using the TNM stage. Tumours of the gastro-oesophageal junction were further classified according to site, using the Siewert system; type 1 and 2 lesions of the gastro-oesophageal junction were designated as cancers of the oesophagus. Type 3 tumours of the cardia were designated gastric cancers.[13]

Routine pre-operative laboratory measurements of albumin and C-reactive protein were carried out prior to staging laparoscopy. The coefficient of variation for these methods, over the range of measurement, was less than 10% as established by routine quality control procedures. The limit of detection of the assay was a C-reactive protein concentration of less than 5 mg/l with the upper limit of normal values being ≤10 mg/l.

The Edinburgh Clinical Risk Score (ECRS) was constructed as previously described.[7] An elevated C-reactive protein concentration (>5 mg/l) scores 20, rate of weight loss of >2.75% per month scores 20, Karnofsky PS of <60 scores 68, 60–70 scores 32 and 80–100 scores 0, and clinical stage IV scores 94, III scores 46, II scores 30 and I scores 0 (Table 1).

The mGPS was calculated as previously described.[8] Briefly, patients with an elevated C-reactive protein concentration (>10 mg/L) and a decreased albumin concentration (<35 g/L) score 2. Those patients with an elevated C-reactive protein concentration (>10 mg/L) score 1 and patients with a C-reactive protein concentration of <10 mg/L and any albumin concentration score 0 (Table 1).

Statistics

Deaths up to the end of July 2008 have been included in the analysis. Univariate survival analysis and calcu-

Table 1 Prognostic Scoring Systems in Patients with Gastro-oesophageal Cancer

Edinburgh Clinical Risk Score (ECRS)	Score	Modified Glasgow Prognostic Score (mGPS)	Score
CRP <5 mg/l	0	CRP <10 mg/l	0
CRP >5 mg/l	20		
Rate of weight loss			
<2.75 (% per month)	0	CRP >10 mg/L	1
>2.75 (% per month)	20		
Karnofsky Score			
80–100	0	CRP >10 mg/L	
60–70	32	Albumin <35 g/l	2
<60	68		
Clinical stage (cTNM)			
I	0		
II	30		
III	46		
IV	94		

lation of hazard ratios (HR) were performed using Cox proportional hazard model on age, sex, tumour site, histological tumour type, clinical TNM stage (cTNM), weight loss, Karnofsky performance status, C-reactive protein concentration, Edinburgh Clinical Risk Score mGPS and treatment. Multivariate survival analysis, including all covariates that were significant on univariate analysis, was performed using a stepwise backward procedure to derive a final model of the variables that had a significant independent relationship with survival. To remove a variable from the model, the corresponding *P* value had to be greater than 0.10. Analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA).

Table 2 Pre-treatment Clinical Characteristics and Cancer-specific Survival Rates of Patients with Gastro-oesophageal Cancer: Univariate Survival Analysis

	Patients *n*=217 (%)	2-year survival rate % (SE)	3-year survival rate % (SE)	*P* value (log-rank)
Age				
≤65 years	87 (40)	40 (5)	29 (5)	0.017
65–74 years	53 (24)	57 (7)	32 (6)	
≥75 years	77 (36)	33 (5)	12 (4)	
Sex				
Male	49 (69)	43 (4)	24 (4)	0.546
Female	68 (31)	35 (6)	21 (5)	
Site				
Oesophageal	121 (56)	45 (5)	26 (4)	0.057
Gastric	96 (44)	35 (5)	20 (4)	
Type				
Adenocarcinoma	160 (74)	41 (4)	23 (3)	0.796
Squamous	57 (26)	39 (7)	24 (6)	
Edinburgh clinical risk score				
Clinical TNM stage				
I	29 (13)	75 (8)	54 (9)	<0.001
II	31 (14)	70 (8)	57 (9)	
III	60 (28)	46 (6)	24 (6)	
IV	97 (45)	17 (4)	3 (2)	
Weight loss				
No	83 (38)	52 (6)	34 (5)	0.003
Yes	134 (62)	33 (4)	16 (3)	
Karnofsky PS				
80–100	203 (93)	39 (3)	24 (3)	0.978
60–70	12 (6)	58 (14)	22 (12)	
<60	2 (1)	50 (35)	0 (0)	
C-reactive protein				
≤5 mg/l	86 (40)	64 (5)	44 (5)	<0.001
>5 mg/l	131 (60)	25 (4)	10 (3)	
Edinburgh clinical risk score (tertiles)	58 (27)	79 (5)	59 (7)	<0.001
	102 (47)	32 (5)	14 (3)	
	57 (26)	16 (5)	3 (3)	
mGPS (0/1/2)	107 (49)	63 (5)	42 (5)	<0.001
	78 (36)	21 (5)	5 (3)	
	32 (15)	11 (6)	7 (5)	
Treatment				
Surgery	38 (18)	87 (6)	73 (7)	<0.001
Chemoradiotherapy with curative intent	14 (6)	64 (13)	50 (13)	
Palliative chemotherapy/radiotherapy	91 (42)	33 (5)	11 (3)	
Stent/dilatation/laser/by-pass/symptomatic	74 (34)	21 (5)	7 (3)	

Results

The characteristics of patients, undergoing staging for gastro-oesophageal cancer are shown in Table 2. The majority of patients were male, greater than 65 years, had adenocarcinomas and had clinical TNM stage (cTNM) III disease. Thirty-eight patients underwent surgery with curative intent, 14 patients received radical chemo-radiotherapy, 91 patients received chemo/radiotherapy, 35 patients were treated with laser, five underwent palliative by-pass surgery and 34 patients underwent stenting or received palliative care only. One hundred and ten patients had an elevated C-reactive protein concentration (>10 mg/l). Of the 38 patients with hypo-albuminaemia, 32 (84%) had an elevated C-reactive protein concentration (>10 mg/l).

During the follow-up period 188 (87%) patients died; 178 of these patients died from the disease. The minimum follow-up was 46 months, and the median follow-up of the survivors was 65 months. On univariate analysis, age ($P<0.05$), tumour site ($P<0.01$), cTNM stage ($P<0.001$), weight loss ($P<0.01$), C-reactive protein concentration >5 mg/l ($P<0.001$), ECRS ($P<0.001$), mGPS ($P<0.001$) and treatment ($P<0.001$), were significantly associated with cancer-specific survival (Table 2).

On multivariate survival analysis of the significant factors, excluding treatment; age (HR 1.41, 95% CI 1.17–1.69, $p<0.001$), tumour position (HR 1.49, 95% CI 1.10–2.01, $P=0.010$), cTNM stage (HR 1.90, 95% CI 1.59–2.28, $P<0.001$) and mGPS (HR 2.07, 95%CI 1.67–2.58, $P<0.001$), were independently associated with cancer-specific survival (Table 3).

When treatment was included in the multivariate analysis, only cTNM stage (HR 1.84, 95% CI 1.56–2.17, $P<0.001$), treatment (HR 2.12, 95% CI 1.73–2.60, $P<0.001$) and mGPS (HR 1.67, 95% CI 1.35–2.07, $P<0.001$) were independently associated with cancer-specific survival (Table 3).

When those patients who underwent surgery were tested independently ($n=38$) to establish prognostic variables, on univariate analysis only C-reactive protein <5 mg/l ($P<0.01$) and mGPS ($P<0.01$) were associated with cancer-specific survival. On multivariate analysis, only the mGPS was significantly associated with cancer-specific survival HR 4.34, 95%CI 1.44–13.13, $P=0.009$).

Patients with clinical stage III disease are the most challenging group in which to allocate the treatment, from which they are most likely to benefit. Figure 1 demonstrates how the mGPS can be used to provide additional prognostic information to aid decision making, along with clinical stage (HR 1.89, 95% CI 1.17–3.06, $P=0.01$). Figures 2, 3 and 4 demonstrate the relationship between cTNM stage and survival, in patients with an mGPS of 0, 1 and 2, respectively.

The relationship between the patient clinical characteristics and the mGPS is shown in Table 4. An elevated mGPS was associated with advanced cTNM stage ($P<0.001$), poor performance status ($P<0.05$), an elevated ECRS ($P<0.001$) and more conservative treatment ($P<0.001$).

Table 3 Pre-Treatment Clinical Characteristics and Cancer-specific Survival of Patients with Gastro-oesophageal Cancer: Multivariate Survival Analysis

	Patients $n=217$	Survival HR (95% CI)	P value
Age (≤65/65–74/≥75 years)	87/53/77	1.41 (1.17–1.69)	<0.001
Site (oesophageal/gastric)	121/96	1.49 (1.10–2.01)	0.010
Clinical TNM Stage (I/II/III/IV)	29/31/60/97	1.90 (1.59-2.28)	<0.001
Weight loss (no/yes)	83/134	1.32 (0.95–1.82)	0.098
C-reactive protein (≤5/>5 mg/l)	86/131	1.07 (0.68–1.67)	0.777
mGPS (0/1/2)	107/78/32	2.07 (1.67–2.58)	<0.001
Age (≤65/65–74/≥75 years)	87/53/77	1.08 (0.89–1.32)	0.430
Site (oesophageal/gastric)	121/96	1.15 (0.84-1.58)	0.387
Clinical TNM stage (I/II/III/IV)	29/3/6/97	1.84 (1.56–2.17)	<0.001
Weight loss (no/yes)	83/134	1.21 (0.87–1.68)	0.263
mGPS (0/1/2)	107/78/32	1.67 (1.35–2.07)	<0.001
Treatment			
(Surgery/chemoradiotherapy with curative intent/palliative chemotherapy radiotherapy/ Stent,dilatation, laser, by-pass, symptomatic)	38/14/91/74	2.12 (1.73–2.60)	<0.001

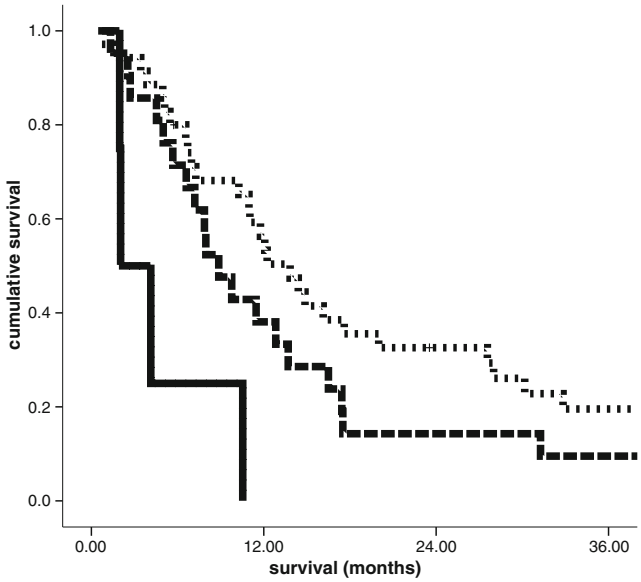

Figure 1 The relationship between the mGPS (0/1/2 from *top* to *bottom*) and survival in patients with cTNM stage III gastro-oesophageal cancer (Kaplan–Meier log-rank $p<0.01$).

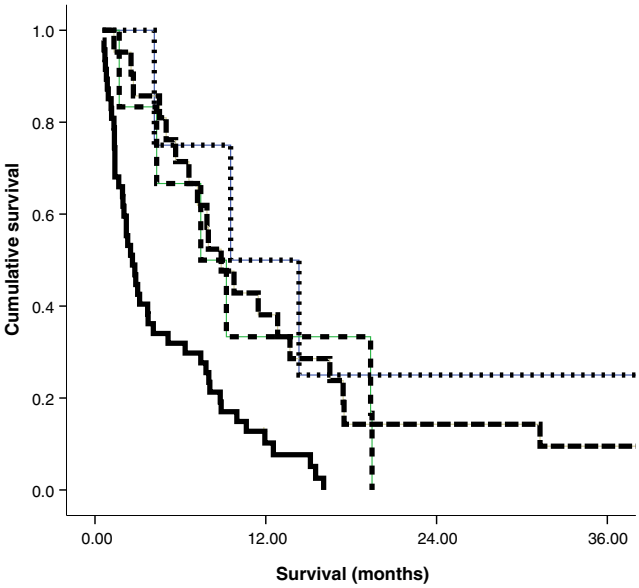

Figure 3 The relationship between the cTNM stage (I/II/III/IV from top to bottom) and survival in patients with gastro-oesophageal cancer and a mGPS score 1 (Kaplan–Meier log-rank $p<0.001$).

Discussion

In the present study of a comparison of pre-treatment clinical prognostic factors in patients with gastro-oesophageal cancer, only clinical TNM stage, treatment and the mGPS were shown to have independent prognostic significance. These results suggest that the systemic inflammatory response, as evidenced by the mGPS, is the most important patient related factor in determining outcome in patients with gastro-oesophageal cancer. Therefore, a measure of the systemic inflammatory response, in particular the mGPS, should be included in the pre-treatment assessment of these patients, and subsequent discussion at a multi-disciplinary team meeting.

In the present study 18% of patients underwent resection. This may appear low compared with the resection rate in other countries, however, in the UK the majority of patients with gastro-oesophageal cancer present with advanced, inoperable disease. Moreover in recent years there has been a decrease in the resection rate for gastric

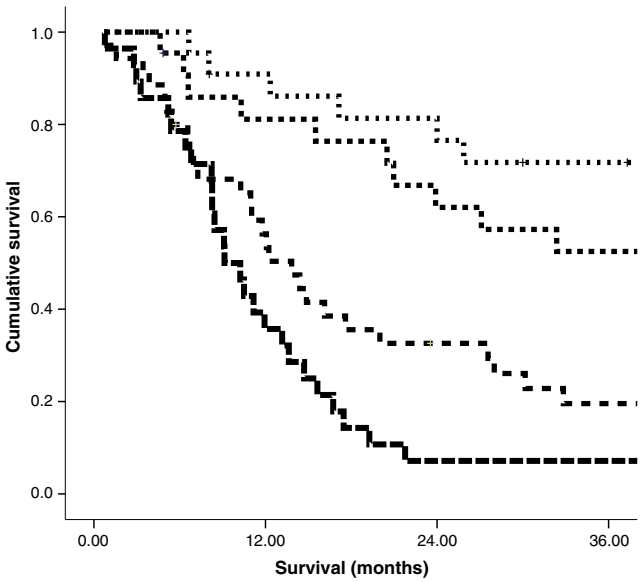

Figure 2 The relationship between the cTNM stage (I/II/III/IV from top to bottom) and survival in patients with gastro-oesophageal cancer and a mGPS score 0 (Kaplan–Meier log-rank $p<0.001$).

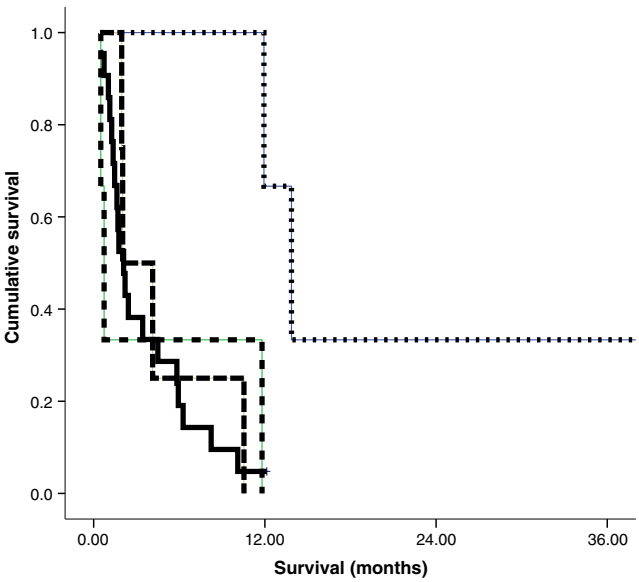

Figure 4 The relationship between the cTNM stage (I/II/III/IV from *top* to *bottom*) and survival in patients with gastro-oesophageal cancer and a mGPS score 2 (Kaplan–Meier log-rank $p=0.06$).

Table 4 Relationship Between Clinical Characteristics and the mGPS

	mGPS 0 (n=107)	mGPS 1 (n=78)	mGPS 2 (n=32)	P value
Age (≤65/65–74/≥75 years)	43/28/36	36/15/27	8/10/14	0.302
Sex (male/female)	74/33	52/26	23/9	0.920
Site (oesophageal/gastric)	63/44	45/33	13/19	0.122
Type (adenocarcinoma/squamous)	8/24	53/25	24/8	0.430
cTNM stage (I/II/III/IV)	22/22/35/28	4/6/21/47	3/3/4/22	<0.001
Weight loss (no/yes)	49/58	21/7	13/19	0.158
Karnofsky PS (80–100/60–70/<60)	103/3	74/4/0	26/5/1	0.018
ECRS (tertiles)	48/54/5	7/35/36	3/13/16	<0.001
Treatment				
Surgery	36	2	0	<0.001
Chemoradiotherapy with curative intent	9	5	0	
Palliative chemotherapy/radiotherapy	35	44	12	
Stent/dilatation/laser/by-pass/symptomatic	27	27	20	
2-year survival rate % (SE)				
Surgery	77 (7)	0 (0)		
Chemoradiotherapy with curative intent	56 (17)	40 (22)		
Palliative chemotherapy/radiotherapy	21 (7)	5 (3)	13 (10)	
Stent/dilatation/laser/by-pass/symptomatic	16 (7)	0 (0)	5 (5)	

and oesophageal cancer with the recognition that although the resection rate was approximately 40% only 60% of operations were considered to be curative by the surgeon.[14] With the advent of EUS and high resolution CT in more recent years, accurate clinical staging has improved and the percentage of patients selected for potentially curative surgery has therefore decreased.

In the present study the aim was to compare pre-treatment prognostic variables which may useful in informing treatment decisions and therefore cTNM staging was used in all patients. This reflects the situation faced by clinicians at multi-disciplinary team meetings. Nevertheless, it has long been recognised that the level of concordance between pre-operative clinical stage and post-operative pathological stage is sub-optimal even with enhanced imaging techniques.[15–18] In the present study, the numbers of patients who underwent surgery and had pathological stage was small 38 (18%) and therefore it remains to be determined whether the mGPS improves the prediction of pathological TNM stage in patients with gastro-oesophageal cancer.

Similarly, the assessment of patient fitness by the amount of weight loss or performance status is known to be sub-optimal. For example, there remains controversy about what weight loss (the amount of and over what period) significantly impacts on outcome.[5,6] Also, differences in the assessment of performance status have been reported between oncologists, nurses and patients, oncologists being the most optimistic in their assessment and patients the least.[4]

It is of note that the 2-year survival of the group receiving endoscopic/symptomatic treatment and who had a mGPS of 0, was greater than the 2-year survival of patients receiving palliative chemo/radiotherapy who's mGPS was greater than 0. Thus, it would appear that according to survival, some patients may have received more aggressive treatment without necessarily benefiting them and conversely, some patients may have been denied more aggressive treatment, which may have prolonged their life.

In contrast to the mGPS, the ECRS comprises four variables, two of which are subjective; performance status and weight loss. These two subjective variables account for almost half of the possible risk score and in the present study did not retain independent significance when compared with the mGPS. Although both scores have incorporated C-reactive protein, in the ECRS C-reactive protein can account for a score of 20 out of a possible 202 (10%). In contrast, C-reactive protein can account for a score of 1 out of a possible 2 (50%). In addition, in the present study the C-reactive protein threshold of >5 mg/l did not retain independent significance when compared with the mGPS.

Therefore, the mGPS offers a simple to perform, objective and well standardised pre-treatment assessment to guide treatment. For example, since an elevated pre-treatment mGPS identifies patients at high risk of dying of their disease, they should be offered low morbidity treatment tailored to symptomatic control. Indeed, recent evidence from surgical and chemoradiotherapy studies are consistent with this approach.[9,10,12,19] In the present study, it would appear that in those patients with evidence of an

elevated systemic inflammatory response, clinical stage performs less well in predicting cancer-specific survival (Figs. 2, 3 and 4).

In summary, the pre-treatment measurement of the mGPS improves clinical staging in patients with gastro-oesophageal cancer. Therefore, it is likely to aid clinical decision making for these difficult to treat patients.

References

1. Cancer Research UK Information Resource Centre. CancerStats. http://infocancerresearchuk.org/cancerstats. 2004.
2. Jamieson GG, Mathew G, Ludemann R, Wayman J, Myers JC, Devitt PG. Postoperative mortality following oesophagectomy and problems in reporting its rate. Br J Surg 2004;91: 943–947.
3. Hundahl SA, Phillips JL, Menck HR. The National Cancer Data Base Report on poor survival of U.S. gastric carcinoma patients treated with gastrectomy: Fifth Edition American Joint Committee on Cancer staging, proximal disease, and the "different disease" hypothesis. Cancer 2000;88:921–932.
4. Ando M. Prognostic value of performance status assessed by patients themselves, nurses and oncologists in advanced non-small cell lung cancer. Br J Cancer 2001;85:1634–1639.
5. Morley JE, Thomas DR, Wilson MM. Cachexia: pathophysiology and clinical relevance. Am J Clin Nutr 2006;83(4):735–743.
6. Fearon KC, Voss AC, Hustead DS, Cancer Cachexia Study Group. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. Am J Clin Nutr 2006;83(6):1345–1350.
7. Deans DA, Wigmore SJ, deBeaux AC, Paterson-Brown S, Garden OJ, Fearon KC. Clinical prognostic scoring system to aid decision making in gastro-oesophageal cancer. Br J Surg 2007;94(12):1501–1508.
8. McMillan DC. An inflammation based prognostic score and its role in the nutrition based management of patients with cancer. Proc Nutr Soc 2008;67(3):257–262.
9. Crumley AB, McMillan DC, McKernan M, Going JJ, Shearer CJ, Stuart RC. An elevated C-reactive protein concentration, prior to surgery, predicts poor cancer-specific survival in patients undergoing resection for gastro-oesophageal cancer. Br J Cancer 2006;94:1568–1571.
10. Crumley AB, McMillan DC, McKernan M, McDonald AC, Stuart RC. Evaluation of an inflammation-based prognostic score in patients with inoperable gastro-oesophageal cancer. Br J Cancer 2006;94:637–641.
11. Crumley AB, Stuart RC, McKernan M, McDonald AC, McMillan DC. Comparison of an inflammation based prognostic score (GPS) with performance status (ECOG-ps) in patients receiving palliative chemotherapy for gastro-oesophageal cancer. J Gastroenterol Hepatol 2008;23(8 Pt2):e325–e329.
12. Kobayashi T, Teruya M, Kishiki T, Endo D, Takenaka Y, Tanaka H, Miki K, Kobayashi K, Morita K. Inflammation based prognostic score, prior to neo-adjuvent chemoradiotherapy, predicts post operative outcome in patients with esophageal squamous cell carcinoma. Surgery 2008;144 (5):729–735.
13. Siewert JR, Bottcher K, Stein HJ, Roder JD. Relevant prognostic factors in gastric cancer: ten-year results of the German Gastric Cancer Study. Ann Surg 1998;228:449–461.
14. Clinical Research and Audit Group (CRAG). Scottish Audit of Gastric and Oesophageal Cancer: Report 1997-2000. Edinburgh CRAG 2002. http://www.show.scot.nhs.uk/crag/
15. Ziegler K, Sanft C, Zimmer T, Zeitz M, Felsenberg D, Stein H, Germer C, Deutschmann C, Reiken EO. Comparison of computed tomography, endosonography, and intraoperative assessment in TN staging of gastric carcinoma. Gut 1993;34:604–610.
16. JKelly S, Harris KM, Berry E, Hutton J, Roderick P, Cullingworth J, Gathercole M, Smith MA. A systematic review of the staging performance of endoscopic ultrasound in gastro-oesophageal carcinoma. Gut 2001;49:534–539.
17. Blackshaw GR, Barry JD, Edwards P, Allison MC, Thomas GV, Lewis WG. Laparoscopy significantly improves the perceived preoperative stage of gastric cancer. Gastric Cancer 2003;6:225–229.
18. Lightdale CJ, Kulkarni KG. Role of endoscopic ultrasonography in the staging and follow-up of esophageal cancer. J Clin Oncol 2005;23:4483–4489.
19. Ikeda M, Natsugoe S, Ueno S, Baba M, Aikou T. Significant host- and tumor-related factors for predicting prognosis in patients with esophageal carcinoma. Ann Surg 2003;238:197–202.

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ORIGINAL ARTICLE

Effect of Preoperative Single-Dose Corticosteroid Administration on Postoperative Morbidity Following Esophagectomy

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Abstract
Background Eight clinical trials involving the administration of preoperative i.v. methylprednisolone have been undertaken in order to decrease the considerable inflammatory response to esophageal resection, in an effort to decrease the supposedly associated morbidity and mortality
Method A meta-analysis was performed for eight clinical end-points. Due to quality problems in seven of the eight included studies, a Bayesian meta-analysis using a skeptical prior derived from the results of the classical analysis was also performed.
Results The end-points including any organ dysfunction (OR=0.30), respiratory complication (OR=0.41), sepsis (OR=0.37), liver dysfunction (OR=18), cardiovascular dysfunction (OR=0.28), and surgical anastomotic leak (OR=0.42) were significantly decreased by methylprednisolone pretreatment. Following the Bayesian analysis, despite the use of skeptical priors, there is a 95% probability to obtain a relative risk reduction of at least 23% to 54%, depending of the end-point, by methylprednisolone pretreatment.
Conclusion We are in the presence of a potential benefit that cannot be accepted at face value due to the quality problems of the included studies. But in the presence of a remaining potential benefit after a Bayesian analysis starting from a skeptical prior, the best option would be the planning of a large multicenter prospective randomized study.

Keywords Glucocorticoids · Postoperative complication · Esophagectomy · Meta-analysis, Bayesian model

Introduction

Esophageal cancer is the sixth most common cause of cancer-related death worldwide.[1] Esophageal resection is the mainstay therapy for malignancy of the esophagus;[2] this is a major surgical procedure still associated with significant morbidity and mortality.[3]

During the past 15 years, several clinical trials involving the administration of a high-dose i.v. methylprednisolone have been undertaken in order to decrease the considerable inflammatory response to surgery, in an effort to decrease the supposedly associated morbidity and mortality.

The present meta-analysis presents the incidence of the clinical complications reported in these trials. This is done as well by using classical meta-analysis, as a Bayesian meta-analytical technique which, unlike the classical method, supports direct statements about the probability of the magnitude of an effect.

Material and Methods

This article considers the efficacy of preoperative corticosteroid administration on the postoperative morbidity and cytokine response in patients undergoing surgery for esophageal cancer.

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Search Strategy

Embase, Medline, Pubmed, Biosis, CAB Abstracts, Derwent Drug File, Current Content Search, and the Cochrane database were searched for controlled trials using the search criteria '(methylprednisolone OR dexamethasone OR corticoid OR corticosteroid OR glucocorticoid OR glucocorticoids) AND (((esophageal OR oesophageal) AND surgery) OR (esophagectomy OR oesophagectomy))'. No language or date limits were used.

A list of 115 references was obtained, in which seven relevant studies were found.[4–10] After searching the references sections from these studies, one more study could be identified.[11]

All were single center studies carried out in Japan. Seven articles were published in English and one article in Japanese[11] with the results, tables, and figures in English. An English translation of this article was kindly provided by Pfizer Japan.

Studies Description

The description of the eight studies included in the analysis is given in Tables 1 and 2. Six studies were randomized controlled studies and two studies[6,10] were open label including consecutive patients with historical controls.

Judging from the Jadad scores[12] and the description of the studies in Tables 1 and 2, all but the study by Sato[7] can be considered as low quality when the clinical end-points are considered.

The clinical postoperative complications were among the primary end-points in three studies.[6,7,9] These clinical end-points were defined a priori in the "Materials and Methods" section in these three studies and anastomotic leak was also described in the study by Takeda.[4] Changes in one or several blood components were listed as primary end-points in six studies.[4–6,8,9,11]

Statistical Analysis

Clinical End-Points

A meta-analysis was performed for eight clinical end-points: death, respiratory complication, sepsis, liver dysfunction, renal dysfunction, cardiovascular dysfunction, surgical anastomotic leak, and number of patients with any postoperative organ dysfunction or complication (excluding death). The wording or criteria used for defining these end-points varied between the studies and are listed in Table 2, and presented by using the exact wording used by the authors of the studies. The durations of hospital stay were also analyzed.

Review Manager version 5.0.20 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2009) was used for data analysis. The meta-analysis was performed using the Mantel–Haenszel method. A fixed effect analysis model was used for all clinical end-points, as no analysis displayed heterogeneity. An odds ratio (OR) with a 95% confidence interval was computed and a Forest plot produced for each end-point. Statistical significance, defined as a $p<0.05$, was assessed by a z test.

A Funnel plot was also produced for each end-point in order to assess a possible publication bias.

However, due to the quality problem surrounding most of the studies, it is reasonable to express some skepticism about results that cause surprise, or about favorable results that seem unbelievably large.

Therefore, for the end-points that would be found statistically significantly different in the treated group as compared to the control group, a technique described by Mattews[13] and Spiegelhalter[14] would be used. This allows to calculate a value of OR (called critical OR), using the 95% confidence interval from our meta-analysis. To consider the results credible, we must accept that an OR smaller than the value calculated is a reasonable value that could be obtained by the treatment. We took the skeptical stand that this is not the case, that the results are 'too good to be true', and that our prior belief lies for 95% inside an interval that would produce a posterior probability that just includes the OR value of 1.

This is the formal mathematical expression of a statement that in plain English would be 'I do not believe that the treatment has an effect (the prior distribution is centered on an OR of 1), but I do not exclude the possibility that there can be a favorable or an unfavorable effect. But the favorable effect would anyway be smaller than the one produced by the classical meta-analysis'.

To be able to include this statement in a Bayesian analysis, one must compute a 95% critical prior interval, with a lower border value equals to the critical OR and an upper border equal to 1/critical OR.[14] These values are than transformed in mean value and SD, and these are used as initial prior to calculate the Bayesian meta-analysis. For a detailed presentation of the computational method of the Bayesian meta-analysis, the reader is referred to Appendix 1 at the end of the article and to appendixes 1 and 3 in Engelman et al.[15] and appendix C in Engelman and Salengros.[16] The Bayesian analysis was computed using Microsoft Excel 2002 SP3 (Microsoft Corporation, Redmond, WA)

Cytokine Blood Levels

Cytokine blood levels measurement were available in order to perform a meta-analysis of the effect of methylprednisolone on IL-6 on postoperative day (POD) 1 and POD7, and on IL-8 and IL-10 on POD1.

Table 1 Description of the Studies Included in the Analysis

Trial	Description of esophageal pathology	Exclusion criteria	Type of study	Jadad score	Surgery	Additional surgical details	Anesthetic technique	Nutritional support	MTP dose	Number of patients included in analysis	
										Control	MTP
Sayama[11]	Esophageal carcinoma	None stated	Randomized, controlled	1	Esophageal resection	NA	NA	Nothing stated	250 mg single dose preoperatively	9	8
Takeda[4]	Squamous cell carcinoma	Circulatory, respiratory, or metabolic disease	Randomized, placebo controlled	1	Esophageal resection (Right thoracotomy)	Reconstruction of the gastric tube in the chest. Thoracic, abdominal and cervical lymph node dissection.	Isoflurane in O_2/N_2O + Epidural Mepivacaine. Postoperative epidural analgesia with mepivacaine and buprenorphine	Nothing stated	30 mg/kg single dose before induction of anesthesia	15	15
Matsutani[5]	Squamous cell carcinoma	None stated	Randomized, placebo controlled	2	Total esophagectomy (Right thoracotomy + laparotomy)	Stomach tube for replacement. Thoracic, abdominal and cervical lymph node dissection.	NA	Total parenteral nutrition from POD2 to POD7	10 mg/kg single dose at the time of induction of anesthesia	19	14
Shimada[6]	Esophageal cancer	None stated	Open label consecutive patients, historical controls	0	Radical esophagectomy	NA	NA, but stated that no epidural anesthesia	Nothing stated	250 mg one hour before surgery + 125 mg on POD1 and POD2	50	57
Sato[7]	Squamous cell carcinoma	Preoperative chemotherapy, radiotherapy or immunotherapy. Older than 76 years. Liver cirrhosis, diabetes mellitus, creatinine clearance <60 mL/min. Vital capacity <80% or forced expiratory volume in 1 sec <70%. HBS-antigen or HCV-antibody positive. Multiple cancer. Old tuberculosis.	Randomized, double blind, placebo controlled	5	Radical esophagectomy (Right thoracotomy + midline laparotomy)	Stomach tube for replacement. Thoracic, abdominal and cervical lymph node dissection.	NA	Enteral nutrition via jejunostomy from POD3	10 mg/kg single dose within 30 min. of the start of surgery	33	33
Takeda[8]	Esophageal carcinoma	Circulatory, respiratory, or metabolic disease	Randomized, placebo controlled	1	Subtotal esophagectomy (Right thoracotomy)	Stomach tube for replacement. Thoracic, abdominal and cervical lymph node dissection.	Sevoflurane in O_2/N_2O + Fentanyl	Nothing stated	10 mg/kg single dose before induction of anesthesia	10	7
Yano[9]	Esophageal cancer	None stated	Randomized, double blind, placebo controlled	2	Subtotal esophagectomy	Stomach tube, right-side colon, or jejunum for replacement. Two-field or three-field lymph node dissection.	NA	Nothing stated	500 mg single dose 2 hours before surgery	20	20
Tsukada[10]	Esophageal cancer	None stated	Open label consecutive patients, historical controls	0	Radical esophagectomy (Right thoracotomy)	Cervico-thoraco-abdominal three-field lymph node dissection	NA	Nothing stated	250 mg single dose 1 hour before surgery	15	21

MTP methylprednisolone, *NA* not available, *POD* postoperative day

Table 2 Definition of the End-points (Taken Verbatim from the Articles)

TRIALS	Primary endpoint	Secondary end-points	A priori definition of events in the 'Method' section	Respiratory complication	Sepsis	Liver dysfunction	Renal dysfunction	Cardiovascular dysfunction	Surgical anastomotic leak	Number of patients presenting a complication (eventually multiple) specifically stated
Sayama[11]	Changes in plasma cytokine levels	Clinical course	No	Cases with tracheotomy or persistent hypoxemia (PO2/FiO2 < 300 at POD7)	Post operative infection (within 5 days after surgery)			Cases with arrhythmia or receiving catecholamines	Suture insufficiency in anastomotic site	No
Takeda[4]	Plasma concentration of epinephrine, norepinephrine, arginine vasopressin, cholesterol, albumin, alphatocopherol	Length of stay in ICU. In-hospital mortality and morbidity. Anastomotic leak	For anastomotic leak only	Pneumonia Respiratory failure	Sepsis Pneumonia	Hepatic failure	Renal failure		Leakage of contrast medium on chest or abdominal radiograph	Yes
Matsutani[5]	Antithrombin-III, thrombin–antithrombin III, prothrombin time, activated partial thromboplastin time. Serum concentration of TNF-α, IL-6	None	No	Pulmonary disorders						Yes
Shimada[6]	Serum Level IL-6, polymorphonuclear cell elastase, C-reactive protein. "Postoperative clinical course" composed of: pulmonary complication, hyperbilirubinemia, hepatic dysfunction, and anastomotic leakage	None	Yes	Respiratory index (RI) >3		Peak bilirubin level >4 mg/dL, or aspartate aminotransferase or alanine aminotransferase > 200 IU/L (normal <40 IU/L)		Arrhythmia	Leakage diagnosed by gastrography and clinical features	Yes
Sato[7]	Medical complications during first 7 days	Plasma concentration of IL-6, IL-8, IL-10, IL-1ra, cortisol Duration of mechanical ventilation Long-term survival rate	Yes	$PaCO_2$>50 mmHg[a] or bilateral pulmonary infiltrates on radiograph or RI>2.5	Positive culture of blood, sputum, or other fluids in presence of clinical evidence of infection	Serum bilirubin level >3 mg/dL or aspartate aminotransferase or alanine aminotransferase >200 IU/L	Urine output <6 mL/kg/12 h or NAGI>30	Arrhythmia requiring medication or PAR>15 persisting >6 hours	Anastomotic leakage	Yes
Takeda[8]	Plasma and bronchoalveolar concentrations of IL-6, IL-8	None	No	Pneumonia Lung atelectasis					Anastomotic leaks	Yes
Yano[9]	Systemic oxygenation. Water/blood balance during postoperative periods. Proinflammatory and anti-inflammatory cytokine production (IL-6, IL-8, IL-10). Incidence of postoperative infections. Survival time.	None	No	Pulmonary complication	Infection complication				Anastomotic leakage	No
Tsukada[10]	« Postoperative clinical course »	Secretory leukocyte protease inhibitor concentration in bronchoalveolar lavage fluid	Yes	$PaCO_2$>50 mmHg	Infectious complication	Aspartate aminotransferase or alanine aminotransferase > 200 IU/L		Arrhythmia requiring medication	Leakage diagnosed by gastrography and clinical features	Yes

Respiratory index(RI) $= [FiO_2 \times (760 - 47) - PaCo_2/0.8]/PaO_2$

[a] The article says $PaCO_2$<50 mmHg but it is presumed to be a typographic error

NAGI N-acetyl-β-D-glucosamidase index=urinary NAG/urinary creatinine

PAR pressure adjusted heart rate=heart rate×central venous pressure/mean blood pressure

The results are expressed as weighted mean differences and their associated 95% confidence intervals. The results were obtained by using a random effects model, and the inverse variance weighting method. A Funnel plot was also produced for each analysis in order to assess a possible publication bias.

Results

Methylprednisolone was the only glucocorticoid used in all studies. A single administration immediately before surgery was used in seven studies; in one study, a further bolus of 125 mg was administered on POD1 and POD2. The doses used ranged from 250 mg to 30 mg/kg.

In all, 346 patients were included in the studies (175 in the methylprednisolone groups and 171 in the control groups). The two largest studies, including the study with a Jadad score of 5, account for 50% of the included patients.

Clinical End-points—Classical Meta-analysis

The frequencies of clinical end-points as reported in all studies are listed in Table 3.

Only two studies reported the occurrence of death, and the meta-analysis shows a non-significant difference (Fig. 1).

For the end-point including any organ dysfunction or complication (death excluded), there is a highly statistical significantly difference in favor of the methylprednisolone treatment (Fig. 2).

Respiratory complication (Fig. 3), sepsis (Fig. 4), liver dysfunction (Fig. 5), cardiovascular dysfunction (Fig. 6), and surgical anastomotic leak (Fig. 7) were also significantly decreased by methylprednisolone pretreatment. There was no difference regarding renal dysfunction between the groups (Fig. 8).

Duration of hospital stay was shorter in methylprednisolone-treated groups (Fig. 9).

There was no indication of publication bias after examination of the Funnel plots (Fig. 10).

Clinical End-points—Bayesian Meta-analysis

Based on the results from the classical analysis, a skeptical prior value that would be used to start the Bayesian meta-analysis was computed. These are reported in Table 4.

The results of the Bayesian meta-analysis are reported in Table 5.

Despite the use of these skeptical priors, the upper border of the 95% credible intervals of the OR remained smaller than 1 for all end-points.

There is a 95% probability to obtain a relative risk reduction of at least 23% to 54%, depending of the end-

Table 3 Number of Patients Presenting the outcome (Number of Events / Number of Patients in Group)

Trials	Death		Number of patients with any postoperative organ dysfunction or complication (excluding death). Possibly multiple by patient		Respiratory complication		Sepsis		Liver dysfunction		Renal dysfunction		Cardiovascular dysfunction		Surgical anastomotic leak	
	Control	MP	Control	MP	Control	MP	Control	MP	Control	MP	Control	MP	Control	MP	Control	MP
Sayama[11]	NA	NA	NA	NA	2/9	2/8	3/9	0/8	NA	NA	NA	NA	4/9	1/8	2/9	0/8
Takeda[4]	2/15	0/15	5/15	0/15	5/15	0/15	4/15	0/15	1/15	0/15	1/15	0/15	0/15	0/15	2/15	0/15
Matsutani[5]	NA	NA	5/19	0/14	2/19	0/14	NA	NA	NA	NA	NA	NA	NA	NA	0/19	0/14
Shimada[6]	1/50	1/57	32/50	22/57	20/50	16/57	NA	NA	7/50	1/57	NA	NA	3/50	1/57	8/50	2/57
Sato[7]	0/33	0/33	20/33	11/33	10/33	3/33	2/33	3/33	5/33	2/33	8/33	7/33	13/33	5/33	2/33	1/33
Takeda[8]	0/10	0/7	NA	NA	0/10	0/7	NA	NA	NA	NA	NA	NA	NA	NA	0/10	0/7
Yano[9]	NA	NA	NA	NA	6/20	3/20	7/20	3/20	NA	NA	NA	NA	NA	NA	3/20	4/20
Tsukada[10]	0/15	0/21	4/15	3/21	4/15	3/21	3/15	2/21	1/15	0/21	NA	NA	1/15	1/21	2/15	2/21
TOTAL (%)	3/123 (2.4)	1/133 (0.75)	66/132 (50.0)	36/140 (25.7)	49/171 (28.6)	27/175 (15.4)	19/92 (20.6)	8/97 (8.2)	14/113 (12.4)	3/126 (2.4)	9/48 (18.75)	7/48 (14.6)	21/122 (17.2)	8/134 (6.0)	19/171 (11.1)	9/175 (5.1)

Patient can have multiple complications

MP patients with methylprednisolone, *NA* not available

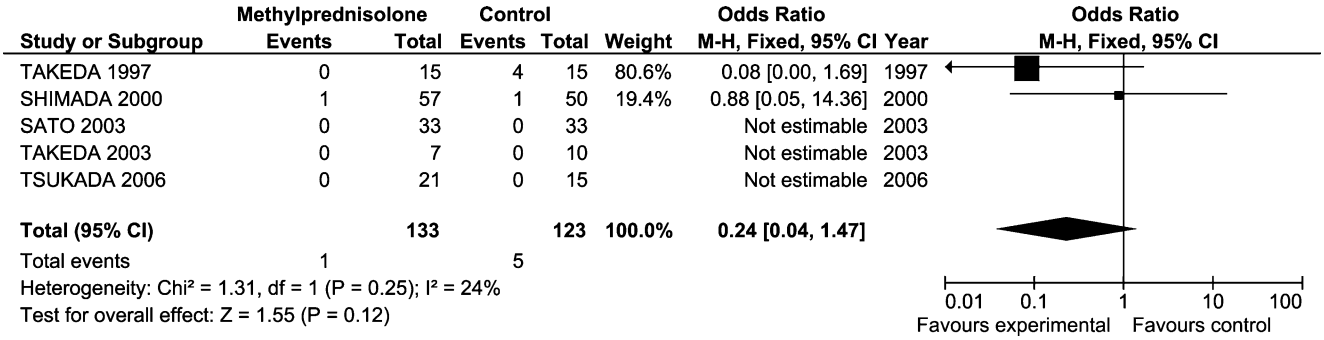

Figure 1 Outcome: death. Forrest plot summarizing the odds ratio (OR) of the comparison between the methylprednisolone-treated patients versus the control patients for the incidence of death. An odds ratio less than 1 indicates less adverse events with active compared with control. When the 95% confidence interval (CI) does not include 1, the difference is considered statistically significant.

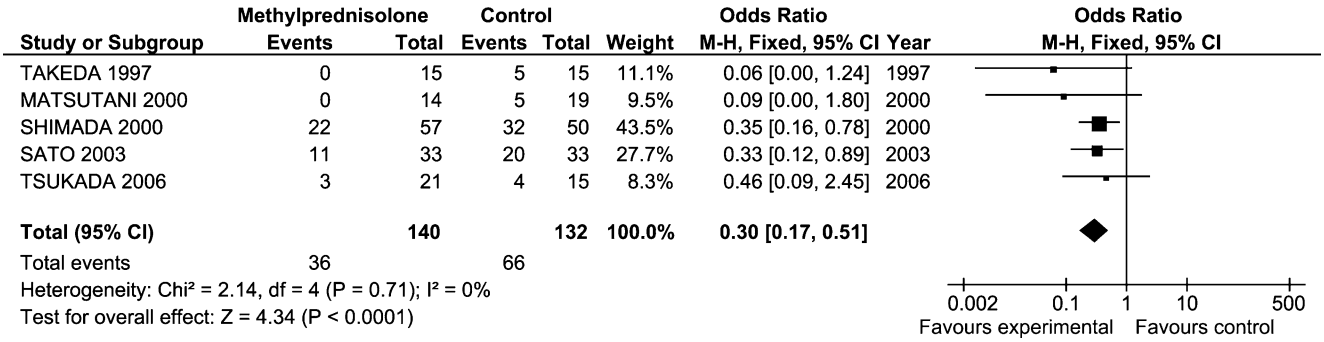

Figure 2 Outcome: any organ dysfunction or complication (death excluded). Forrest plot summarizing the odds ratio (OR) of the comparison between the methylprednisolone-treated patients versus the control patients for the incidence of any organ dysfunction or complication (death excluded). An odds ratio less than 1 indicates less adverse events with active compared with control. When the 95% confidence interval (CI) does not include 1, the difference is considered statistically significant.

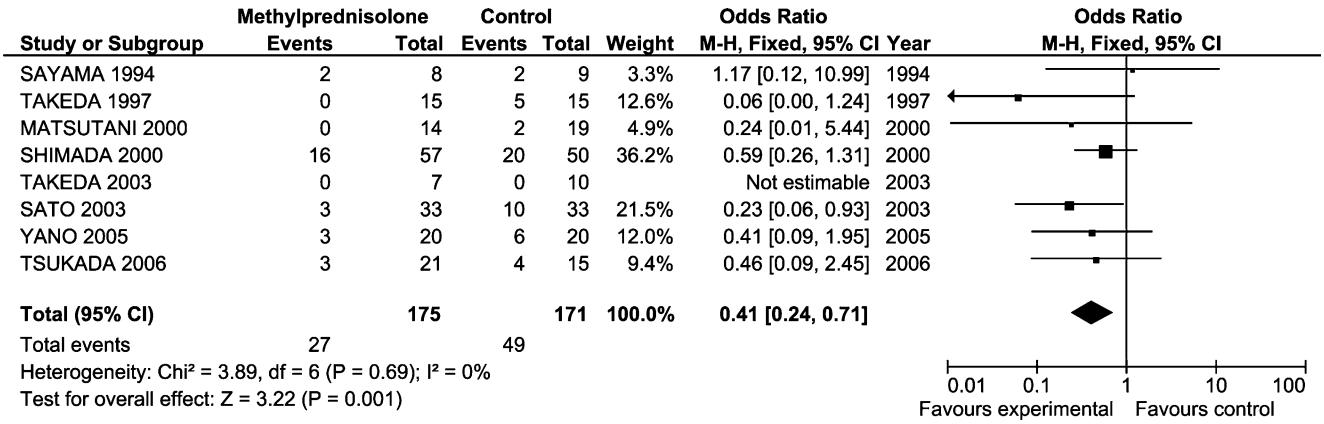

Figure 3 Outcome: respiratory complication. Forrest plot summarizing the odds ratio (OR) of the comparison between the methylprednisolone-treated patients versus the control patients for the incidence of respiratory complication. An odds ratio less than 1 indicates less adverse events with active compared with control. When the 95% confidence interval (CI) does not include 1, the difference is considered statistically significant.

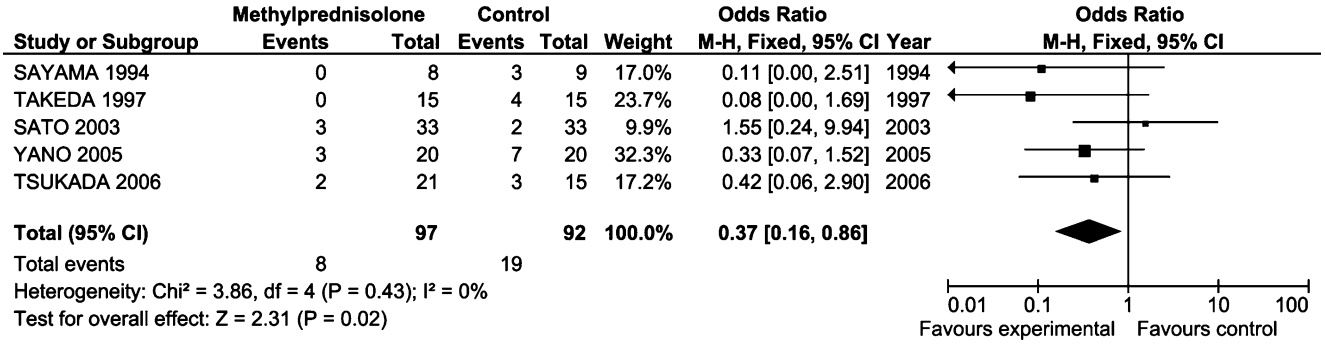

Figure 4 Outcome: sepsis. Forrest plot summarizing the odds ratio (OR) of the comparison between the methylprednisolone-treated patients versus the control patients for the incidence of sepsis. An odds ratio less than 1 indicates less adverse events with active compared with control. When the 95% confidence interval (CI) does not include 1, the difference is considered statistically significant.

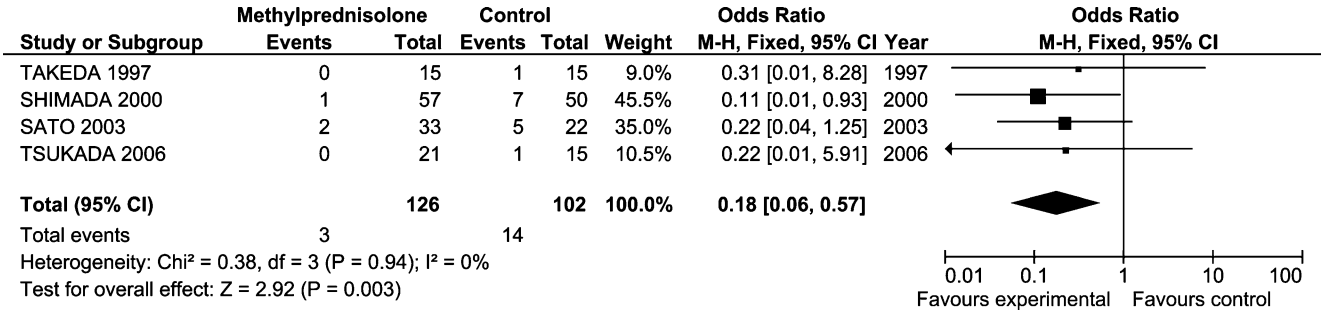

Figure 5 Outcome: liver dysfunction. Forrest plot summarizing the odds ratio (OR) of the comparison between the methylprednisolone-treated patients versus the control patients for the incidence of liver dysfunction. An odds ratio less than 1 indicates less adverse events with active compared with control. When the 95% confidence interval (CI) does not include 1, the difference is considered statistically significant.

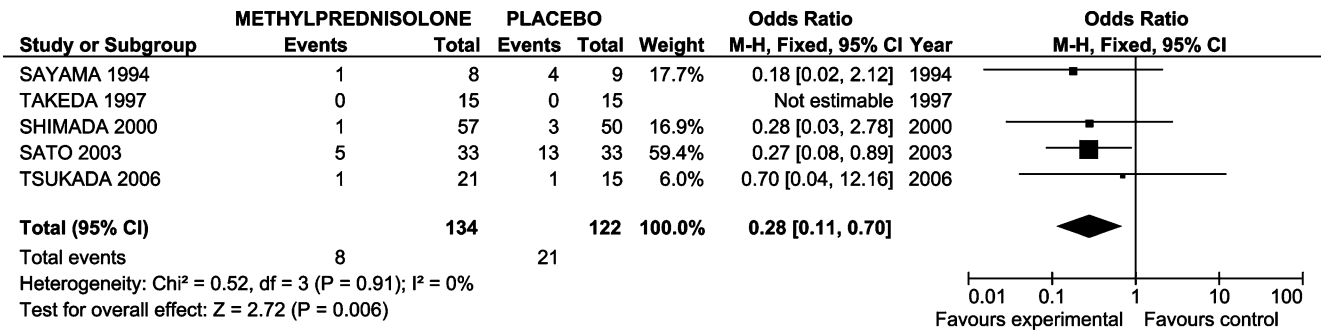

Figure 6 Outcome: cardiovascular dysfunction. Forrest plot summarizing the odds ratio (OR) of the comparison between the methylprednisolone-treated patients versus the control patients for the incidence of cardiovascular dysfunction. An odds ratio less than 1 indicates less adverse events with active compared with control. When the 95% confidence interval (CI) does not include 1, the difference is considered statistically significant.

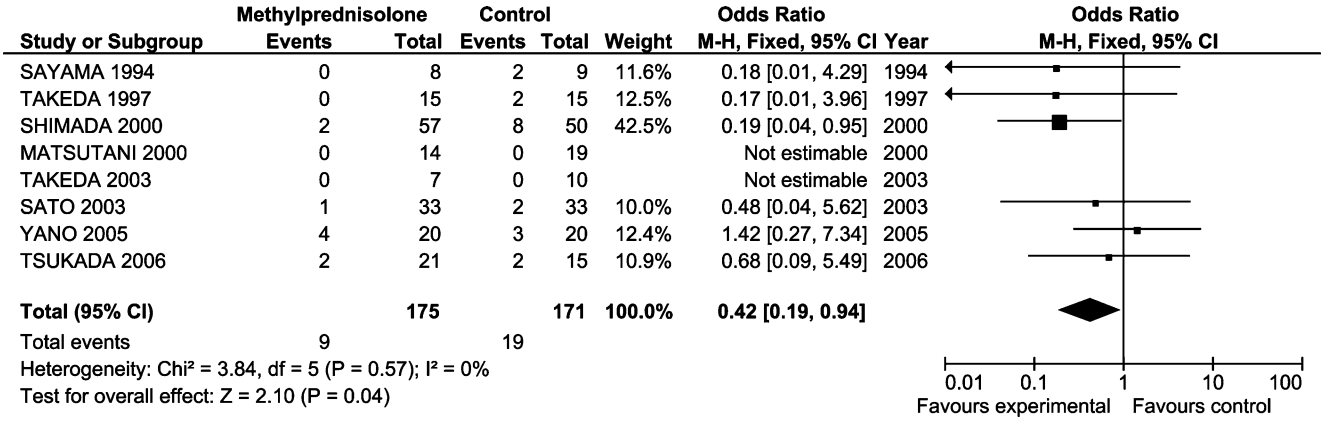

Figure 7 Outcome: surgical anastomotic leak. Forrest plot summarizing the odds ratio (OR) of the comparison between the methylprednisolone-treated patients versus the control patients for the incidence of surgical anastomotic leak. An odds ratio less than 1 indicates less adverse events with active compared with control. When the 95% confidence interval (CI) does not include 1, the difference is considered statistically significant.

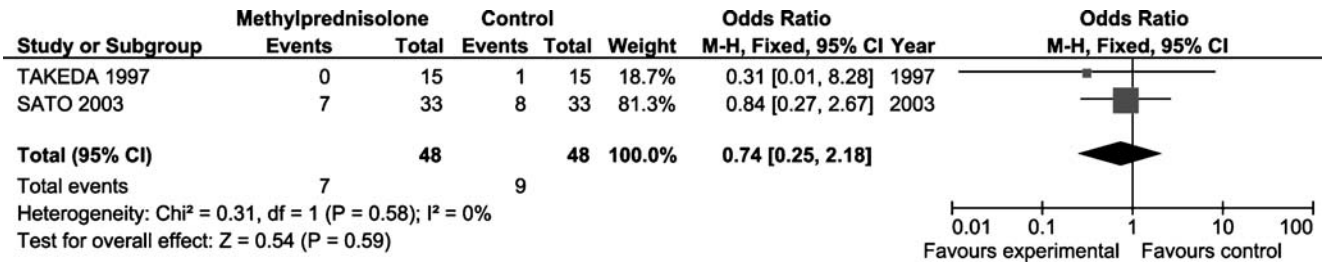

Figure 8 Outcome: renal dysfunction. Forrest plot summarizing the odds ratio (OR) of the comparison between the methylprednisolone-treated patients versus the control patients for the incidence of renal dysfunction. An odds ratio less than 1 indicates less adverse events with active compared with control. When the 95% confidence interval (CI) does not include 1, the difference is considered statistically significant.

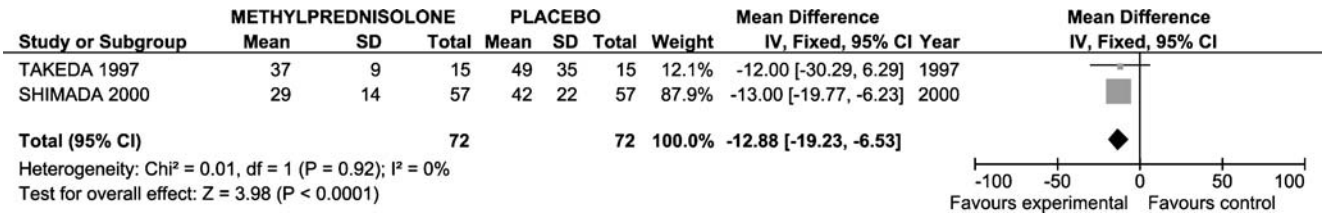

Figure 9 Duration of hospital stay. A weighted mean difference less than 0 indicates a shorter hospital stay with active compared with control. When the 95% confidence interval (CI) does not include 0, the difference is considered statistically significant.

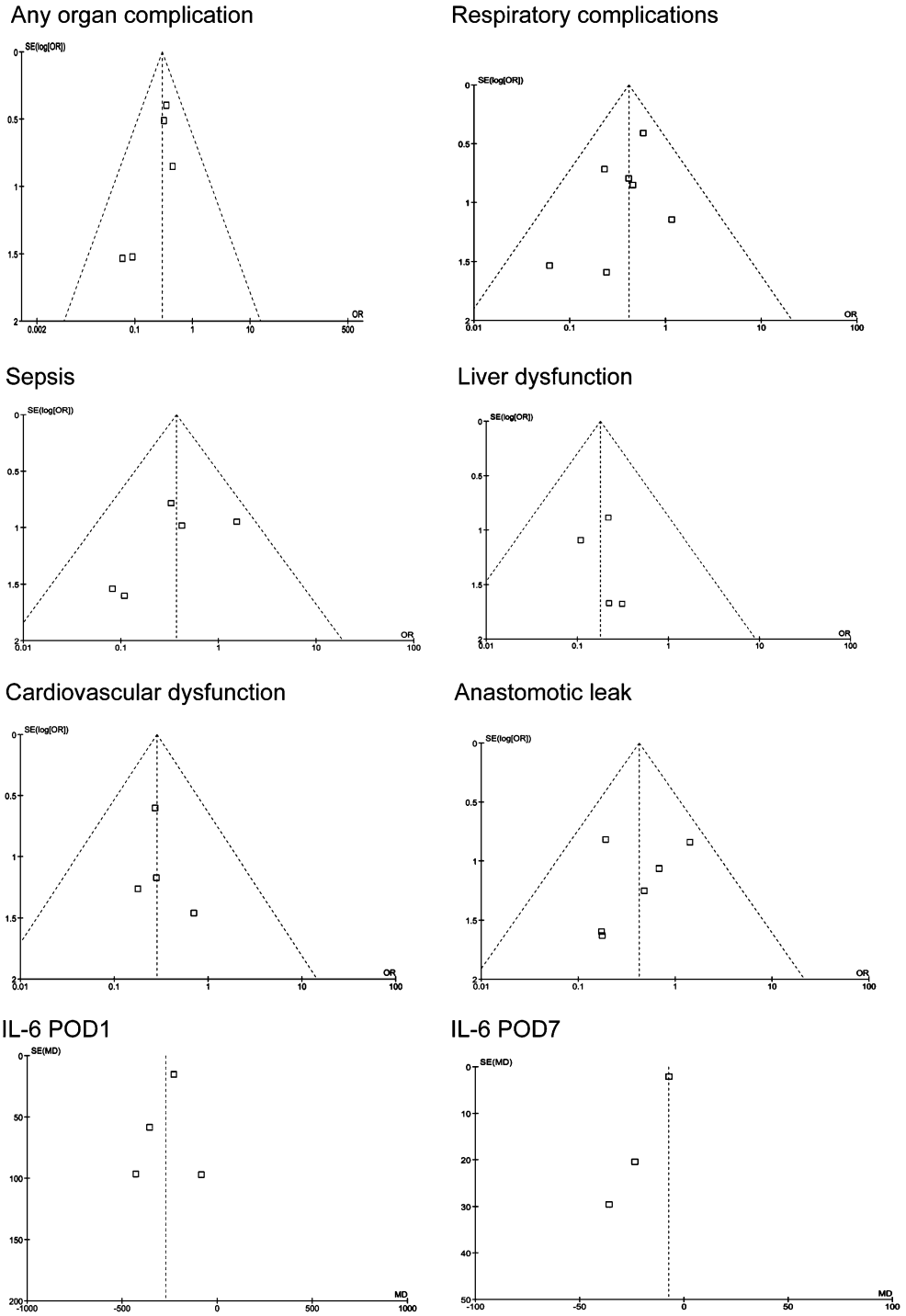

Figure 10 Funnel plots of the treatment effect on clinical endpoints and plasma concentration of IL-6. For the clinical endpoints, the odds ratio (OR) for each study are represented on the *x* axis, against the standard error (SE) of the log(OR) in each study on the *y* axis. For the IL-6 concentrations the weighted mean differences (MD) are plotted on the *x* axis against the SE of the MD on the *y* axis.

point, in the methylprednisolone group as compared to the control group (Table 5).

Cytokine Levels

Meta-analysis of IL-6 blood levels on POD1 and POD7 showed statistically significantly lower levels on POD1 and POD7 (Fig. 11) in the methylprednisolone groups.

IL-8 (Fig. 12) and IL-10 (Fig. 13) blood levels on POD1 were not statistically different between the groups.

Discussion

The main results from this meta-analysis show a decrease in the postoperative clinical complications following esoph-

Table 4 Calculation of the Skeptical Priors Used in the Bayesian Analysis

	95% CI from the classical meta-analysis	Critical OR: Believable that OR at least as small as	Skeptical prior	
			OR 95% CI	log OR (mean ± SD)
Any complication	0.17 to 0.51	0.76	0.76–1.31	−0.002±0.139
Respiratory complication	0.24 to 0.71	0.66	0.66–1.51	−0.002±0.211
Surgical anastomotic leak	0.19 to 0.94	0.14	0.14–7.14	−0.0002±1.003
Sepsis	0.16 to 0.86	0.26	0.26–3.85	0.0005±0.688
Liver dysfunction	0.06 to 0.57	0.37	0.37–2.70	−0.001±0.507
Cardiovascular dysfunction	0.11 to 0.70	0.38	0.38–2.63	−0.0003±0.494

CI confidence interval, *OR* odds ratio

agectomy with a single preoperative bolus of methylprednisolone. These complications include such critical complications as anastomotic leak.

However, due to the poor methodological quality of the detection of clinical complications and the lack of reporting several key randomization or blinding techniques in the majority of these studies, it is natural to express some skepticism concerning these favorable results. It would be difficult to find a consensus concerning the level of skepticism that should be included as starting point of the Bayesian analysis; therefore, the technique used has the advantage to be based on the actual results of the classical meta-analysis and partially avoid a totally arbitrary prior probability.

It is nevertheless interesting to note that heterogeneity was not detected for any clinical end-point, meaning that the results from the one high-quality study[7] were not different from the results obtained in the other studies.

Glucocorticoids are well known for their analgesic,[17] and antiemetic effects;[18] however, the authors of the present studies used methylprednisolone for its anti-inflammatory[19] and immune-modulating effects, hypothesizing that it could decrease the inflammatory reaction induced by surgery[20,21] and the associated clinical complications.

The effect of a single administration of glucocorticoids on reducing the perioperative inflammatory response is well documented by data obtained in many other studies than those included in the present analysis,[22,23] and therefore the results on IL-6 in the present analysis are not surprising. In six studies, the emphasis was placed on obtaining blood concentration measurements of cytokines, and these data are probably less susceptible to a measurement bias in case of poor blinding techniques.

Pulmonary complications remain the most common postoperative morbidity[24,25] after esophagectomy. The favorable results on the respiratory complications described in the present meta-analysis are in fact difficult to interpret as four of the eight studies used, at least in part, indices of pulmonary function rather than clinical entities (pneumonia or atelectasis for example), as definition of pulmonary complications. This also reflects the situation found in the literature. Three other studies during abdominal surgery[23,26,37] reported improvement of pulmonary function parameters in patients receiving a single preoperative dose of glucocorticoids. Although improvement of postoperative pulmonary function is certainly a desirable effect, it is hard to equate pulmonary function to clinically relevant pulmonary complications. Furthermore, one study of elective pulmonary resection[27] showed no improvement of pulmonary function with 25 mg/kg of preoperative methylprednisolone as compared to placebo. The review by Holte and Kehlet[22] lists two studies[28,29] reporting a decrease of pulmonary complications, but they too used a combination of clinical, radiological and biological parameters.

Anastomotic leak remains one of the most deleterious complications after esophagectomy, with incidences during recent years of between 3% and 9% reported by centers with considerable experience with esophagectomies;[30,31] a collective series of 73 American centers[32] reported an incidence of 11.3%, and even an incidence as high as 21% was reported.[33] The incidence of these complications in the control groups of the studies included in the present meta-analysis tend to be in the upper part of the range of values reported in the referenced articles,[24,25,30–32,80] which probably excludes a massive underreporting of complications. The death rates (0.75% and 2.4%) are compatible with the best results obtained in high-volume centers,[2] the Society of Thoracic Surgeons General Thoracic Database,[32] and are inside the range reported by the most recent review.[34]

The effects of glucocorticoids on digestive sutures are, the least to say, controversial, with most available studies reported in the setting of colorectal surgery.[35] Only recently[36] has it been convincingly showed that long-term preoperative steroid use with perioperative steroid coverage is associated with an increased risk of leak (mean odds ratio, 8.7; 95% CI, 1.2–45.1).

Specifically during esophagectomy, the risk model developed from the data available from the Society of Thoracic Surgeons General Thoracic Database[32] deter-

Table 5 Results of the Bayesian Meta-analysis Using a Skeptical Prior

Clinical end-points	Results	
Any organ dysfunction or complication (death excluded)	OR [95% CI]	0.62 [0.51–0.77]
	RR [95% CI]	0.77 [0.67–0.87]
	Probability RRR>0%	100%
	Probability RRR>25%	95.9%
	Probability RRR>50%	1.7%
	Maximal RRR with 95% probability	25.5%
Respiratory complication	OR [95% CI]	0.58 [0.47–0.72]
	RR [95% CI]	0.66 [0.55–0.79]
	Probability RRR>0%	100%
	Probability RRR>25%	98.8%
	Probability RRR>50%	8.1%
	Maximal RRR with 95% probability	30.0%
Sepsis	OR [95% CI]	0.48 [0.28–0.82]
	RR [95% CI]	0.53 [0.32–0.84]
	Probability RRR>0%	99.7%
	Probability RRR>25%	95.1%
	Probability RRR>50%	57.1%
	Maximal RRR with 95% probability	25%
Liver dysfunction	OR [95% CI]	0.43 [0.22–0.86]
	RR [95% CI]	0.46 [0.24–0.87]
	Probability RRR>0%	99.2%
	Probability RRR>25%	94.3%
	Probability RRR>50%	66.6%
	Maximal RRR with 95% probability	23%
Cardiovascular dysfunction	OR [95% CI]	0.40 [0.25–0.63]
	RR [95% CI]	0.44 [0.29–0.67]
	Probability RRR>0%	100%
	Probability RRR>25%	99.7%
	Probability RRR>50%	84.1%
	Maximal RRR with 95% probability	41.5%
Surgical anastomotic leak	OR [95% CI]	0.32 [0.20–0.49]
	RR [95% CI]	0.34 [0.22–0.52]
	Probability RRR>0%	100%
	Probability RRR>25%	99.9%
	Probability RRR>50%	97.4%
	Maximal RRR with 95% probability	54%

OR odds ratio, *RR* relative risk, *RRR* relative risk reduction

mined that a history of steroids treatment is an independent predictor of major morbidity with an OR of 1.81 (95% CI, 1.07–3.06). However, the 'history of steroids treatment' is not defined neither in term of duration nor of dose of glucocorticoid used.

In the case of the present meta-analysis, a single dose, although relative high, was used. The review of the literature by Holte and Kehlet[22] concludes that a single dose of glucocorticoids is not associated with an increased incidence of delayed wound healing or higher incidence of sepsis, but the available studies, although including thousands of patients, are very heterogeneous, with primary end-points as PONV, pain, outcome of spinal trauma, very different from the end-points analyzed in the present article.

The effects of a single dose of glucocorticoids given before colonic surgery have been studied in three randomized, prospective studies[23,37,38] including a total of 113 patients. Five anastomotic leaks (two in the glucocorticoid groups and three in the placebo groups) were reported. The small numbers involved preclude any firm conclusion, but at least these data are not in contradiction with the results of the present meta-analysis.

Five randomized controlled studies of liver surgery[39–43] with a single preoperative methylprednisolone injection (500 mg or 30 mg/kg single bolus) were published, among which four reported the incidence of postoperative bile leaks. The primary end-points of these studies were cytokines levels, the clinical end-points being only secondary end-points or simply reported as postoperative complications. A classical meta-analysis (Fig. 14) of these data shows no difference in the incidence of bile leak between the groups.

Two hypothesis can be advanced concerning the underlying mechanisms of a beneficial effect on suture healing; an effect on fibroblast growth, and consequently on collagen production, and an effect on angiogenesis in the vicinity of the suture. Wound healing is a complex process,[44] but collagen deposition[44–47] and angiogenesis play a major role.[44] Blood supply during esophagectomy is a major concern to the surgeon.[48]

Glucocorticoids were reported to initiate human[49] and mouse[49–51] fibroblasts proliferation using in vitro models. These actions occur only in presence of fibroblast growth factors. Another putative mechanism could be related to inhibition of protease nexin-1 (PN-1) by dexamethasone.[52] PN-1 inhibits thrombin, which is mitogenic for fibroblasts[53] and smooth muscle cells.[54] Glucocorticoids could thus inhibit an inhibitor of fibroblasts and smooth muscle cell proliferation.

On the other hand, an older study using a different in vitro model had reported an inhibition of mouse fibroblasts growth.[55] In patients undergoing colonic surgery,[37] serum concentrations of two procollagens (PICP and PIIINP) were lower (PICP) or less increased (PIIINP) in patients receiving a single 30 mg/kg methylprednisolone bolus as compared to the placebo patients. Nevertheless, in these patients,[37] this did not translate into reduced collagen accumulation in two high-porosity prothesis implanted in a subcutaneous wound, but there was no sign of increased

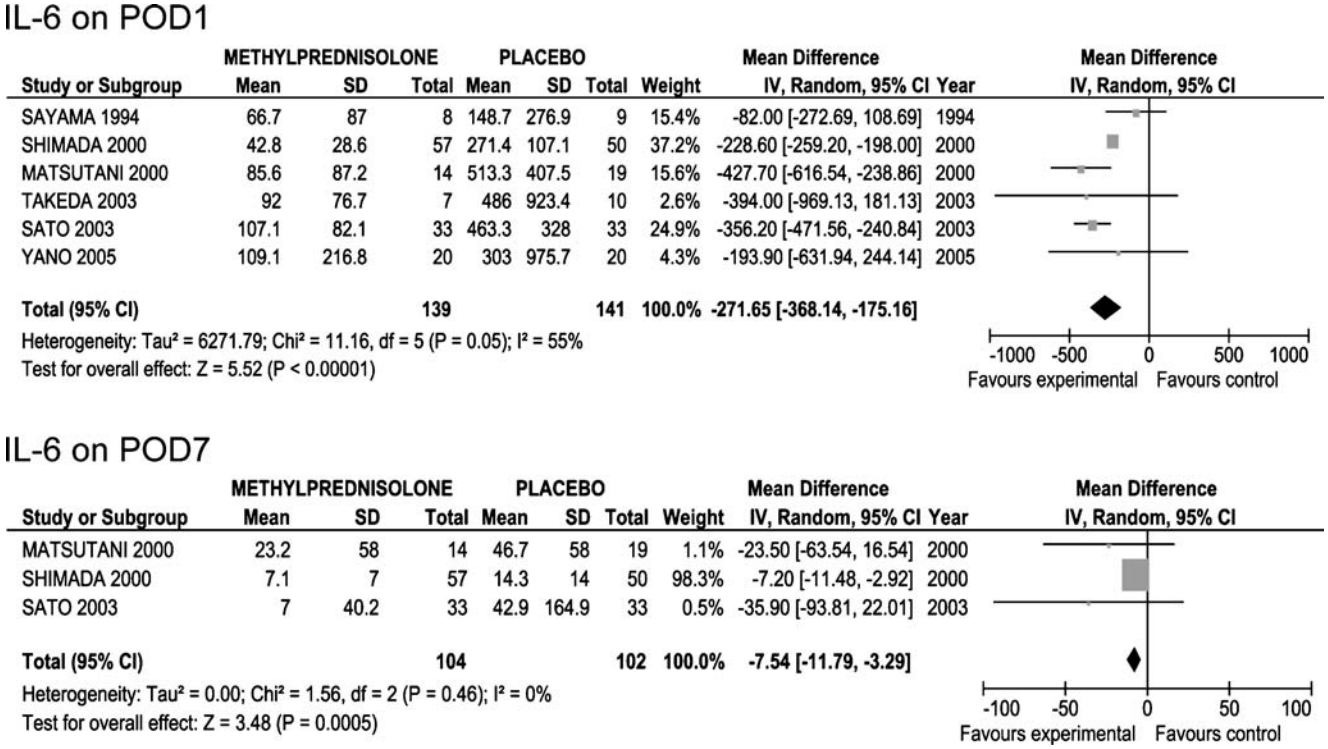

Figure 11 Plasma concentration of IL-6 (in pg/ml) measured on first and seventh postoperative day (POD1 and POD7). A weighted mean difference less than 0 indicates lower plasma concentration with active compared with control. When the 95% confidence interval (CI) does not include 0, the difference is considered statistically significant.

accumulation of collagen in patients having received methylprednisolone.

Recently, Dvorak[56] reviewed the mechanisms of angiogenesis. The potential importance of angiogenesis has been further highlighted by a study reporting the acceleration of wound healing by vascular endothelial cell growth factor (VEGF) in a rabbit model of colonic anastomoses,[57] and improved anastomotic healing in an opossum esophagectomy model by using gene therapy using VEGF transfection[58] showing a strong correlation between bursting pressure and the amount of neovascularization. Glucocorticoids could influence angiogenesis through several mechanisms.

Leptin is a protein hormone produced by white and brown adipose tissues. It has mitogenic effects on endothelial cells.[59–61] Moreover, in a rat model of colonic suture, leptin accelerates the healing of colonic anastomoses.[62] In leptin-treated rats, intestinal injury was significantly decreased in a model of ischemia–reperfusion injury.[63] Leptin blood concentration is increased by prednisolone administration (60 mg/day for 1 week) in normal men.[64] In dogs, a single injection of smaller doses of methylprednisolone (1 or 5 mg/kg) increased serum level of leptin, but a high dose (10 mg/kg) decreased serum level of leptin.[65]

Endothelins, a family of vasoactive peptides, stimulate the synthesis of VEGF.[66] This is modulated through endothelin B-type receptors.[67] But endothelin-1 also acts as a potent vasoconstrictor by interacting with endothelin A-type receptors mostly situated in vascular smooth muscle cells. Glucocorticoids (dexamethasone, prednisolone, and hydrocortisone) down-regulate the expression of endothelin

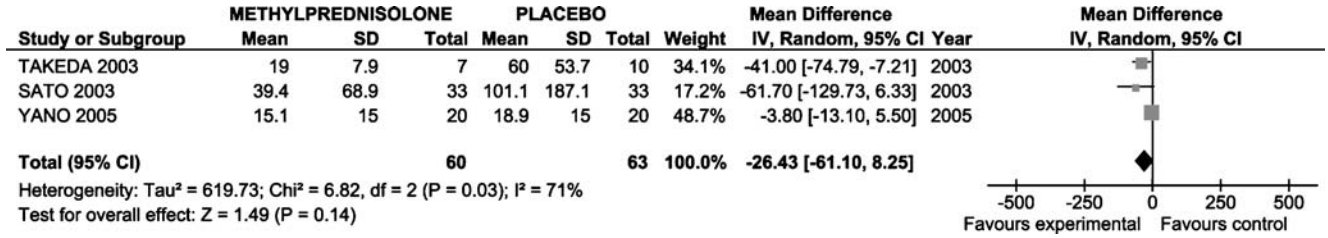

Figure 12 Plasma concentration of IL-8 (in picograms per milliliter) measured on the first postoperative day. A weighted mean difference less than 0 indicates lower plasma concentration with active compared with control. When the 95% confidence interval (CI) does not include 0, the difference is considered statistically significant.

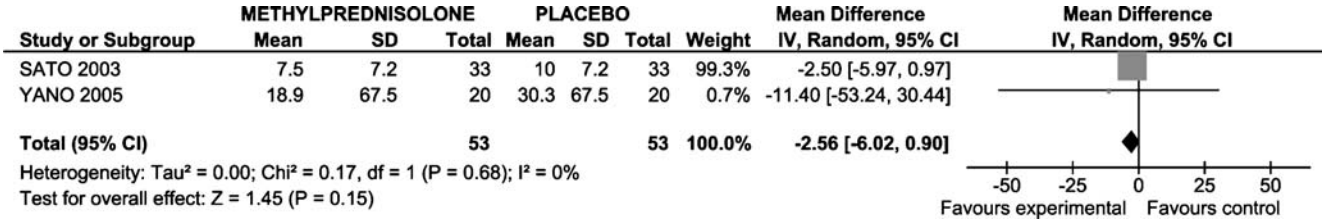

Figure 13 Plasma concentration of IL-10 (in picograms per milliliter) measured on the first postoperative day. A weighted mean difference less than 0 indicates lower plasma concentration with active compared with control. When the 95% confidence interval (CI) does not include 0, the difference is considered statistically significant.

A-type receptors in an in vitro model, resulting in an attenuating response to endothelin-1.[68]

The transforming growth factor-β (TGF-β) produced by vascular smooth muscle stimulates the release of VEGF.[69,70] Dexamethasone and corticosterone suppressed TGF-β-induced VEGF release from aortic smooth muscle cells.[71]

The Notch signaling pathway regulates cell proliferation, differentiation, and cell fate in many tissues.[72] Notch4 has an almost exclusive vascular expression pattern and physiologic concentrations are required for normal vascular development.[73] Cortisol and dexamethasone combined with FGF-2 strongly induced Notch4 expression.[74] However, Notch4 activation in endothelial cells in vivo may inhibit angiogenesis.[75]

Finally, fibroblast growth and angiogenesis are not independent phenomena, but it has been highlighted that fibroblasts were necessary for formation of capillary-like structures when using the human umbilical vein endothelial cells (HUVEC) model.[76,77]

To further highlight the complex inter-relation of all these pathways, thrombin has mitogenic effects on fibroblasts[53] and angiogenic activity,[78] but has also antiangiogenic properties.[78] The antiangiogenic properties are mediated through cleavage of antithrombin, which results in blocking of thrombin-induced mitogenicity and VEGF-induced endothelial cell proliferation. In one of the included studies,[5] the methylprednisolone-treated group had higher antithrombin-III blood level than the control group during at least seven postoperative days. The net effect on suture healing of an

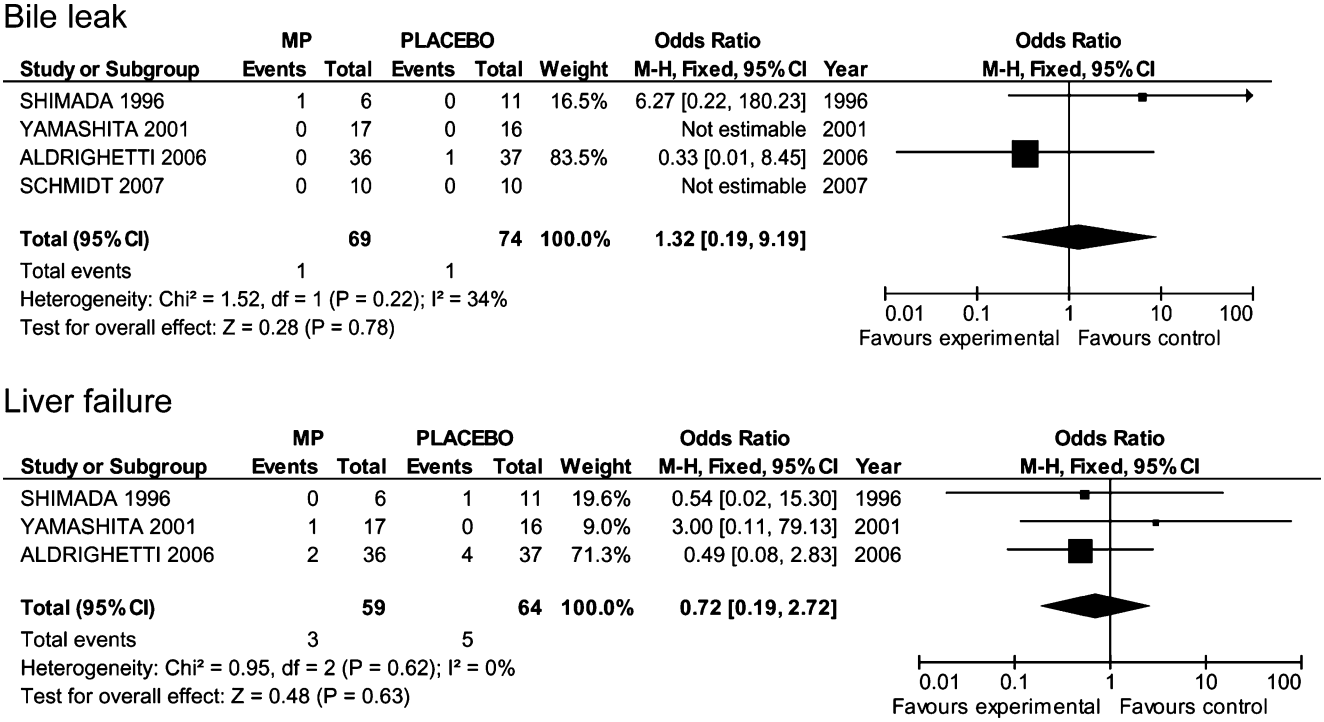

Figure 14 Outcome: bile leak and hepatic failure during the studies of hepatic surgery. Forrest plot summarizing the odds ratio (OR) of the comparison between the methylprednisolone-treated patients versus the control patients for the incidence of surgical anastomotic bile leak and hepatic failure. An odds ratio less than 1 indicates less adverse events with active compared with control. When the 95% confidence interval (CI) does not include 1, the difference is considered statistically significant.

increase in thrombin activity and antithrombin-III plasma levels by glucocorticoids can only be speculative.

In summary, glucocorticoids act on several pathways that could be involved in suture healing. Effects favoring or inhibiting suture healing have been described using these various in vitro models and this does not take into account the eventual differences that would result by using a single administration as opposed to chronic use. This last point is highlighted by the fact that a same amount of dexamethasone given either over 1 week or in a single injection, had different effects, as the longer-timed administration impaired healing of tracheal anastomoses in a rat model but the single injection had no effect.[79]

Cardiovascular complications such as cardiac arrhythmia are common, affecting about 20% of patients.[80] Holte and Kehlet[22] have reviewed the effects of preoperative glucocorticoids on postoperative cardiac function and cardiac arrhythmias, studied essentially after cardiac surgery. They conclude that a lower incidence of arrhythmia after cardiopulmonary bypass is suggested, but that no formal clinical conclusion can be reached due to the low statistical power of the studies. They did not however conduct a formal meta-analysis. Data after cardiac[81,82] and non-cardiac[83] surgery correlate an increased level in IL-6 with a higher incidence in complication. This does not automatically imply that a lower value would be associated with a lower incidence of cardiovascular complication, but it nevertheless provides a level of plausibility to the results of the present meta-analysis.

As for the lower rate of hepatic failure in the methylprednisolone-treated groups it must be noted that during the studies in hepatic surgery, no difference between the groups can be showed (Fig. 14) regarding the incidence of hepatic failures. In three of the four esophagectomies studies reporting this complication the definition of hepatic failure was clearly given (Table 2), but in the hepatic surgery studies, only one study[42] clearly defined the entity 'hepatic failure'. Another study during hepatic surgery[41] reported no difference in the postoperative serum level of hepatic enzymes between the groups.

Conclusion

In conclusion, we are in the presence of a potential benefit that cannot be accepted at face value due to the quality problems of the included studies, of potential biological mechanisms of glucocorticoids that could be beneficial as well as detrimental, and the mechanism by which a single dose of methylprednisolone would markedly decrease each of these complications is hard to fathom. All studies were single center and single country, and most were considered low quality; but in the presence of a remaining potential benefit after a Bayesian analysis starting from a skeptical prior, the best option would be the planning of a large multicenter prospective randomized study that would have to be carefully monitored.

Appendix 1

The Bayesian paradigm considers that the role of data is to update our knowledge of a question under scrutiny which is considered as a parameter of interest in a statistical model.

In our case, the parameter of interest is the odds ratio.

Therefore, a fundamental feature of Bayesian analysis is the incorporation of prior information about the parameter of interest. Bayes' theorem gives a simple and uncontroversial result in probability theory, relating probabilities of events before (the 'prior' in Bayesian parlance) and after an experiment (the 'posterior' in Bayesian parlance).

Thus, the prior information, expressed as a probability distribution for the parameter of interest, represents what is known or believed to be true before the data are taken into account; the data are expressed as a probability distribution known as the likelihood function which demonstrates the degree of support from the data for the various possible values of the parameter of interest. The likelihood function is integrated with the prior to produce the posterior distribution which represents our updated knowledge of the parameter of interest, given the data.

Computation of a Skeptical Prior

In the present situation, an interesting feature of the Bayesian techniques can be use to tackle the two obvious problems that appear at the end of our initial classical analysis. The first is the size of the risk reduction which tends to illicit considerable skepticism, in the form of a 'this is too good to be true' attitude. The second problem is the possibility of facing a bias related to the single institutional, single country, low quality, of these studies.

Skepticism about large treatment effects can be formally expressed in mathematical form and used in interpretation of results that cause surprise.

For the present analysis, we took the stand to begin the Bayesian analysis from a skeptical view, which is that we do not believe the results from the classical meta-analysis.

Formally, this is done by computing from the results of the classical meta-analysis, a prior in the form of a probability distribution, which would be able to cancel the significant statistical results obtained by the classical meta-analysis. This is done by computing a critical odds ratio and, from this odds ratio, a 95% confidence interval. This

interval contains the formal mathematical expression of our skepticism. This interval is calculated as follows:

Ud upper border of 95% confidence interval for the odds ratio from the classical meta-analysis
Ld lower border of 95% confidence interval for the odds ratio from the classical meta-analysis

We will use as example the respiratory complications, for which the results from the classical meta-analysis was an OR [95% CI] of 0.41 [0.24–0.71]; thus Ud=0.71 and Ld=0.24.

Ln(Ud) natural logarithm of Ud (example: Ln(0.71)= −0.34249)
Ln(Ld) natural logarithm of Ld (example: Ln(0.24)= −1.427116)
N Ln(Ud/Ld) where Ln stands for natural logarithm (example: Ln(0.71/0.24)=1.084626)

$$M = -\left(\frac{N^2}{4 \times \sqrt{\mathrm{Ln(Ud)} \times \mathrm{Ln(Ld)}}}\right)$$

Example:

$$M = -\left(\frac{(1.084626)^2}{4 \times \sqrt{-0.34249 \times -1.427116}}\right) = -0.420675$$

ORc critical odds ratio

$$\mathrm{ORc} = e^{M}$$
$$\mathrm{ORc} = e^{-0.420675} = 0.66$$

From this critical odds ratio, we can now compute the 95% confidence interval which contains the distribution of our prior belief that would be needed to nullify the results of the classical meta-analysis. This is the interval equal to:

ORc to $\frac{1}{\mathrm{ORc}}$, and thus for our example 0.66 to 1.51

Following the work of Spiegelhalter,[14] we use normal distributions to summarize the information about the odds ratios on the natural log scale. Therefore, the 95% confidence interval for the odds ratio that we just computed must be transformed into a mean±standard deviation.

Computation of the Mean and Standard Deviation for a 95% Confidence Interval of the Associated Normal Distribution with All Possible Value of the Odds Compatible with One's Belief

A maximal expected decrease in odds ratio (in our example use 0.66)
B maximal expected increase in odds ratio (in our example use 1.51)
log(A) natural logarithm of A (for our example −0.4155)
log(B) natural logarithm of B (for our example 0.4121)
logOR natural logarithm of mean odds ratio
SD(logOR) standard deviation of the distribution of the natural logarithm of the odds ratios

$$\log \mathrm{OR} = \frac{\log(A)+\log(B)}{2}$$
$$\mathrm{SD}(\log \mathrm{OR}) = \frac{|\log(A)|+|\log(B)|}{3.92}$$

For our example:

$$\log \mathrm{OR} = \frac{-0.4155+0.4121}{2} = -0.002$$
$$SD(\log \mathrm{OR}) = \frac{0.4155+0.4121}{3.92} = 0.211$$

These values are used as the initial prior probabilities to begin the Bayesian meta-analysis as explained in detail in appendixes 1 and 3 in Engelman et al.[15]

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
2. Law S, Wong J. Current management of esophageal cancer. J Gastrointest Surg 2005;9:291–310.
3. Leigh Y, Goldacre M, McCulloch P. Surgical specialty, surgical unit volume and mortality after oesophageal cancer surgery. Eur J Surg Oncol 2009;35:820–825.
4. Takeda S, Ogawa R, Nakanishi K, Kim C, Miyashita M, Sasajima K, Onda M, Takano T. The effect of preoperative high dose methylprednisolone in attenuating the metabolic response after oesophageal resection. Eur J Surg 1997;163:511–517.
5. Matsutani T, Onda M, Sasajima K, Miyashita M. Glucocorticoid attenuates a decrease of antithrombin III following major surgery. J Surg Res 1998;79:158–163.
6. Shimada H, Ochiai T, Okazumi S, Matsubara H, Nabeya Y, Miyazawa Y, Arima M, Funami Y, Hayashi H, Takeda A, Gunji Y, Suzuki T, Kobayashi S. Clinical benefits of steroid therapy on surgical stress in patients with esophageal cancer. Surgery 2000;128:791–798.
7. Sato N, Koeda K, Ikeda K, Kimura Y, Aoki K, Iwaya T, Akiyama Y, Ishida K, Saito K, Endo S. Randomized study of the benefits of preoperative corticosteroid administration on the postoperative morbidity and cytokine response in patients undergoing surgery for esophageal cancer. Ann Surg 2002;236:184–190.
8. Takeda S, Kim C, Ikezaki H, Nakanishi K, Sakamoto A, Okawa K, Miyashita M, Sasajima K, Tajiri T, Tanaka K, Ogawa R. Preoperative administration of methylprednisolone attenuates cytokine-induced respiratory failure after esophageal resection. J Nippon Med Sch 2003;70:16–20.
9. Yano M, Taniguchi M, Tsujinaka T, Fujiwara Y, Yasuda T, Shiozaki H, Monden M. Is preoperative methylprednisolone beneficial for patients undergoing esophagectomy? Hepatogastroenterology 2005;52:481–485.
10. Tsukada K, Miyazaki T, Katoh H, Masuda N, Fukuchi M, Manda R, Fukai Y, Nakajima M, Sohda M, Kimura H, Kuwano H. Effect of perioperative steroid therapy on the postoperative course of

patients with oesophageal cancer. Dig Liver Dis 2006;38:240–244.
11. Sayama J, Shineha R, Yokota K, Hirayama K, Higuchi N, Ohe H, Nakano T, Miyata G, Sugawara K, Ueda H, Nishihira T, Mori S. Control of the excessive reaction after surgery for esophageal carcinoma with preoperative administration of the cortico-steroids. Jpn J Gastroenterol 1994;27:841–848.
12. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
13. Mattews RAJ. Methods for assessing the credibility of clinical trial outcomes. Drug Inf J 2001;35:1469–1478.
14. Spiegelhalter DJ, Abrams KR, Myles JP. An overview of the Bayesian approach. In Spiegelhalter DJ, Abrams KR, Myles JP, ed. Bayesian Approaches to Clinical Trials and Health-Care Evaluation. Chichester: John Wiley & Sons, Ltd, 2004, pp 49–120.
15. Engelman E, Salengros JC, Barvais L. How much does pharmacologic prophylaxis reduce postoperative vomiting in children? Calculation of prophylaxis effectiveness and expected incidence of vomiting under treatment using Bayesian meta-analysis. Anesthesiology 2008;109:1023–1035.
16. Engelman E, Salengros JC. IONSYS™ versus morphine PCA: analysis of the current literature using a Bayesian approach. Acute Pain 2008;10:83–91.
17. Kehlet H. Glucocorticoids for peri-operative analgesia: how far are we from general recommendations? Acta Anaesthesiol Scand 2007;51:1133–1135.
18. Gan TJ, Meyer TA, Apfel CC, Chung F, Davis PJ, Habib AS, Hooper VD, Kovac AL, Kranke P, Myles P, Philip BK, Samsa G, Sessler DI, Temo J, Tramèr MR, Vander Kolk C, Watcha M: Society for ambulatory anesthesia guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2007;105:1615–1628.
19. Rhen T, Cidlowski HA. Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. N Engl J Med 2005;353:1711–1723.
20. Wilmore DW. Metabolic response to severe surgical illness: overview. World J Surg 2000;24:705–711.
21. Desborough JP. The stress response to trauma and surgery. Br J Anaesth 2000;85:109–117.
22. Holte K, Kehlet H. Perioperative single-dose glucocorticoid administration: pathophysiologic effects and clinical implications. J Am Coll Surg 2002;195:694–712.
23. Vignali A, Di Palo S, Orsenigo E, Ghirardelli L, Radaelli G, Staudacher C. Effect of prednisolone on local and systemic response in laparoscopic vs. open colon surgery: a randomized, double-blind, placebo-controlled trial. Dis Colon Rectum 2009;52:1080–1088.
24. Bailey SH, Bull DA, Harpole DH, Rentz JJ, Neumayer LA, Pappas TN, Daley J, Henderson WG, Krasnicka B, Khuri SF. Outcomes after esophagectomy: a ten-year prospective cohort. Ann Thorac Surg 2003;75:217–222.
25. Morita M, Yoshida R, Ikeda K, Egashira A, Oki E, Sadanaga N, Kakeji Y, Yamanaka T, Maehara Y. Advances in esophageal cancer surgery in Japan: an analysis of 1000 consecutive patients treated at a single institute. Surgery 2008;143:499–508.
26. Nagelschmidt M, Fu ZX, Saad S, Dimmeler S, Neugebauer E. Preoperative high dose methylprednisolone improves patients outcome after abdominal surgery. Eur J Surg 1999;165:971–978.
27. Bigler D, Jonsson T, Olsen J, Brenoe J, Sander-Jensen K. The effect of preoperative methylprednisolone on pulmonary function and pain after lung operations. J Thorac Cardiovasc Surg 1996;112:142–145.
28. Fecht DC, Magovern GJ, Park SB, Merkow LP, Dixon CM, Dosios T, Pardo M. Benficial effects of methylprednisolone in patienst on cardiopulmonary bypass. Circ Shock 1978;5:415–422.
29. Zotti GC, Salzano de Luna F, Caiazza A, Santaniello W, Micheletti G, Bruno A, Casadei CL. Prevention of pulmonary complications by 6-methylprednisolone in major abdominal surgery. Ital Surg Sci 1988;18:369–375.
30. Law S. Esophagectomy without mortality: what can surgeons do? J Gastrointest Surg 2009; September Epub ahead of print.
31. Orringer MB, Marshall B, Chang AC, Lee J, Pickens A, Lau CL. Two thousand transhiatal esophagectomies. Changing trends, lessons learned. Ann Surg 2007;246:363–374.
32. Wright CD, Kucharczuk JC, O'Brien SM, Grab JD, Allen MS. Predictors of major morbidity and mortality after esophagectomy for esophageal cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk adjustment model. J Thorac Cardiovasc Surg 2009;137:587–596.
33. Rizk NP, Bach PB, Schrag D, Bains MS, Turnbull AD, Karpeh M, Brennan MF, Rusch VW. The impact of complications on outcomes after ressection for oesophageal and gastroesophageal junction carcinoma. J Am Coll Surg 2004;198:42–50.
34. Dunst CM, Swanträm LL. Minimally invasive esophagectomy. J Gastrintest Surg 2010; Sep 30. [Epub ahead of print].
35. Kingham TP, Pachter HL. Colonic anastomotic leak: risk factors, diagnosis, and treatment. J Am Coll Surg 2009;208:269–278.
36. Konishi T, Watanabe T, Kishimoto J, Nagawa H. Risk factors for anastomotic leakage after surgery for colorectal cancer: results of prospective surveillance. J Am Coll Surg 2006;202:439–444.
37. Schultze S, Andersen J, Overgaard H, Norgaard P, Nielsen HJ, Aasen A, Gottrup F, Kehlet H. Effect of prednisolone on the systemic response and wound healing after colonic surgery. Arch Surg 1997;132:129–135.
38. Kirdak T, Yilmazlar A, Cavun S, Ercan I, Yilmazlar T. Does single, low-dose preoperative dexamethasone improve outcomes after colorectal surgery based on an enhanced recovery protocol? Double-blind, randomized clinical trial. Am Surg 2008:74:106–167.
39. Shimada M, Saitoh A, Kano T, Takenaka K, Sugimachi K. The effect of a perioperative steroid pulse on surgical stress in hepatic resection. Int Surg 1996;81:49–51.
40. Yamashita Y, Shimada M, Hamatsu T, Rikimaru T, Tanaka S, Shirabe K, Sugimachi K. Effects of preoperative steroid administration on surgical stress in hepatic resection. Arch Surg 2001;136:328–333.
41. Muratore A, Ribero D, Ferrero A, Bergero R, Capussotti L. Prospective randomized study of steroids in the prevention of ischaemic injury during hepatic resection with pedicle clamping. Br J Surg 2003;90:17–22.
42. Aldrighetti L, Pulitano C, Arru M, Finazzi R, Catena M, Soldini L, Comotti L, Ferla G. Impact of preoperative steroids administration on ischemia-reperfusion injury and systemic responses in liver surgery: a prospective randomized study. Liver Transpl 2006;12:941–949.
43. Schmidt SC, Hamann S, Langrehr JM, Höflich C, Mittler J, Jacob D, Neuhaus P. Preoperative high-dose steroid administration attenuates the surgical stress response following liver resection: results of a prospective randomized study. J Hepatobiliary Pancreat Surg 2007;14:484–492.
44. Thornton FJ, Barbul A. Healing in the gastrointestinal tract. Surg Clin North Am 1997;77:549–573.
45. Kovacs T, Koves I, Orosz Z, Nemeth T, Pandi E, Kralovanszky J. Healing of esophageal anastomoses performed with the biofragmentable anastomosis ring versus the end-to-end anastomosis stapler: comparative experimental study in dogs. World J Surg 2003;27:464–472.
46. Jiborn H, Ahonen J, Zederfeldt B. Healing of experimental colonic anastomoses. IV. Effect of suture technique on collagen metabolism in the colonic wall. Am J Surg 1980;139:406–413.
47. Fedakar-Sebyucel M, Bingol-Kologlu M, Vargun R, Akbay C, Sarac FN, Renda N, Hasirci N, Gollu G, Dindar H. The effects of local and sustained release of local and sustained release of

fibroblast growth factor on wound healing in esophageal anastomoses. J Pediatr Surg 2008;43:290–295.
48. Reavis KM. The esophageal anastomosis: how improving blood supply affects leak rate. J Gastrointest Surg 2009;13:1558–1560.
49. Thrash CR, Cunningham DD. Stimulation of division of density inhibited fibroblasts glucocorticoids. Nature 1973;242:399–401.
50. Thrash CR, Ho TS, Cunningham DD. Structural features of steroids which initiate proliferation of density-inhibited 3T3 mouse fibroblasts. J Biol Chem 1974;249:6099–6103.
51. Armelin HA. Pituitary extracts and steroid hormones in the control of 3T3 cell growth. Proc Nat Acad Sci 1973;70:2702–2706.
52. Guttridge DC, Lau AL, Cunningham DD. Protease nexin-1, a thrombin inhibitor, is regulated by interleukin-1 and dexamethasone in normal human fibroblasts. J Biol Chem 1993;268:18966–18974.
53. Carney DH, Glenn KC, Cunningham DD. Conditions which affect inhibition of animal cell division by trypsin and thrombin. J Cell Physiol 1978;95:13–22.
54. McNamara CA, Sarembock IJ, Gimple LW, Fenton JW, Coughlin SR, Owens GK. Thrombin stimulates proliferation of cultured rat aortic smooth muscle cells by a proteolytically activated receptor. J Clin Invest 1993;91:94–98.
55. Ruhmann AG, Berliner DL. Effect of steroids on growth of mouse fibroblasts in vitro. Endocrinology 1965;76:916–927.
56. Dvorak FH. Angiogenesis: update 2005. J Thromb Haemost 2005;3:1835–1842.
57. Ishii M, Tanaka E, Imaizumi T, Sugio Y, Sekka T, Tanaka M, Yasuda M, Fukuyama N, Shinozaki Y, Hyodo K, Tanioka K, Mochizuki R, Kawai T, Mori H, Makuuchi H. Local VEGF administration enhances healing of colonic anastomoses in a rabbit model. Eur Surg Res 2009;42:249–257.
58. Enestvedt CK, Hosack L, Winn SR, Diggs BS, Uchida B, O'Rourke RW, Jobe BA. VEGF Gene therapy augments localized angiogenesis and promotes anastomotic wound healing: a pilot study in a critically relevant animal model. J Gastrointet Surg 2008;12:1762–1772.
59. Suganami E, Takagi H, Ohashi H, Suzuma K, Suzuma I, Oh H, Watanabe D, Ojima T, Suganami T, Fujio Y, Nakao K, Ogawa Y, Yoshimura N: Leptin stimulates ischemia-induced retinal neovascularization: possible role of vascular endothelial growth factor expressed in retinal endothelial cells. Diabetes 2004;53:2443–2448.
60. Cao R, Brakenhielm E, Wahlestedt C, Thyberg J, Cao Y. Leptin induces vascular permeability and synergistically stimulates angiogenesis with FGF-2 and VEGF. Proc Natl Acad Sci 2001;98:6390–6395.
61. Bouloumie A, Marumo T, Lafontan M, Busse R: Leptin induces oxidative stress in human endothelial cells. FASEB J 1999;13:1231–1238.
62. Tasdelen A, Algin C, Ates E, Kiper H, Inal M, Sahin F: Effect of leptin on healing of colonic anastomoses in rats. Hepatogastroenterology 2004;51:994–997.
63. Hacioglu A, Algin C, Pasaoglu O, Pasaoglu E, Kanbak G. Protective effect of leptin against ischemia-reperfusion injury in the rat small intestine. BMC Gastroenterol 2005;5:37.
64. Rieth N, Jollin L, Le Panse B, Lecoq AM, Arlettaz A, De Ceaurriz J, Collomp K. Effects of short-term corticoid ingestion on food intake and adipokines in healthy recreationally trained men. Eur J Appl Physiol 2009;105:309–313.
65. Yilmaz Z, Ilcol YO, Golcu E. Serum leptin and ghrelin levels in response to methylprednisolone injection in healthy dogs. Res Vet Sci 2007;82:187–194.
66. Pedram A, Razandi M, Hu RM, Levin ER. Vasoactive peptides modulate vascular endothelial cell growth factor production and endothelial cell proliferation and invasion. J Biol Chem 1997;272:17097–17103.
67. Mobidelli L, Orlando C, Maggi CA, Ledda F, Ziche M. Proliferation and migration of endothelial cells is promoted by endothelins via activation of ETB receptors. Am J Physiol 1995;269:H686–695.
68. NambiS P, Pullen M, Wu HL, Nuthulagantig P, Elshourbagys N, Kumarg C. Dexamethasone down-regulates the expression of endothelin receptors in vascular smooth muscle cells. J Biol Chem 1992;267:19555–19559.
69. Brogi E, Wu T, Namiki A, Isner JM. Indirect angiogenic cytokines upregulate VEGF and bFGF gene expression in vascular smooth muscle cells whereas hypoxia upregulates VEGF expression only. Circulation 1994;90:649–652.
70. Yamamoto T, Kozawa O, Tanabe K, Akamatsu S, Matsuno H, Dohi S, Uematsu T. Involvement of p38 MAP kinase in TGF-β-stimulated VEGF synthesis in aortic smooth muscle cells. J Cell Biochem 2001;82:591–598.
71. Tanabe K, Tokuda H, Takai S, Matsushima-Nishiwaki R, Hanai Y, Hirade K, Katagiri Y, Dohi S, Kozawa O. Modulation by the steroid/thyroid hormone superfamily of TGF-β-stimulated VEGF release. J Cell Biochem 2006;99:187–195.
72. Kimble J, Simpson P. The LIN-12/Notch signaling pathway and its regulation. Annu Rev Cell Dev Biol 1997;13:333–361.
73. Uyttendaele HG, Marazzi G, Wu QY, Sassoon D, Kitajewski J. Notch4/int-3, a mammary proto-oncogene, is an endothelial cell-specific Notch gene. Development 1996;122:2251–2259.
74. Wu J, Bresnick EH. Glucocorticoid and growth factor synergism requirement for Notch4 chromatin domain activation. Mol Cell Biol 2007;27:2411–2422.
75. Leong KG, Hu X, Li L, Noseda M, Larrivée B, Hull C, Hood L, Wong F, Karsan A. Activated Notch4 inhibits angiogenesis: role of β1-Integrin activation. Mol Cell Biol 2002,22:2830–2841.
76. Velazquez OC, Snyder R, Liu ZJ, Fairman RM, Herlyn M. Fibroblast-dependent differentiation of human microvascular endothelial cells into capillary-like 3-dimensional networks. FASEB J 2002;16:1316–1318.
77. Nakatsu MN, Sainson RCA, Aoto JN, Taylor KL, Aitkenhead M, Pérez-del-Pulgar S, Carpenter PM, Hughes CCW. Angiogenic sprouting and capillary lumen formation modeled by human umbilical vein endothelial cells (HUVEC) in fibrin gels: the role of fibroblasts and Angiopoietin-1. Microvasc Res 2003;66:102–112.
78. Tsopanoglou NE, Maragoudakis ME. Role of thrombin in angiogenesis and tumor progression. Semin Thromb Hemost 2004;30:63–69.
79. Talas DU, Nayci A, Atis S, Polat A, Comelekoglu U, Bagdatoglu C, Renda N. The effects of corticosteroids on the healing of tracheal anastomoses in a rat model. Pharmacol Res 2002;45:299–304.
80. Murthy SC, Law S, Whooley BP, Alexandrou A, Chu KM, Wong J. Atrial fibrillation after esophagectomy is a marker for postoperative morbidity and mortality. J Thorac Cardiovasc Surg 2003;126:1162–1167.
81. Deng MC, Dasch B, Erren M, Möllhoff T, Scheld HH. Impact of left ventricular dysfunction on cytokines, hemodynamics, and outcome in bypass grafting. Ann Thorac Surg 1996;62:184–190.
82. Hennein HA, Ebba H, Rodriguez JL, Merrick SH, Keith FM, Bronstein MH, Leung JM, Mangano DT, Greenfield LJ, Rankin JS. Relationship of the proinflammatory cytokines to myocardial ischemia and dysfunction after uncomplicated coronary revascularization. J Thorac Cardiovasc Surg 1994;108:626–635.
83. Roumen RM, Hendriks T, van der Ven-Jongekrijg J, Nieuwenhuijzen GA, Sauerwein RW, van der Meer JW, Goris RJ. Cytokine patterns in patients after major vascular surgery, hemorrhagic shock, and severe blunt trauma. Relation with subsequent adult respiratory distress syndrome and multiple organ failure. Ann Surg 1993;218:769–776.

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ORIGINAL ARTICLE

Duodenal Fistula after Elective Gastrectomy for Malignant Disease

An Italian Retrospective Multicenter Study

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Abstract
Background Duodenal fistula (DF) after gastrectomy continues to be a life-threatening problem. We performed a retrospective multicenter study analyzing the characteristics of DF after elective gastrectomy for malignant disease.
Methods Three thousand seven hundred eighty-five patients who had undergone gastrectomy with duodenal stump in 11 Italian surgical units were analyzed.
Results Sixty-eight DFs occurred, with a median frequency of 1.6% and a mortality rate of 16%. Complications were mainly septic but fistulas or bleeding of surrounding organs accounted for about 30%. Reoperation was performed in 40% of patients. We observed a correlation between mortality and age (hazard ratio 1.09; 95% CI 1.00–1.20) and serum albumin (hazard ratio 0.90; 95% CI 0.83–0.99). The appearance of further complications was associated with reoperation ($P<0.001$) and death ($P=0.054$), while the preservation of oral feeding was related to DF healing ($P<0.001$).
Conclusions This paper represents the largest series ever published on DF and shows that its features have changed in the last 20 years. DF alone no longer leads to death and some complications observed in the past have disappeared, while new ones are emerging. Nowadays, medical therapy is preferred and surgery is indicated only in cases of abdominal sepsis or bleeding.

Keywords Gastrectomy · Complications · Duodenal fistula

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Introduction

Duodenal fistula (DF) after gastrectomy has a low frequency, occurring in about 3% of cases, but continues to be a life-threatening problem with a high rate of complications and a very long period of hospitalization. Published studies dealing with postoperative DF were based on small series of patients; moreover, DFs were reported after different types of surgery for different causes and in many cases as an emergency, so the reported data are very heterogeneous and the clinical pictures are not comparable.[1–6] In fact, according to these data, the overall mortality ranges from 7% to 67%[1–3] and spontaneous fistula closure from 28% to 92%.[2,4,5]

Possible causes of postoperative DF include inadequate closure of the duodenal stump, devascularization, cancer involvement of resection line, inflamed duodenal wall, local hematoma, incorrect drain position, and postoperative distension of the duodenum.

Patients affected by DF very often develop other complications, such as intraabdominal abscess, wound infection, necrosis or dehiscence, diffuse peritonitis, sepsis, malnutrition, fluid and electrolyte disturbances, dermatitis, acute cholecystitis, pancreatitis, abdominal bleeding, and pneumonia.[1]

Many surgical procedures have been proposed for the treatment of DF: from tube duodenostomy,[7] to repair with a rectus abdominis muscle flap,[8] from closure by a Roux-en-Y duodenojejunostomy[9] to pancreatoduodenectomy.[10]

Also percutaneous treatments are often used in the treatment of DF: abscess drainage; transhepatic biliary drainage;[11], and fistula obliteration by cyanoacrylate or prolamine.[12]

The management of DF remains controversial and is mainly based on the prevention or early detection and treatment of complications, as well as nutritional support by enteral nutrition (EN) or total parenteral nutrition (TPN) and use of somatostatin or its analogu octreotide.[13]

The aim of this paper is to report the characteristics of a homogeneous group of patients who developed DF after elective gastrectomy for malignant disease in an attempt to describe the natural history of this rare but fearful complication of gastric surgery.

Material and Methods

We performed a multicenter retrospective study involving 11 Italian surgical units. A diagnosis of DF was made on the basis of the presence of duodenal juice in the surgical drainage or its leakage through the abdominal wall, and confirmed by CT scan and/or fistulography. The frequency and characteristics of DF were analyzed after 3,785 elective gastrectomies with duodenal stump carried out from 1991 to 2006 for malignant diseases. The procedures included 1,613 total gastrectomies (TG) and 2,172 subtotal gastrectomies (SG). Surgical access was by laparotomy in most cases, with only 21 cases of laparoscopic or video-assisted gastrectomy. For each DF, we collected a series of clinical data regarding the patient and his/her outcome. All charts filled out at the different centers were validated by the main investigator (L.C.). In Table 1 the characteristics of the participating centers are reported. In our search for factors predicting the outcome of DF, we analyzed correlations with morbidity and mortality.

Statistical Analysis

Categorical data are presented as absolute frequency and percent proportion; their confidence intervals were computed by the exact method based on binomial distribution. Continuous data are presented as median and range because the corresponding variables were asymmetrically distributed. Parametric and nonparametric tests were used as appropriate in order to evaluate the significance of differences in the distribution of the variables (*t* test, Fisher's exact test, Wilcoxon's rank-sum test, and Pearson's chi-square). Survival analysis was carried out according to the Kaplan–Meier method and the Cox regression model to evaluate prognostic factors. The heterogeneity test was used to explore differences in DF incidence among centers.

Results

Out of 3,785 gastrectomies for malignant disease a total of 68 DFs were observed (1.8%); histology was carcinomas in 66 patients, lymphoma in one, and GIST in one. The median age of the patients was 66 years (range 42–83 years). In Table 2, the frequency of DF for a single center is reported. The variability in the frequency of DF between centers

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Table 1 Characteristics of the Centers Participating in the Study

Centers	Gastrectomies performed	TG	TG Roux	TG Omega loop	SG	SG Roux	SG BII
1	905	355	355	0	550	11	539
2	89	55	55	0	34	28	6
3	675	358	345	13	317	7	310
4	108	93	93	0	15	0	15
5	163	59	55	4	104	104	0
6	287	111	111	0	176	176	0
7	236	81	76	5	155	42	113
8	250	140	140	0	110	0	110
9	417	137	137	0	280	3	277
10	346	115	115	0	231	172	59
11	309	109	109	0	200	200	0
Total	**3,785**	**1,613**	**1,591**	**22**	**2,172**	**743**	**1,429**
Median	287	111	111	0	176	28	59
Range	89–905	55–358	55–355	0–13	15–550	0–200	0–539

TG total gastrectomy, *SG* subtotal gastrectomy, *Roux* Roux-en-Y reconstruction, *BII* Billroth II reconstruction

(Table 2) was statistically significant ($P<0.001$), but no correlation was found among the 11 centers between DF frequency and total number of gastrectomies performed.

The extent of gastrectomy did not affect the frequency of DF (1.7% after TG and 1.9% after SG). Concerning the method of reconstruction of the digestive tract after TG, we did not observe any difference in DF frequency between patients with Roux-en-Y or omega loop reconstructions, but SG patients with Roux-en-Y reconstruction had a higher frequency of DF than patients with Billroth II reconstruction (3.4% versus 1.1%, respectively; $P<0.001$). The median time of DF onset was on postoperative day 7 (range 0–22), and the median daily output was 290 mL (range 40–2,200 mL). The DF healing rate was 84% (57 patients) after a median of 19 days (range 1–1,035 days). In our series DF onset and daily output did not affect DF time to healing or mortality. The overall mortality rate was 16% (11 patients) due to multiple organ failure in ten patients and in one case to pulmonary embolism, after a median of 18 days (range 4–60 days). Complications occurred in 51 patients (75%; Table 3), most of them were septic, but more than 30% of patients developed a new fistula, acute inflammation or bleeding at surrounding abdominal organs.

Reoperation was performed in 27 patients (40%) for abdominal sepsis in all but one, in whom the indication was

Table 2 Duodenal Fistulas

Centers	Gastrectomies performed	Duodenal fistulas	Frequency of duodenal fistulas (%)
1	905	4	0.4
2	89	2	2.2
3	675	7	1.0
4	108	1	0.9
5	163	5	3.1
6	287	17	5.9
7	236	15	6.3
8	250	4	1.6
9	417	8	1.9
10	346	1	0.3
11	309	4	1.3
Total	3,785	68	
Median	287	4	1.6
Range	89–905	1–17	0.3–6.3

Table 3 Complications in Patients with Duodenal Fistula

Complications	51/68 patients (75%)
Abdominal abscess	26 (38%)
Wound infection	19 (28%)
Sepsis	18 (26%)
Central line infection	10 (15%)
Pneumonia	9 (13%)
Acute renal failure	7 (10%)
Colonic fistula	5 (7%)
Pancreatic fistula	4 (6%)
Acute pancreatitis	4 (6%)
Intraabdominal bleeding	4 (6%)
Abdominal wall necrosis	3 (4%)
Pulmonary embolism	2 (3%)
Jejunal fistula	2 (3%)
Roux-en-Y syndrome	2 (3%)
Esophagojejunal fistula	2 (3%)
Heart failure	2 (3%)
Others	11 (16%)

Others cholecystitis, septic arthritis, deep venous thrombophlebitis, bilateral pleuritis, dermatitis, fascitis, cerebral ischemia, urinary tract infection, respiratory failure, bowel occlusion, and hypertensive attacks

failure to DF heal. Surgery was performed once, twice, and three times in 18, six, and three patients, respectively; and it consisted of peritoneal drainage, duodenal suture, and tube duodenostomy; a Roux-en-Y duodenojejunostomy was performed in only one patient. In Table 4 are also reported the frequency and types of percutaneous treatment and medical therapy; among them nutritional support was the main therapy, especially TPN. No TPN-related death occurred in the 51 patients receiving this type of nutrition, but the rate of related complications was high (20%), including ten central line infections; thrombosis or liver failure, on the other hand, were never reported. Twenty patients (29%) received EN, but only three as the sole nutrition, while 12 in addition received TPN, two oral feeding, and three both. Thirty-three patients (48%) maintained oral feeding despite the presence of DF: 19 as the only source of food, two combined with EN, nine with TPN, and three with both. Among the 33 patients maintaining oral feeding, only one death occurred (3%) versus ten deaths among 35 fasting patients (29%; $P<0.001$). Higher daily DF output was often treated by octreotide or somatostatin; the median output in treated patients was 375 mL (range 80–1,500 mL) versus 180 mL (40–220 mL) in untreated patients, but this difference was not statistically significant.

Treatment with octreotide or somatostatin did not affect outcome, time of DF healing, or development of other complications.

About one third of patients (23 cases) were malnourished with a weight loss greater than 10%, and or a serum albumin level <35 g/L (21 cases), and a lymphocyte count <1,500/mL (11 cases). Over two thirds of patients (52) had comorbidities mainly involving the cardiovascular system. Two patients had received preoperative chemotherapy and 12 (17.5%) had duodenal resection line involvement.

In an attempt to detect prognostic factors for DF outcome, we analyzed the influence on mortality of all the variables reported in Tables 1, 2, 3, and 4, nutritional status, and associated comorbidities. Using univariate Cox regression, we found a correlation between mortality and age: the median age of deceased patients was 71 years, range 60–83, versus 64.5 years, range 42–81, for surviving patients; $P=0.017$; hazard ratio per 1 year increase in age is 1.09, 95% CI 1.00–1.20, $P=0.036$. Correlations with mortality were also found for serum albumin level (hazard ratio per 1 g/L increase in serum albumin level is 0.90; 95% CI 0.83–0.99, $P=0.040$), development of further complications, and the need for surgery or TPN in DF management.

In the 11 patients who died, the median number of further complications was 3.5 (range 1–6), and only two patients had only one complication (pulmonary embolism and sepsis, respectively). While in the 57 patients who fully recovered from DF, the median number of further complications was 1.5 (range 0–4), and 17 patients had none at all. No patient without further complications died, while the presence of further complications caused death in over 20% of patients (11/51; $P=0.054$). The recovery time was shorter in patients without complications (median 21 days, range 7–65 days) than in those with complications (median 31 days, range 1–1,035 days), but the difference was not statistically significant.

Table 4 Therapies and Procedures for 68 Duodenal Fistulas

Surgery	27 (39.7%)
One operation	18 (26.5%)
Two operations	6 (8.8%)
Three operations	3 (4.4%)
Percutaneous treatments	
Percutaneous abdominal drainage	15 (22%)
PTBD	4 (6%)
Percutaneous duodenostomy	2 (3%)
Medical therapies	
TPN	51 (75%)
EN	20 (29.4%)
Somatostatin	15 (22%)
Octreotide	14 (20.6%)
Gabexate mesylate	1 (1.5%)

PTBD percutaneous transhepatic biliary drainage, *TPN* total parenteral nutrition, *EN* enteral nutrition

The need for repeat surgery was related to the development of further complications ($P<0.001$), and prolonged the recovery time to 58 days (range 1–1,035 days), versus 25 days (range 7–65 days) ($P=0.004$) in no surgical patients. Furthermore, eight of the 11 (73%) patients who died had undergone repeat surgery versus 19 of the 57 (33%) survivors ($P=0.020$).

The need for intensive management in seriously ill patients was demonstrated also by the use of TPN; in fact, all patients who subsequently died received TPN versus 70% (40) of surviving patients ($P=0.054$).

Discussion

The series of DF after gastrectomy reported in the literature are small and not homogeneous,[1–5] so an accurate description of the natural history and management of this complication is still lacking. In order to reduce the background variability and collect a large number of DFs, the present retrospective multicenter study was performed in 11 Italian centers and was focused on elective gastrectomies for malignancies. Hence the largest series published up to now was collected. Out of 3,785 gastrectomies for malignant diseases 68 DF (1.8%; median 1.6%; range 0.3–6.3) were recorded, confirming data of frequency reported in literature.[1–7] Regarding the causes of DF, it seems that duodenal resection line involvement facilitates the development of this complication. Resection line involvement was reported in the literature in about 1–10% of patients,[14,15] and is generally considered as a cause of high surgical morbidity;[16] in our series of DF patients its frequency was 17.5%.

Concerning technical causes, some authors maintain that DF after SG is more frequently associated with Billroth II reconstruction due to difficult emptying of the afferent jejunal loop.[17] Our data do not support this hypothesis and even suggest the opposite, i.e., that the risk of DF is higher after Roux-en-Y than after Billroth II reconstruction (3.4% vs. 1.1%, respectively). This observation must be interpreted with caution because almost all the participating centers performed only one type of reconstruction without an internal control submitted to the other technique (Table 1).

DF onset is usually delayed (median postoperative day 7), but the variability is very large (range 0–22 days); the occurrence of this complication must therefore be suspected also in outpatients who have recently undergone a gastrectomy if fever or right abdominal pain is present.

In contrast to what was previously reported by other authors,[1] daily fistula output did not affect DF duration or mortality. In our series, DF with abundant output was commonly treated with octreotide or somatostatin but, in contrast with other experiences on other gastrointestinal fistulas,[13] its use did not affect DF closure time or outcome; so we can conclude that this therapy is not indicated for DF.

Many factors can influence the mortality rates, and our study confirms reports by other authors that age, a low serum albumin level, complications, and multiple reoperations are correlated with death.[1,4,7]

The treatment of patients with DF should be aimed at facilitating spontaneous fistula closure. Nowadays, the presence of DF alone no longer leads to death, but the problem is the development of new complications. Since the risk of death is linked to the number of complications arising, particularly sepsis, maximum effort to prevent and promptly treat septic complications is mandatory.[6] Only if sepsis has been adequately managed can spontaneous closure of a fistula take place.[4]

To treat DF and prevent complications, several surgical procedures have been proposed: tube duodenostomy alone or coupled with continuous intraluminal infusion and aspiration,[7] fistula repair with a rectus abdominis muscle flap,[8] or Roux-en-Y duodenojejunostomy to close a large duodenal defect not controlled for more than 6 weeks;[9] occasionally, pancreaticoduodenectomy may be necessary and can be lifesaving.[10] In the present series, Roux-en-Y duodenojejunostomy was performed only in one patient; the other 26 patients were submitted to drainage of peritoneal abscess, duodenal suture, and tube duodenostomy with a 30% of recurrence rate of abdominal sepsis with the need of another surgical procedure. Therefore, surgery is indicated only if necessary to drain an abscess or close a DF that is very large, persistent or otherwise difficult to manage. In the surgical treatment of DFs the main questions are the choice of operative versus non-operative treatment and the timing and type of surgery.[18] It is advisable to avoid surgery on fistulas occurring within 10 days to 6 weeks of the initial operation, although an undrainable abscess, bacteremia, peritonitis, and intestinal bleeding always require emergency surgery. Careful attention must be paid to the choice and management of abdominal drainage in order to avoid its possible migration into the fistula, which hinders spontaneous closure,[19] and to prevent bleeding and formation of new fistulas in neighboring abdominal organs. In the present study, we observed an approximately 20% frequency of new fistulas. Such a high frequency had not been reported previously and is perhaps attributable to the fact that better patient management leads to longer survival associated with a long recovery time; in other words, while healing DF, patients may be at risk of developing new fistulas.

Rossi et al. suggested prophylactic cholecystectomy in cases of surgery for DF because of the high frequency of cholecystitis.[1] Our results do not justify this management, as only one case of cholecystitis was observed in our series.

In the past, many authors suggested nasogastric suction and withholding oral intake,[20] but more recent data demonstrated a better outcome in patients in whom oral intake was maintained.[21] In our series, about half of the patients were able to maintain an oral diet, plus or less combined with EN and/or TPN, and their outcome was better than that of fasting patients, confirming that nasogastric suction and bowel rest are indicated only in the presence of diffuse peritonitis and ileus, whereas oral feeding should always be encouraged. Furthermore, the low rate of cholecystitis in our study might be linked to the preservation of oral feeding.

Several complications of DF commonly reported in the past, such as water and electrolyte loss, acid/base imbalance, and dermatitis, were not observed in our study, probably owing to improved techniques and patient care.

The role of TPN in the treatment of DF is well established, and TPN is routinely used in all cases of high-output and many cases of low-output fistulas. EN could be a good and cheap alternative to TPN, but data reported in the literature show that less than 50% of DF patients tolerate adequate amounts of EN.[5] In our series, about 30% of the patients received EN, but only 25% of them did not need any other nutritional support. Prolonged starvation without careful nutritional support results in severe malnutrition, sometimes leading to superior mesenteric artery syndrome with duodenal obstruction inhibiting DF closure.[20]

Conclusions

In conclusion, our study shows that the features of DF have partially changed with respect to the latest data reported in the literature, which date back about 30 years. Some new characteristics have been acquired and others lost. In general, we can confirm that DF is a rare but serious complication of gastrectomy with a high mortality rate, and improved surgical techniques or the use of staplers have not decreased its frequency; however, newly available therapies such as nutritional support and percutaneous drainage have dramatically reduced the mortality (from 40% to 16% since 1980), and today the presence of DF alone no longer causes death. In fact, some complications, such as fluid, electrolyte, and acid/base imbalance or dermatitis, typically observed in patients with DF in the past, no longer occur. Also the incidence of cholecystitis has decreased, probably because patients are encouraged to eat or have EN, and the practice of fasting or nasogastric suction has been abandoned. Moreover, we demonstrated with this study that oral feeding is related to DF healing.

The onset of DF varies greatly in terms of timing, output, and clinical presentation, and surgeons must always beware the possibility of a DF after gastrectomy because of the high risk associated with a delay in DF diagnosis coupled with the appearance of other complications. The main complication remains sepsis, often requiring repeated surgery and still burdened by a very high mortality. Mortality is highest in the first weeks (median 18 days, range 4–60 days), despite a very long healing time with recurrences also after several months, necessitating the maximum medical effort at an early stage.

Nowadays, medical therapy is preferred to surgery, the latter being indicated only for abdominal sepsis, bleeding, or fistulas in neighboring organs.

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References

1. Rossi JA, Sollenberger LL, Rege RV, Glenn J, Johel RJ External duodenal fistulas. Arch Surg 1986; 121: 908–912.
2. Tarazi R, Coutsofides T, Steiger E, Fazio VW. Gastric and duodenal cutaneous fistulas. World J Surg 1983; 7: 463–473.
3. Edmunds LH jr, Williams GM, Welch CE. External fistulas arising from the gastrointestinal tract. Ann Surg 1960; 152: 445–471.
4. Reber HA, Roberts C, Way LW, Dumphy JE. Management of external gastrointestinal fistulas. Ann Surg 1978; 188: 460–467.
5. Garden OJ, Dikes EH, Carter DC. Surgical and nutritional management of postoperative duodenal fistulas. Dig Dis Sci 1988; 33:30–35.
6. Fazio VW, Coutsoftides T, Steiger E. Factors influencing the outcome of treatment of small bowel cutaneous fistulas. World J Surg 1983; 7: 481–488.
7. Levy E, Cugnenc PH, Frileux P, Hannoun N, Parc R, Huguet C, Loygue J. Postoperative peritonitis due to gastric and duodenal fistulas. Operative management by continuous intraluminal infusion and aspiration: report of 23 cases. Br J Surg 1984; 7: 543–546.
8. Chander J, Lal P, Ramteke VK. Rectus abdominis muscle flap for high-output duodenal fistula: novel technique. World J Surg 2004; 28:179–182.
9. Ujiki GT, Shields TW. Roux-en-Y operation in the management of postoperative fistulas. Arch Surg 1981; 116:614–617.
10. Musicant ME, Thompson JC. The emergency management of lateral duodenal fistula by pancreatoduodenectomy. Surg Gynecol Obstet 1969; 128:108–114.
11. Villar R, Fernàndez R, Gonzàles J, Oliver JM, Parga G, Garcia-Hidalgo E. High-output external duodenal fistula: treatment with percutaneous transhepatic biliary/duodenal drainage. Cardiovasc Intervent Radiol 1996; 19: 371–373.
12. Bianchi A, Solduga C, Ubach M. Percutaneous obliteration of a chronic duodenal fistula. Br J Surg 1988; 7: 572.
13. Hesse U, Ysebaert D, de Hemptinne B. Role of somatostatin-14 and its analogues in the management of gastrointestinal fistulae: clinical data. Gut 2001; 49 Suppl 4:iv11–iv21.
14. Songun I, Bonenkamp JJ, Hermans J, van Krieken JH, van de Velde CJ. Prognostic value of resection line involvement in

patients undergoing curative resection for gastric cancer. Eur J Cancer 1996; 32A: 433–437.
15. Sano T, Mudan SS. No advantage of reoperation for positive resection margin in node positive gastric cancer patients? Jpn J Clin Oncol 1999; 2: 283–284.
16. Keighley MR, Moore J, Lee JR, Mailins D, Thompson H. Perioperative frozen section and cytology to assess proximal invasion in gastro-esophageal carcinoma. Br J Surg 1981; 68: 73–74.
17. de Alves JB. Treatment of the postgastrectomy external duodenal fistula. International Surgery 1968; 49: 248–251.
18. Cozzaglio L, Farinella E, Bagnoli P, Scianameo F, Doci R. Gastrointestinal fistulas. Nutr. Therapy and Met 2007; 25: 113–134.
19. Ravishankar HR, Malik RA, Burnett H, Carlson GL. Migration of abdominal drains into the gastrointestinal tract may prevent spontaneous closure of enterocutaneous fistulas. Ann R Coll Surg Engl 2001; 83: 337–338.
20. Sandler JT, Deitel M. Management of duodenal fistulas. Can J Surg 1981; 24: 124–125.
21. Campos AC, Meguid MM, Coelho JC. Factors influencing outcome in patients with gastrointestinal fistula. Surg Clin North Am 1996; 76: 1191–1198.

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ORIGINAL ARTICLE

Microscopic Findings in Sigmoid Diverticulitis—Changes after Conservative Therapy

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Abstract
Introduction The indications for prophylactic surgery for phlegmonous and covered perforated type of acute sigmoid diverticulitis (SD) are currently matters of debate, and a more conservative approach has been advocated. However, it has not yet been clarified to what extent CT findings indicative of acute SD correlate with histological findings, and it is still uncertain how these findings change in the time interval between initial antibiotic treatment and late elective surgery. The aim of this study was to record time-course changes of inflammation in phlegmonous and abscess-forming diverticulitis after conservative treatment in order to check the indication for surgery.
Material and methods This study included all patients who underwent surgery for CT morphologically phlegmonous and covered perforated SD from January 2002 to June 2007. Two groups were formed to record time-course changes: early elective surgery (7–10 days after antibiotic treatment) and late elective surgery (4–6 weeks after conservative treatment). Exclusion criteria were emergency interventions, free perforations (Hinchey III and IV), recurrent inflammations, and contrast allergy. The extent of the inflammation recorded preoperatively by CT scan was compared with histological findings.
Results A total of 257 patients (142 male and 115 female; mean age, 56.6 years) underwent surgery (116 early elective and 141 late elective) for phlegmonous and covered perforated SD. Phlegmonous SD was seen in 127 cases and covered perforated SD in 130 cases. In the phlegmonous type of SD, early surgery led to conformity with the preoperative stage in 56%, to more extensive findings in 11%, and to subsided inflammation in 33%. Late surgery led to conformity in 0% and to signs of subsided inflammation in 100%. In the covered perforated type of SD, early surgery led to conformity in 90%, to subsided inflammation in 10%, and to milder manifestation in 0%. In contrast, late surgery here led to conformity in 26% of the cases and to subsided inflammation in 74%.
Summary Considerable histological changes can be detected under conservative therapy. The acute inflammation subsides under antibiotic therapy as awaited. It must be clarified whether the phlegmonous form of SD should, in principal, be regarded as an indication for surgery, since it shows early and nearly complete regression of the inflammation. Otherwise, the covered perforated type of SD still shows marked inflammatory changes after conservative therapy in a high percentage of patients and should thus preferably be treated by surgery. However, the clinical appearance of the patient with sigmoid diverticulitis still remains the most important part of decision making.

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Keywords Diverticular disease · Complicated diverticulitis · Indication for surgical intervention

Introduction

Sigmoid diverticular disease is one of the most common diseases in the Western world, and its incidence is rising with the increasing average age of the population.[1,2] Its clinical spectrum extends from asymptomatic diverticulosis through recurrent courses to symptomatic disease with potentially fatal complications. Sigmoid resection with restoration of continuity has been the prevailing modality for treating acute and recurrent sigmoid diverticulitis in recent years and is mostly performed as a laparoscopy-assisted procedure.[3] The indications for this procedure were supported by several consensus recommendations in which resection was favored after the first attack of complicated and the second attack of recurrent diverticulitis.[4,5] These recommendations have been called in question by numerous publications in recent years, and there is still controversy about the stages at which surgery is really indicated.[6,7] Problematic in this connection is the fact that there have been few prospective and no randomized studies to support an evidence-based recommendation. A consensus has thus far only been reached regarding the indication for conservative treatment of diverticulosis as well as uncomplicated diverticular disease and for surgery on detection of free perforation or after the development of stenoses and fistulas. The indications for phlegmonous and covered perforated type of sigmoid diverticulitis (SD) are currently matters of debate, and a more conservative approach has been advocated.[6] This shows the importance of precise pretherapeutic differentiation and staging of patients, thus allowing to select the appropriate treatment in SD. Computed tomography (CT) is gaining increasing importance in staging of acute SD.[8] This valuable diagnostic tool can determine the extent of the disease and can differ between all stages of diverticulitis.[9–12]

However, it has not yet been clarified to what extent CT findings indicative of phlegmonous or covered perforated type of SD correlate with histological findings, and it is still uncertain how these findings change in the time interval between initial antibiotic treatment and late elective surgery. The aim of this prospective study was to record time-course changes of inflammation in phlegmonous and covered perforated diverticulitis after conservative treatment in order to check the indication for surgery.

Material and Methods

Patients and Therapeutic Strategy

From January 2002 to June 2007, all patients with clinically suspected SD have undergone abdominal CT with intravenous and rectal contrast within 12 h after hospitalization at Campus Benjamin Franklin, Charité–Universitätsmedizin Berlin. All patients with signs of acute diverticulitis, and no evidence of free perforation or diffuse peritonitis received an initial i.v. antibiotic dose of sulbactam and ampicillin (1 g of sulbactam and 2 g of ampicillin) for at least 7 days or until normalization of the infection parameters. In patients with a penicillin allergy, antibiotic treatment was done with ciprofloxacin and metronidazole. This antibiotic regimen was uniformly applied over the entire study period. Any intra-abdominal abscess detected was drained by interventional techniques when suitable. In the further course, patients were then submitted to early or late elective sigmoid resection with restoration of continuity (laparoscopic or conventional procedure) and descendorectostomy. All patients underwent diagnostic colonoscopy after abatement of the acute inflammation and before late elective sigmoid resection to exclude other conditions like bowel cancer. The aim of early elective surgery (7–10 days after initial antibiotic treatment) was pursued between January 2002 and January 2004. As of 2004, we changed our treatment regimen because of a relatively high complication rate after early elective sigmoid resection.[13] Instead, from January 2004 to June 2007, patients requiring surgery underwent late elective sigmoid resection 4–6 weeks after the initial antibiotic treatment in the inflammation-free period. If symptoms persisted or the infection exacerbated under ongoing antibiosis, patients continued to undergo early elective surgery or emergency surgery. We have used these two chronological groups to analyze the data of our study. Data were prospectively recorded from admission to discharge after surgery. The preoperative CT morphological findings were compared with the histological findings. Exclusion criteria were emergency interventions, a chronic recurrent or free perforated diverticulitis, allergy to contrast medium, colorectal cancer during the admission period or a known history of colorectal cancer, inflammatory bowel disease, infectious colitis or immunosuppression. Perioperative data were prospectively documented (clinical examination, CT findings, histological findings, and postoperative course).

Abdominal CT Examination

The CT examination was performed with oral [(30 ml of Gastrografin® (Schering, Berlin, Germany) in 1 l of H_2O], intravenous [150 ml of Ultravist 300® (Schering, Berlin, Germany)], and transrectal contrast (200 ml of Peritrast®-RE/36). An initial scout view (topogram) was used for planning the actual examination. During intravenous contrast application (flow velocity, 3 ml/s), spiral acquisition was performed from the diaphragm to the pelvic floor. Examination parameters were as follows: the computer tomography scanner Somatom Sensation 16 (Siemens AG

Medical Solutions, Erlangen, Germany), a slice thickness of 16×1.5 mm, and secondary reformatting in coronary orientation. Forms of diverticulitis distinguished by CT scan are shown in Table 1. All CT findings were interpreted by three experienced radiologists. These radiologists had the task of standardizing the extent of inflammation on the basis of the classification of Hansen and Stock.[14] This was not a control for interobserver variability. Here, stage 0 denotes irritation-free diverticulosis with detection of only gas- or contrast-filled diverticula and no inflammatory signs in the CT. Stage I is the stage of acute uncomplicated diverticulitis. The CT morphological correlative here is bowel wall thickening. Stage II designates acute complicated diverticulitis and is further subdivided into stages IIa, IIb, and IIc according to the severity of inflammation. Stage IIa involves peridiverticulitis or phlegmonous diverticulitis with spread of the bowel inflammation to the pericolic fatty tissue. The CT shows inflammatory infiltration of pericolic fat. Stage IIb is characterized by CT morphological detection of a covered perforation with or without a mesocolic or retroperitoneal abscess or an abscess in the minor pelvis. In stage IIc, the CT detects free air and/or fluid as the correlative of free bowel perforation. Stage III is the stage of chronic diverticulitis. The typical CT sign of chronic inflammation is bowel wall thickening, sometimes with stenosis or fistulas.

Surgical Technique

The sigmoid resection was assisted laparoscopy as a routine procedure without loop ileostomy in all patients with the need for surgery. Four experienced surgeons performed the operation with patients in the lithotomy position. Supraumbilical (camera) trocars were placed medial to the superior iliac spine on both sides and 10 cm cranial to the symphysis at the median line. After laparoscopic mobilization of the left hemicolon, the left flexure was mobilized in relation to bowel mobility. The inferior mesenteric artery was left as is. The colon was severed in the upper third of the rectum by an endocutter. Extra-abdominal mobilization of the colon was achieved by widening the left hypogastric trepanation opening to 4–5 cm, and the oral resection border was set a hand-breadth proximal to the inflammatory tumor. The mean length of the resected bowel specimen was 24.5±3.2 cm. A tension-free anastomosis was created with a stapler (size, 29–33 mm). The surgical technique remained unaltered during the entire study period.

Pathology

The histopathological workup of colon specimens was routinely performed by the Institute of Pathology, Charité–Universitätsmedizin Berlin, Campus Benjamin Franklin. Histological criteria were also recorded and used to establish histological forms of diverticulitis (Table 2). Evaluation of the histopathological specimens was done by two experienced pathologists familiar with the classification of Hansen and Stock, who applied this classification according to the standardized classification of the extent of the inflammation. This score was then used for correlation with the CT morphological findings. Attention was focused particularly on checking for an acute or chronic inflammation and for pericolic changes (e.g., abscesses).

Statistics

Statistical significance was calculated by using the rank sum test, t test and chiχ^2 test ($p<0.05$=statistically significant). If not otherwise specified, the values are means±standard deviations.

Results

Patient Characteristics

A total of 257 patients (142 male and 115 female) underwent surgery for phlegmonous and abscess-forming (covered perforation) diverticulitis. Of these, 116 patients underwent early and 141 late elective surgery. Phlegmonous type of SD was seen in 127 patients, 55 of whom had early and 72 late elective surgery. Of 130 patients with CT morphological covered perforated diverticulitis, 61 had early and 69 late elective surgery. The mean age of all patients was 56.6 years. The patients did not differ in their demographic data. There were no differences in the American Society of Anesthesiology (ASA) classification

Table 1 CT Morphological Forms of Diverticulitis

Forms of diverticulitis	CT Scan
Irritation-free diverticulosis	Gas- or contrast-filled diverticulum
Mild diverticulitis	+Intestinal wall thickening
Phlegmonous diverticulitis	+Inflammatory reaction in pericolic fatty tissue
Covered perforated diverticulitis	+Mesocolic or retroperitoneal abscess, lower pelvis abscess
Free perforated diverticulitis	Free air, free fluid, abscesses where applicable
Chronic recurrent diverticulitis	Intestinal wall thickening, stenosis or fistula

Table 2 Histological forms of Diverticulitis

Histological forms	Description
Mild diverticulitis	Local inflammation of intestinal wall
Phlegmonous diverticulitis	Acute inflammation of pericolic fatty tissue
Covered perforated diverticulitis	Perforation (covered), (micro-) abscesses
Free perforated diverticulitis	Free perforation with purulent or fecal peritonitis
No signs of acute inflammation	Signs of subsided inflammation, wall thickening

(1.85) or the frequency of comorbidity (Table 3). Sigmoid resection was performed as an early elective procedure 6.7± 1.8 days after initial antibiotic treatment and as a late elective procedure after a mean of 36.4±5.2 days. Antibiotic therapy lasted 7.6±1.2 days for early and 8.4±1.1 days for late elective surgery. Six patients had to undergo surgery because of symptom progression in the first 4 days under conservative therapy (two patients between 2001 and 2003 and four between 2003 and 2006). These patients were not included in the study. Fifteen patients were drained by interventional techniques in cause of an intra-abdominal abscess.

Histological Findings of Patients with Phlegmonous Diverticulitis

The histological workup of surgical specimens from patients with phlegmonous diverticulitis who underwent early elective surgery disclosed 31 cases (56%) with acute inflammation and pericolic fat infiltration indicative of pericolic phlegmon. Six cases (11%) showed more extensive inflammation with covered perforation and/or purulent abscess-forming peridiverticulitis. In 18 cases (33%), diverticulosis was detected with signs of subsided inflammation of single diverticula. In the group of patients with CT morphological phlegmonous diverticulitis and late elective surgery, the histological findings revealed no more signs of acute inflammation in all 72 patients. Here, diverticulosis was detected with signs of subsided inflammation of single diverticula.

Histological Findings of Patients with Abscess-Forming (Covered Perforation) Diverticulitis

In the group of 61 patients with CT morphological abscess-forming (covered perforation) diverticulitis and early elective surgery, we found a correlation with the preoperative stage in 55 patients (90%). In six cases (10%), diverticulosis was detected with signs of subsided inflammation of single diverticula. In the group of 69 patients with late elective surgery, we found a correlation with the preoperative stage in only 18 patients (26%) and an overstaging in 51 patients (74%), who had histologically no signs of acute inflammation.

Conformity Between CT and Histological Findings

CT stage IIa showed conformity with microscopic findings in 56% of patients with early elective surgery and in 0% of those with late elective surgery. Conformity was found in 90% of CT stage IIb patients with early elective surgery and in 26% of those with late elective surgery. The conformity of CT examination in correlation to histological findings is shown in Table 4.

Discussion

Acquired diverticular disease of the colon has been estimated to occur in 30% of the population over the age of 45, with 10–25% of these individuals developing symptomatic diverticulitis.[15,16] Of the patients who develop symptomatic diverticulitis, 15–20% develop significant complications such as perforation, abscess, phlegmon, or obstruction.[16–18] Sigmoid resection with restoration of continuity has been the prevailing modality for treating acute and recurrent SD in recent years and is mostly performed as a laparoscopy-assisted procedure.[3,19] The indications for this procedure were supported by several consensus recommendations in which resection was favored after the first attack of complicated and the second

Table 3 Patient Characteristics

	Early elective surgery	Late elective surgery	Statistical significance
Patients	116	141	NS
Age	55.8	57.4	NS
Comorbidity	51	64	NS
No comorbidity	65	77	NS
ASA	1.8	1.9	NS
m/f	64/52	78/63	NS

Table 4 Conformity Between CT and Histological Findings

CT Scan	Histological forms of diverticulitis				Conformity with histological findings (%)
	Phlegmonous diverticulitis	Covered perforated diverticulitis	No acute inflammation	*n*	
Phlegmonous diverticulitis					
Early surgery	31	6	18	55	56
Late surgery	0	0	72	72	0
Covered perforated diverticulitis					
Early surgery	0	55	6	61	90
Late surgery	0	18	51	69	26

attack of recurrent diverticulitis.[4,5] These recommendations have been called into question by numerous publications in recent years,[6,7] and the indication and time for surgery in cases of phlegmonous and abscess-forming (covered perforation) SD are currently controversial issues. While the necessity for an emergency intervention may be regarded as a consensus view in the stages of free perforation, unanimity no longer prevails for the stages of abscess-forming (covered perforation) or transmural phlegmon. According to EAES guidelines, surgery is indicated after the first attack of complicated SD.[4] No strict definition exists about the disease stages that should be defined as complicated diverticulitis. There is no doubt that a free perforation, stenosis, or fistulas should be regarded as a complicated disease. The questions remains whether the phlegmonous form of SD should also be regarded as a complicated stage as in the study of Hansen and Stock.[14]

However, Janes et al.[6] showed that only about one third of the patients with an acute attack of SD have a recurrence and that the probability of perforation as the basis for sigmoid resection is highest during the first attack. The American Society of Colon and Rectal Surgeons guidelines likewise provide no general indication for surgery after the first attack of complicated sigmoid diverticulitis.[5] It is therefore necessary to reconsider the original EAES consensus indication for elective surgery after the first attack of complicated SD.

To better clarify the surgical indication, it is necessary to know whether the CT-detected wall phlegmon or abscess forming (covered perforation) is also reflected in the histological examination and to determine what time-course changes occur under conservative antibiotic therapy. Thus, the aim of this study was to evaluate histological time-course changes in phlegmonous and abscess-forming (covered perforation) SD in correlation to CT morphological findings.

This study was prompted by a change in our routine procedure several years ago: Early elective surgery within a few days was abandoned in favor of late elective resection several weeks after conservative therapy and antibiotic treatment

In our study, the preoperative stage conformed to the histological findings in only about half of the patients who had early elective surgery in the stage of transmural phlegmon. In fact, one third of the patients only showed signs of subsided inflammation. This suggests CT over-rating with regard to phlegmonous inflammatory changes in the mesosigmoid but may also be attributable to successful initial drug therapy of SD. Here, precise assessment would require direct comparison with immediate bowel resection after the CT examination, which does not appear to be clinically justifiable, since markedly increased morbidity must be expected in the acute inflammatory stage.[7,20] The further follow-up of this early inflammatory stage in our study supports the assumption that conservative therapy leads to progressive regression of the inflammation in SD. Nearly 100% of the patients with late elective surgery had no signs of an acute inflammatory reaction. This raises the question of whether phlegmonous diverticulitis should really be assessed as a complicated stage of the disease or whether it reflects a normal inflammatory reaction that is easy to cure and may be treated by conservative measures. On the other hand, none of the patients in this group achieved a complete cure of the disease. Residues of subsided inflammation were always detectable, and the colon thus remained morphologically altered. The data presented here cannot be used to elucidate the possible clinical relevance of these morphological residues. Prospective long-term studies are necessary for this purpose.

Unlike patients with phlegmonous inflammation, those with advanced inflammation and local abscess formation who had early elective surgery showed high conformity between the preoperative classification and the histological

findings. Barely 10% had detectable regression of the inflammation, which may be assessed as an expression of its severity. During follow-up, more than 70% of the patients in this group likewise showed a marked histological change from an abscess-forming to a subsided inflammation. Even then, the remaining patients showed at least microscopic evidence of mesosigmoid abscess formation. Thus, long-term conservative treatment is not promising in a large group of these patients. Investigations of the histological time-course changes in diverticulitis confirm the assumption of other authors that late elective surgical resection should be performed after conservative treatment, since the local inflammatory reactions are then regressive and thus cause fewer complications.[13,21]

Conclusion

We were able to show that major histological changes can be detected under conservative therapy. Antibiotic therapy leads to marked regression of the acute inflammation in both the phlegmonous and abscess-forming types of diverticulitis. However, all patients retain residues of subsided inflammation, whose impact on the long-term course of the disease cannot be definitively evaluated. It must be clarified whether the phlegmonous form of SD should in principal be regarded as an indication for surgery, since it shows early and nearly complete regression of the inflammation. The results of this study have altered our therapeutic management to the extent that, in patients with phlegmonous diverticular disease, the indication for surgery is established only very conservatively after the first attack. Here, we recommend surgery by assessing each case on the basis of individual personal characteristics (age, general condition, and number/frequency of diverticulitis attacks). On the other hand, the abscess-forming type of diverticulitis still shows marked inflammatory changes in a high percentage of patients even after conservative therapy and should thus preferably be treated by surgery. A prospective randomized long-term study should be conducted to reliably assess residual morphological changes in the colon for their surgical indication and clinical significance. However, the clinical appearance of the patient with SD still remains the most important part of decision making.

References

1. Jun S, Stollmann N. Epidemiology of diverticular disease. Best Pract Res Clin Gastroenterol 2002;16:529–542.
2. Parks TG. Natural history of diverticular disease of the colon. Clin Gastroenterol 1975;4:53–69.
3. Jacobs M, Verdeja JC, Goldstein HS. Minimally invasive colon resection (laparoscopic colectomy). Surg Laparosc Endosc 1991;1:144–150.
4. Kohler L, Sauerland S, Neugebauer E. Diagnosis and treatment of diverticular disease: results of a consensus development conference. The Scientific Committee os European Association for Endoscopic Surgery. Surg Endosc 1999;13:430–436.
5. Wong WD et al. Practice parameters for the treatment of sigmoid diverticulitis—supporting documentation. The Standards Task Force. The American Society of Colon and Rectal Surgeons. Dis Colon Rectum 2000;43:290–297.
6. Janes S, Meagher A, Frizelle FA. Elective surgery after acute diverticulitis. Br J Surg 2005;92:133–142.
7. Rafferty J, Shellito P, Hyman NH, Buie WD. Practice parameters for sigmoid diverticulitis. Dis Colon Rectum 2006;49:939–944.
8. Ambrosetti P, Becker C, Terrier F. Colonic diverticulitis: impact of imaging on surgical management—a prospective study of 542 patients. Eur Radiol 2002;12(5):1145–1149.
9. Johnson CD, Baker ME, Rice RP. Diagnosis of acute colonic diverticulitis: comparison of barium enema and CT. AJR Am J Roentgenol 1987;148:541–546.
10. Shrier D, Skucas J, Weiss S. Diverticulitis: an evaluation by computed tomography and contrast enema. Am J Gastroenterol 1991;86:1466–1471.
11. Eggesbo HB, Jacobsen T, Kolmannskog F. Diagnosis of acute left-sided colonic diverticulitis by three radiological modalities. Acta Radiol 1998;39:315–321.
12. Cho KC, Morehouse HT, Alterman DD. Sigmoid diverticulitis: diagnostic role of CT—comparison with barium enema studies. Radiology 1990;176:111–115.
13. Reissfelder C, Buhr HJ, Ritz JP. What is the optimal time of surgical intervention after an acute attack of sigmoid diverticulitis: early or late elective laparoscopic resection? Dis Colon Rectum 2006;49(12):1842–1848.
14. Hansen O, Stock W. Prophylaktische Operation bei der Divertikelkrankheit des Kolons—Stufenkonzept durch exakte Stadieneinteilung. Langenbecks Arch Chir Suppl 1999;II:1257.
15. Rothenberger DA, Wiltz O. Surgery for complicated diverticulitis. Surg Clin North Am 1993;73:975–992.
16. Antolovic D, Reissfelder C, Koch M, Mertens B, Schmidt J, Büchler MW, Weitz J. Surgical treatment of sigmoid diverticulitis—analysis of predictive risk factors for postoperative infections, surgical complications, and mortality. Int J Colorectal Dis 2009;24:577–584.
17. Al-Sahaf O, Al-Azawi D, Fauzi MZ et al. Early discharge policy of patients with acute colonic diverticulitis following initial CT scan. Int J Colorectal Dis 2008;23:979–984.
18. Favuzza J, Friel JC, Kelly JJ, Perugini RC, Counihan TC. Benefits of laparoscopic peritoneal lavage for complicated sigmoid diverticulitis. Int J Colorectal Dis 2009;24:797–801.
19. Schwandner O, Farke S, Fischer F, Eckmann C, Schiedeck TH, Bruch HP. Laparoscopic colectomy for recurrent and complicated diverticulitis: a prospective study of 396 patients. Langenbecks Arch Surg 2004;389:97–103.
20. Siewert JR, Huber FT, Brune IB. Early elective surgery of acute diverticulitis of the colon. Chirurg 1995;66:1182–1189.
21. Aydin HN, Remzi FH. Diverticulitis: when and how o operate. Dig Liver Dis 2004;36:435–445.

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ORIGINAL ARTICLE

Short-Term Outcomes of Laparoscopic Colectomy for Transverse Colon Cancer

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Abstract
Background The role of laparoscopic surgery for transverse colon cancer (TCC) remains controversial. This study aimed to evaluate the safety of laparoscopic resection of TCC.
Methods Fifty-three patients undergoing laparoscopic resection of TCC (group A) were compared with 39 patients undergoing open resection of TCC (group B) and 200 patients undergoing laparoscopic resection of ascending or descending colon cancer (group C).
Results Mean operating time was longer (224 vs. 157 min), and mean estimated blood loss was lower (40 vs. 79 ml) in group A than in group B, but these were similar in groups A and C. The rates of conversion to open surgery were similar in groups A and C (1.9% vs. 1.0%). Tumor stage was more advanced in group B than in group A. All patients in groups A and B underwent pathologic R0 resection. The rates of postoperative complications did not differ significantly between groups (9.4% vs. 7.7% vs. 5.0%). Time to flatus (1.7 vs. 2.5 days), time to liquid diet (2.4 vs. 5.3 days), and hospital stay (12 vs. 15 days) were significantly shorter in group A than in group B, but similar in groups A and C.
Conclusions Laparoscopic resection for TCC can be performed safely with similar short-term postoperative outcomes seen for colon cancer at other sites. Laparoscopic resection may be associated with faster gastrointestinal recovery and shorter length of hospital stay, compared with open surgery.

Keywords Transverse colon cancer · Laparoscopic surgery · Short-term outcomes

Introduction

The safety and oncologic efficacy of laparoscopic surgery for the treatment of colon cancer have been demonstrated in randomized controlled trials (RCTs), which have reported short-term benefits such as reduced blood loss, less intense postoperative pain, and faster gastrointestinal recovery.[1–4] Similar long-term 5-year survival was also recently confirmed in the COST study group trial.[5] However, laparoscopic surgery for transverse colon cancer (TCC) has been considered technically demanding, and it has therefore been excluded from previous RCTs.[1–4] The present study compared the short-term and pathologic outcomes of laparoscopic resection of TCC with those following open resection of TCC or laparoscopic resection of colon cancer at other sites to demonstrate the feasibility of laparoscopic surgery for the treatment of TCC.

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Methods

Patient Selection

The present study included TCCs located between the hepatic and splenic flexures with ligation of at least the right or left branch of the middle colic artery (MCA), or

both, at their origins. The basic indications for laparoscopic surgery in our institution included no evidence of bulky tumor, no evidence of invasion to adjacent organs, no evidence of ileus, no evidence of lymph node metastasis in the root of the MCA, and no evidence of synchronous resectable liver metastasis. However, the final indication for laparoscopy was at the surgeon's discretion. Fifty-three patients underwent laparoscopic surgery for TCC at our institution from July 2005 to October 2009 and were included in the present study (group A). During the same period, 75 patients underwent open surgery for TCC. Cases with non-curative resection (19 cases) or with synchronous resection of other organs (17 cases) were excluded, and 39 patients who underwent open resection for TCC were thus included in further analyses (group B). The reasons for using an open approach in these patients were suspected invasion to adjacent organs in two patients, suspected lymph node metastasis in the root of the MCA in three patients, previous colorectal cancer resection in two patients, previous history of open upper major abdominal surgery in three patients, ileus in one patient, clinical N2 in 11 patients, and surgeon's discretion in 17 patients. Furthermore, 200 patients who underwent laparoscopic surgery for adjacent colon cancer (i.e., cancer in the ascending or descending colon) during the same period (group C) were also compared. Preoperative staging was based on the results of colonoscopy, barium enema, and computed tomography. Indian ink tattooing was performed in patients undergoing laparoscopic surgery, except those with advanced tumors. Age, gender, body mass index, tumor staging, duration of operation, amount of blood loss, conversion to open surgery, and information on postoperative pathology, hospital stay, 30-day morbidity, and mortality were prospectively recorded.

Surgical Procedure

In the present study, right hemicolectomy was defined as a procedure requiring division of the ileocolic, right colic (when present), and right branch of the middle colic vessels at their origins. Left hemicolectomy was defined as a procedure requiring division of the left colic and the left branch of the middle colic vessels at their origins. Transverse colectomy was defined as a procedure requiring the division of the middle colic vessels at their origins. The procedure was chosen based on the location and extent of the tumor. A five-port technique was employed. For right hemicolectomy, the surgeon and the camera operator stood to the left of the patient, with the first assistant between the legs of the patient. First, the peritoneum at the base of the small intestinal mesentery was incised, and the dissection between the ascending mesocolon and the retroperitoneum was performed. The duodenum and pancreas head were

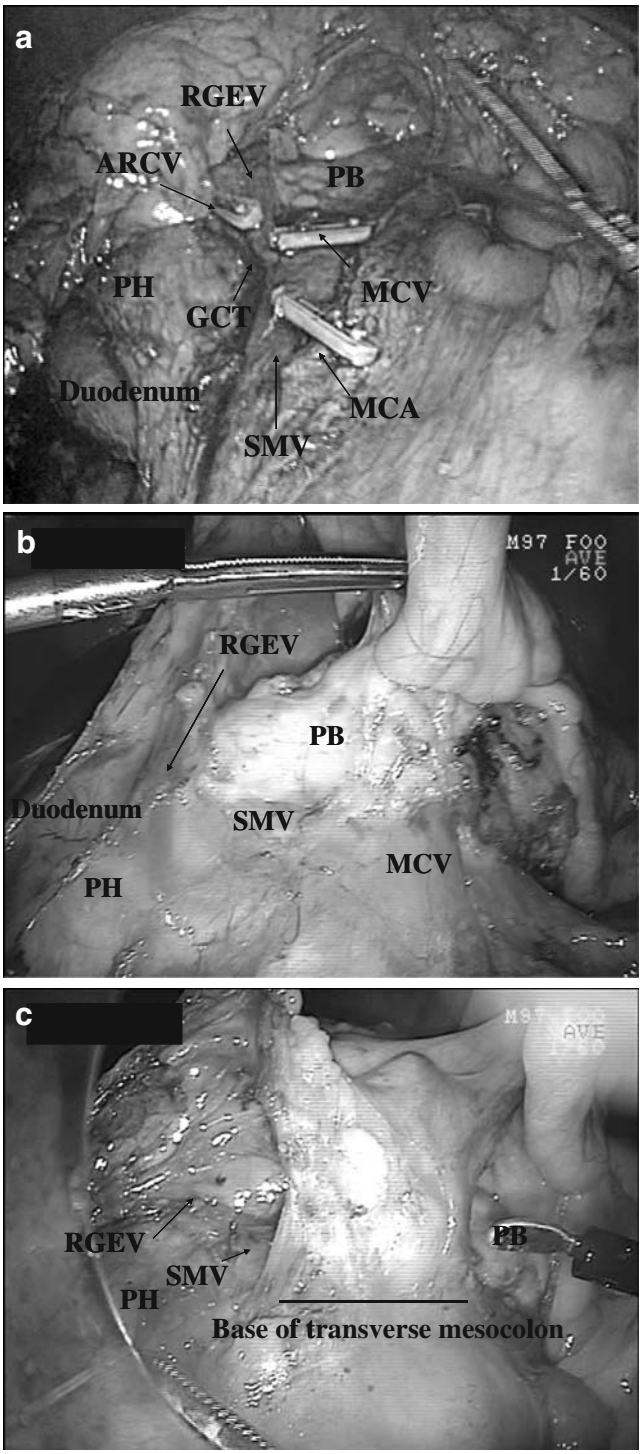

Figure 1 **a** Lymph node dissection at the origin of the middle colic vessels in right hemicolectomy. **b** and **c** Lymph node dissection at the origin of the middle colic vessels in transverse colectomy. **b** Following splenic flexure mobilization, the inferior border of the pancreas was dissected from the transverse mesocolon, and the superior mesenteric vein was exposed from a cranial direction. **c** Base of the transverse mesocolon was gradually skeletonized from a caudal direction after perception of the visual depth and narrowing the width. *SMV* superior mesenteric vein, *MCA* middle colic artery, *MCV* middle colic vein, *GCT* gastrocolic trunk, *ARCV* accessory right colic vein, *RGEV*, right gastroepiploic vein, *PH* pancreas head, *PB* pancreas body.

Table 1 Patient Characteristics

	Group A (n=53)	Group B (n=39)	Group C (n=200)	P value (A vs. B)	P value (A vs. C)
Mean age (year) (range)	66 (36–88)	62 (24–86)	66 (33–90)	0.3003	0.9251
Male/female ratio	32/21	21/18	105/95	0.6698	0.3534
Mean body mass index (kg/m^2)	22.7 (16.6–27.7)	21.7 (16.3–30.4)	23.1 (15.4–33.3)	0.0519	0.5580
Previous abdominal surgery	18 (34%)	13 (33%)	64 (32%)	1	0.8691

dorsally dissected from the mesocolon. The pedicle of the ileocolic vessels was then identified, and the ventral aspect of the caudal portion of the superior mesenteric vein (SMV) was exposed. The vessels were skeletonized in a caudal to cranial direction along the SMV and divided at their origins (Fig. 1a). For left hemicolectomy, the surgeon and the camera operator stood to the right of the patient, with the first assistant to the left or between the legs of the patient. Medial-to-lateral retroperitoneal dissection and division of the left colic artery were performed. The omentum was then transected, and the omental bursa was entered, and splenic flexure mobilization was performed. The left branch of the middle colic vessels was then identified at the inferior border of the pancreas and divided at its origin. For transverse colectomy, either splenic or hepatic flexure mobilization was performed in most cases. The omental bursa was entered, and the transverse mesocolon was dissected from the inferior border of the pancreas (Fig. 1b). The base of the transverse mesocolon was then stretched and dissected from a caudal direction, and the middle colic vessels were skeletonized and divided at their origins (Fig. 1c). The camera port was extended to about 4 cm, and the specimen was extracted through this port. Functional end-to-end anastomosis was then performed extracorporeally.

Statistical Analysis

Differences between the groups were analyzed using Fisher's exact test, χ^2 test, or Mann–Whitney U test, as appropriate. Analysis was performed using SPSS software (Chicago, IL, USA), and P values ≤ 0.05 were considered significant.

Results

Patient characteristics are summarized in Table 1. There were no significant differences between groups in terms of mean age, gender, body mass index, and history of previous abdominal surgery, although the body mass index in group B tended to be lower than in group A (21.7 vs. 22.7 kg/m^2). There were 155 ascending colon cancers and 45 descending colon cancers in group C.

The operative procedures performed for TCC are summarized in Table 2. Right hemicolectomy was the most frequently used procedure. The operative procedures did not differ significantly between groups A and B.

The surgical and pathologic outcomes are summarized in Table 3. Mean operating time was significantly longer (224 vs. 157 min), and mean estimated blood loss was significantly lower (40 vs. 79 ml) in group A than in group B, but these were similar in groups A and C. Conversion to open surgery was required in one patient in group A and two in group C (1.9% vs. 1.0%). The reason for conversion in group A was to dissect firm lymph nodes at the root of the MCA, which were finally shown to be metastatic. The reasons in group C were severe adhesion in one case and bleeding in the other. T-stage was more advanced in group B than in group A, but N-stages were similar in all groups. Mean proximal resection margin was similar in groups A and B (18 vs. 22 cm), but significantly larger in group A than in group C (18 vs. 12 cm). Mean distal resection margin was significantly smaller in group A than in group B (10 vs. 11 cm), although the difference was only 1 cm. Mean number of lymph nodes harvested was significantly smaller in group A than in group B (17 vs. 23), but was similar in groups A and C (17 vs. 18). Pathologic R0 resection was performed in all patients in groups A and B. In group C, four patients underwent R2 resection due to unresectable multiple liver metastases in three patients and para-aortic lymph node metastasis in one patient.

The postoperative outcomes are summarized in Table 4. The rates of postoperative complications did not differ significantly between groups. There was no anastomotic leakage and no mortality in any group. Time to flatus (1.7 vs. 2.5 days), time to liquid diet (2.4 vs. 5.3 days), and mean length of hospital stay (12 vs. 15 days) were all

Table 2 Operative Procedures

	Group A (n=53)	Group B (n=39)	P value
Right hemicolectomy	29 (55%)	27 (69%)	0.3346
Left hemicolectomy	12 (23%)	7 (18%)	
Transverse colectomy	12 (23%)	5 (13%)	

Table 3 Surgical and Pathologic Outcomes

	Group A (n=53)	Group B (n=39)	Group C (n=200)	P value (A vs. B)	P value (A vs. C)
Mean operating time (min) (range)	224 (130–416)	157 (89–271)	205 (94–338)	<0.0001	0.1261
Mean estimated blood loss (ml) (range)	40 (0–330)	79 (3–590)	28 (0–740)	<0.0001	0.4364
Conversion to open surgery	1 (1.9%)		2 (1.0%)		0.5076
T-stage				<0.0001	0.2942
Tis	3 (6%)	0 (0%)	14 (7%)		
T1	15 (28%)	0 (0%)	55 (28%)		
T2	11 (21%)	3 (8%)	34 (17%)		
T3	14 (26%)	29 (74%)	77 (39%)		
T4	10 (19%)	7 (18%)	20 (10%)		
N-stage				0.8474	0.5551
N0	33 (62%)	22 (56%)	134 (67%)		
N1	15 (28%)	13 (33%)	55 (28%)		
N2	5 (9%)	4 (10%)	11 (6%)		
Mean proximal resection margin (cm) (range)	18 (4.5–45)	22 (6–66)	12 (3–40)	0.1153	<0.0001
Mean distal resection margin (cm) (range)	10 (4–32)	11 (5–21)	10 (2–40)	0.0461	0.3476
Mean no. of lymph nodes harvested (range)	17 (7–35)	23 (8–40)	18 (3–46)	0.0002	0.2092
Pathological R0	53 (100%)	39 (100%)	196 (98%)		0.5824

significantly shorter in group A than in group B, but similar in groups A and C.

Discussion

Several RCTs have demonstrated that laparoscopic surgery for colon cancer can achieve favorable short-term results and similar postoperative survival to open surgery.[1–5] However, TCC has been excluded from RCTs, and there have been very limited studies showing the feasibility of laparoscopic surgery for TCC.[6–8] There may be several reasons for the exclusion of TCC from previous RCTs. First, TCC is less common than tumors at other colon sites, with a reported incidence of around 10%.[9–11] Second, the proper operative procedures for TCC vary depending on the relative location of the tumor. Third, lymph node dissection around the middle colic vessels is technically demanding because of the proximity to the pancreas and duodenum. Compared with previous studies,[6–8] the present study reported the short-term outcomes in a relatively large number of patients undergoing laparoscopic surgery for TCC.

In this study, early TCC was treated almost exclusively by laparoscopy, but advanced TCC was often treated using an open approach, at the surgeon's discretion. Thus, the laparoscopic and open groups exhibited different characteristics. This may explain the smaller number of lymph nodes harvested and the smaller distal resection margin in the laparoscopic group compared with the open group. However, the average number of lymph nodes removed in the laparoscopic group exceeded 12, which was the recom-

Table 4 Postoperative Outcomes

	Group A (n=53)	Group B (n=39)	Group C (n=200)	P value (A vs. B)	P value (A vs. C)
Postoperative complication	5 (9.4%)	3 (7.7%)	10 (5.0%)	1	0.3218
Wound infection		1 (2.6%)	3 (1.5%)		
Persistent ileus	3 (5.7%)	2 (5.1%)	4 (2.0%)		
Enteritis			1 (0.5%)		
Anastomotic bleeding	2 (3.8%)		2 (1.0%)		
Time to flatus (postoperative days) (range)	1.7 (0–4)	2.5 (1–4)	1.7 (0–4)	<0.0001	0.4157
Time to liquid diet (postoperative days) (range)	2.4 (2–9)	5.3 (3–14)	2.3 (2–17)	<0.0001	0.9404
Mean length of hospital stay (days) (range)	12 (6–29)	15 (9–24)	12 (6–52)	<0.0001	0.7034

mended number to ensure adequate sampling.[12] Furthermore, the number exceeded that reported in several other RCTs[1–4,13] and was not significantly different from that in the group undergoing laparoscopic surgery for colon cancer at other sites in this study. Together with examinations showing pathologic R0 in all patients undergoing laparoscopic surgery for TCC, our results suggest that laparoscopic surgery was a safe and feasible procedure for TCC, with no oncological disadvantages in well-selected patients.

The present study also demonstrated significantly lower blood loss, faster gastrointestinal recovery, and shorter hospital stays associated with laparoscopy, compared with open surgery. These results are in agreement with those of previous RCTs of colon cancer at other sites.[1–4] Mean operating time tended to be longer for laparoscopic surgery for TCC, compared with that for laparoscopic surgery of ascending or descending colon cancer, but the difference was not significant. The overall postoperative complication rates were comparable between groups, and no serious complications or operative mortality occurred. These results suggest that laparoscopic surgery for TCC has some short-term advantages, compared with open approaches, as found for laparoscopic surgery of colon cancer at other sites.

The conversion rate to open surgery in this study was only 1.9%. Previous studies have shown increases in operating time, hospital stay,[13] and more importantly, morbidity and short-term survival[2,5,14] for converted, compared with laparoscopically completed procedures. Analysis of the CLASICC Trial data demonstrated that locally advanced cancer, identified by an increased distance of tumor spread from the muscularis propria, was an independent risk factor for conversion.[15] Accurate evaluation of tumor spread by preoperative diagnostic imaging allowed exclusion of such difficult cases from laparoscopic surgery in the present study. In addition, all operations in our institution were supervised or performed by a highly experienced, board-certified laparoscopic colorectal surgeon, whose learning curve had already reached its plateau.[16] These factors may help to explain the low conversion rate, as well as the operating time and low blood loss.

Regarding the technical aspects of laparoscopic surgery for TCC, lymph node dissection around the middle colic vessels is a demanding procedure. This is partly due to the highly variable anatomy of the middle colic vessels.[17,18] In addition, the root of the transverse mesocolon is broadly based and close to the pancreas, duodenum, and SMV or superior mesenteric artery. Although the approach for the skeletonization of the middle colic vessels differed according to the operative procedure used (i.e., right/left hemicolectomy or transverse colectomy), exposure of these anatomical landmarks (i.e., pancreas, duodenum, and SMV) is thought to be important in laparoscopic surgery, in which tactile sensation is lacking. In right hemicolectomy, the duodenum and pancreas head are initially dissected from the transverse mesocolon, and the ventral aspect of the SMV is skeletonized from the caudal to cranial direction. Because splenic flexure mobilization is thought to be a difficult procedure,[19] this approach may be the safest method and can be used in most TCCs. Due to our preference for this procedure, transverse colectomy was often accompanied by splenic flexure mobilization. Although transverse colectomy is more technically demanding, our results suggest that it can be performed safely by experienced laparoscopic surgeons.

There were several important limitations associated with this study. First, selection bias and the different backgrounds of patients undergoing laparoscopic and open surgery for TCC made simple comparisons and the drawing of definitive conclusions difficult. Second, this was a retrospective study using prospectively collected data from a single cancer-specializing center, and further multicenter, randomized studies are needed to assess the safety and true incidence of recurrence. However, the results of the current study suggest that laparoscopic surgery can be performed safely in patients with TCC, given careful case selection and surgical expertise, with similar short-term outcomes to those associated with laparoscopic surgery for cancer at other colon sites. Laparoscopic surgery for TCC demonstrated the benefits of lower blood loss, faster gastrointestinal recovery, and shorter hospital stay, compared with open surgery.

Disclosures We have no conflicts of interest or financial ties to disclose.

References

1. Lacy AM, Garcia-Valdecasas JC, Delgado S, Castells A, Taura P, Pique JM, Visa J. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet 2002;359:2224–2229.
2. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet 2005;365:1718–1726.
3. Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004;350:2050–2059.
4. Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, Haglind E, Pahlman L, Cuesta MA, Msika S, Morino M, Lacy AM. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 2005;6:477–684.
5. Fleshman J, Sargent DJ, Green E, Anvari M, Stryker SJ, Beart RW Jr, Hellinger M, Flanagan R Jr, Peters W, Nelson H.

Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. Ann Surg 2007;246:655–662; discussion 662–664
6. Kim HJ, Lee IK, Lee YS, Kang WK, Park JK, Oh ST, Kim JG, Kim YH. A comparative study on the short-term clinicopathologic outcomes of laparoscopic surgery versus conventional open surgery for transverse colon cancer. Surg Endosc 2009;23:1812–1817.
7. Schlachta CM, Mamazza J, Poulin EC. Are transverse colon cancers suitable for laparoscopic resection? Surg Endosc 2007;21:396–399.
8. Lee YS, Lee IK, Kang WK, Cho HM, Park JK, Oh ST, Kim JG, Kim YH. Surgical and pathological outcomes of laparoscopic surgery for transverse colon cancer. Int J Colorectal Dis 2008;23:669–673.
9. Wray CM, Ziogas A, Hinojosa MW, Le H, Stamos MJ, Zell JA. Tumor subsite location within the colon is prognostic for survival after colon cancer diagnosis. Dis Colon Rectum 2009;52:1359–1366.
10. Sjo OH, Lunde OC, Nygaard K, Sandvik L, Nesbakken A. Tumour location is a prognostic factor for survival in colonic cancer patients. Colorectal Dis 2008;10:33–40.
11. Hayne D, Brown RS, McCormack M, Quinn MJ, Payne HA, Babb P. Current trends in colorectal cancer: site, incidence, mortality and survival in England and Wales. Clin Oncol (R Coll Radiol) 2001;13:448–452.
12. Chang GJ, Rodriguez-Bigas MA, Skibber JM, Moyer VA. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. J Natl Cancer Inst 2007;99:433–441.
13. Hewett PJ, Allardyce RA, Bagshaw PF, Frampton CM, Frizelle FA, Rieger NA, Smith JS, Solomon MJ, Stephens JH, Stevenson AR. Short-term outcomes of the Australasian randomized clinical study comparing laparoscopic and conventional open surgical treatments for colon cancer: the ALCCaS trial. Ann Surg 2008;248:728–738.
14. Marusch F, Gastinger I, Schneider C, Scheidbach H, Konradt J, Bruch HP, Kohler L, Barlehner E, Kockerling F. Importance of conversion for results obtained with laparoscopic colorectal surgery. Dis Colon Rectum 2001;44:207-214; discussion 214–216
15. Thorpe H, Jayne DG, Guillou PJ, Quirke P, Copeland J, Brown JM. Patient factors influencing conversion from laparoscopically assisted to open surgery for colorectal cancer. Br J Surg 2008;95:199–205.
16. Akiyoshi T, Kuroyanagi H, Oya M, Konishi T, Fukuda M, Fujimoto Y, Ueno M, Yamaguchi T, Muto T. Safety of laparoscopic total mesorectal excision for low rectal cancer with preoperative chemoradiation therapy. J Gastrointest Surg 2009;13:521–525.
17. Yamaguchi S, Kuroyanagi H, Milsom JW, Sim R, Shimada H. Venous anatomy of the right colon: precise structure of the major veins and gastrocolic trunk in 58 cadavers. Dis Colon Rectum 2002;45:1337–1340.
18. Yada H, Sawai K, Taniguchi H, Hoshima M, Katoh M, Takahashi T. Analysis of vascular anatomy and lymph node metastases warrants radical segmental bowel resection for colon cancer. World J Surg 1997;21:109–115.
19. Jamali FR, Soweid AM, Dimassi H, Bailey C, Leroy J, Marescaux J. Evaluating the degree of difficulty of laparoscopic colorectal surgery. Arch Surg 2008;143:762–767; discussion 768.

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ORIGINAL ARTICLE

Analysis of Function and Predictors of Failure in Women Undergoing Repair of Crohn's Related Rectovaginal Fistula

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Abstract
Purpose Crohn's-related rectovaginal fistulae have significant impact on quality of life including sexual function. The aim of this study was to obtain long-term follow-up of Crohn's related rectovaginal fistulae to assess variables that influence surgical success and determine its effects on quality of life and sexual function.
Methods All women with Crohn's-related rectovaginal fistulas who underwent surgical repair from 1997 to 2007 were contacted for long-term follow-up. Variables assessed were age, body mass index, smoking, presence of active Crohn's disease, type of surgical procedure performed, use of perioperative seton or stoma, number of previous procedures, time interval between last repair and current repair, use of immunomodulators, and steroids. SF-12, Fecal Incontinence Quality-of-Life Scale, and Female Sexual Function Index were used to assess quality of life and sexual function. Multivariable logistic regression model was used to identify variables associated with surgical failure.
Results Sixty-five women were identified at median follow-up of 44.6 months (interquartiles, 13.1–79.1) of which 30 patients (46.2%) were successfully healed. Methods of repair included advancement flap (n=47), episioproctotomy (n=8), colo-anal anastomosis (n=7), and fibrin glue or plug (n=3). Twenty-eight women (43.1%) were sexually active at follow-up, and of those, nine complained of dyspareunia, all within the unhealed group of patients. On multivariate analysis, only immunomodulators were associated with successful healing (p=0.009). Smoking and steroids were associated with failure (p=0.04). Sexual function and quality-of-life scores were comparable between healed and unhealed groups.
Conclusions Crohn's-related rectovaginal fistulae are difficult to treat. Healing increased with use of immunomodulators; however, smoking and steroids were predictors of failure. Dyspareunia was higher in unhealed women.

Keywords Smoking · Repeated repair · RVF · Crohn's · Immunomodulators · QOL · Sexual function

Introduction

Rectovaginal fistulae (RVF) are a potential complication of Crohn's disease (CD) associated with significant morbidity and increased risk of proctectomy.[1,2] Crohn's related RVF have a significant impact on quality of life and is a source of considerable social embarrassment for affected women. In a recent Crohn's population study, the cumulative risk for developing any fistula was 33% after 10 years and 50% after 20 years, with at least one recurrent fistula occurring in 34% of the patients.[3] Up to 10% of women with CD will develop RVF.[4] Common symptoms include chronic vaginal discharge, dyspareunia, and the passage of flatus or stool through the vagina.

Treatment choices depend on several factors, which include the fistula characteristics, sphincter status, anal

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canal CD such as strictures and ulcerations, presence of active CD in the rectum, and the degree of impairment on quality of life. Many techniques have been developed in the attempt to treat RVF with a wide range of success rates quoted in the literature.[4] Crohn's related RVF in particular have a higher propensity for recurrence than other fistulae with reported recurrence rates ranging from 25% to 50%.[5–8]

Data examining long-term surgical success rates and associated information regarding its effect on quality of life (QOL), fecal incontinence (FI), and sexual function is limited.

The aim of this study was to obtain long-term follow-up of surgically treated women with Crohn's related RVF to examine variables influencing surgical success and to determine the effect of surgery on QOL and sexual function.

Methods

Patients

Clinico-pathological data were collected from an IRB-approved pelvic floor database, which was supplemented by a review of medical records, patient administered questionnaires, and direct patient contact in the form of a telephone call by a trained research nurse. Patient's functional outcome and quality-of-life parameters were obtained from the prospectively maintained database for all available follow-up visits. Patients were asked to complete a self- administered, structured questionnaire on each return visit to the office. If the patient did not attend for more than 1 year, the information was requested by means of the same questionnaire delivered by mail.

All women with Crohn's related RVF who underwent surgical repair with intent to close the fistula from 1997 to 2007 were contacted for long-term follow-up. Variables assessed to determine their effect on surgical success rates included age, body mass index (BMI), smoking, CD activity (defined clinically by the presence of active inflammation in the rectum or anal canal, anal/or perineal ulceration, or anal strictures), type of surgical procedure performed, use of a preoperative seton or postoperative diverting stoma, number of previous surgical procedures performed, time interval between last repair and current repair, and use of immunomodulators and steroids within the 3 months prior to surgery.

Long-term closure of RVF was determined by clinical examination in the office or by more invasive evaluation such as examination under anesthesia in suspicious cases. Riddance of preoperative symptoms was also verified by a telephone questionnaire. RVF were considered closed if all preoperative symptoms attributable to the fistula had resolved at the time of follow-up and no fistula was detected by physical exam at the last office visit.

Patients were excluded from the study if a surgical procedure was performed where the intent was not fistula closure such as seton placement, diverting stoma alone, or definitive proctectomy without reconstruction.

Quality of Life and Sexual Function

QOL was assessed using the SF-12 Health Survey,[9] The Irritable Bowel Disease Quality of Life Instrument (IBD-QOL),[10] and Fecal Incontinence Quality of Life Scale (FIQL).[11]

In determining sexual function, we initially asked patients at the time of direct telephone contact if they were currently sexually active. For patients who were sexually active, we further asked if they experienced pain or discomfort with sexual intercourse. Patients who were sexually active were then forwarded the Female Sexual Function Index (FSFI) validated questionnaire. The FSFI assesses domains of sexual functioning such as sexual arousal, orgasm, satisfaction, and pain. This provides a domain score range of (0–36) with a score of zero indicating no sexual activity and a score of 36 indicating best sexual function.[12]

Statistics

Fisher's exact test, Chi-square test, and multivariable logistic regression model were used to identify the variables associated with success or failure. A p value ≤ 0.05 was considered as significant.

Results

Patient Demographics

Over a 10-year period between 1997 and 2007, 65 women with Crohn's related RVF who had surgical procedures with intent to close the fistula at our institution were identified. Median follow-up was 44.6 months (interquartiles, 13.1–79.1) with a mean age of 42.3±2 years and BMI of 27.5± 12 kg/m^2. Information regarding whether a patient's RVF had healed at follow-up was available for all 65 patients. At the time of follow-up, 30 patients (46.2%) were successfully healed (Table 1). Twenty-nine (45%) patients (15 healed and 14 unhealed) agreed to complete the QOL questionnaires, and of the sexually active women, 57.1% completed the FSFI questionnaire.

Preoperative Symptoms

The most common complaints were fluid drainage per vagina (75.4%), gas per vagina (64.6%), stool per vagina

Table 1 Demographic and Patients Characteristics

Variables		Healed, n=30 (46.2%)	Unhealed, n=35 (53.8%)	p value
Age (mean ± SD)		41.3±13.3	43.1±10.8	0.6
BMI (mean ± SD)		28.4±9.4	26.7 ± 6.6	0.4
Smoking		8 (30.8%)	18 (69.2%)	0.04
ASA (mean ± SD)		2.0±0.5	2.3±0.5	0.06
Ethnic group	Caucasian	27 (48.2%)	29 (51.8%)	0.6
	African American	3 (42.9%)	4 (57.1%)	
	Other	0 (0%)	2 (100%)	
Steroids		6 (30.0%)	14 (70.0%)	0.05
Immunomodulators use		16 (61.5%)	10 (38.5%)	0.009
Fecal incontinence		3 (50.0%)	3 (50.0%)	0.7
Follow-up time (mean±SD) months		55.1±52.1	47.4±30.6	0.6
Comorbidity	Diabetes	3 (100%)	0 (0%)	0.09
	Pulmonary	1 (33.3%)	2 (66.7%)	1.0
	Cardiovascular	0 (0%)	3 (100%)	0.2
	Irritable bowel syndrome	2 (66.7%)	1 (33.3%)	0.6

(56.9%), perineal pain (13.8%), and fecal incontinence (9.2%). We did not assess preoperative dyspareunia.

Surgical Repair

The overall healing rate of surgical repair at the time of follow-up was 46.2%. The most common surgical procedures performed were mucosal advancement flaps (72.3%), episioproctotomy (12.3%), proctectomy and pull-through procedure with colo-anal anastomosis (Turnbull–Cutait procedure) (10.8%), fibrin glue (3.1%), and fistula plug placement (1.5%). There was no significant difference in type of RVF repairs between healed and unhealed patients (p=0.6). The median number of attempted repairs between the healed and unhealed groups was similar (p=0.5). Eighteen patients received more than three repairs, with eight patients in this subgroup (44.4%) having their RVF healed at follow-up. No patients who had five or more attempts at repair were healed at follow-up.

Healing rates were not significantly affected by age (p=0.5), BMI (p=0.4), comorbidity (p=0.6), presence of active anorectal CD (p=0.5), time interval between last repair and most recent repair (p=0.1), use of a preoperative seton (p=0.08), or postoperative diverting stoma to protect the RVF repair (p=0.2) (Table 2). On multivariate analysis, use of immunomodulators such as the biologics infliximab (Remicade®) and adalimumab (Humira®) as well as 6-mercaptopurine and azathioprine within the 3 months prior to surgery was the only variable associated with successful healing (p=0.009). Smoking and corticosteroids within the 3 months prior to surgery were both associated with failure (p=0.04).

Quality of Life and Sexual Function

Twenty-nine (45%) patients, consisting of 15 healed and 14 unhealed RVF, agreed to complete the QOL questionnaires. The SF-12 questionnaire showed modest scores in both the healed and unhealed groups with no significant difference in the categories of physical health (p=0.6) and mental health (p=0.7) (Table 3). The IBD-QOL also showed modest scores in both healed (53.7±33.2) and non-healed (42.6±27.1) groups with no significant difference (p=0.4) (Table 3). Results from the FIQL questionnaire demonstrated no significant difference in the overall scores between the healed and unhealed groups (p=0.9). Likewise, when the individual components of the FIQL were examined comparing healed and unhealed women, there was no significant difference in the areas of lifestyle (p=0.7), coping behavior (p=0.9), depression and self-perception (p=0.6), and embarrassment (p=0.5) (Table 3).

Of our total cohort of 65 women, 28 (43.1%) were sexually active at follow-up. This included 15 patients with healed RVF and 13 patients with unhealed RVF. Of this subgroup of sexually active women, nine women (30%) complained of dyspareunia on direct questioning at the time of telephone contact. All women who complained of dyspareunia were in the unhealed group. Of the 28 women that were sexually active, 16 (57.1%) agreed to complete the FSFI sexual function questionnaire. There was no significant difference between healed and unhealed patients in either the overall FSFI score (p=0.9) or the separate domains of the FSFI: desire (p=0.8), arousal (p=0.4), lubrication (p=0.3), orgasm (p=0.5), satisfaction (p=0.4), and pain (p=0.5) (Table 4).

Table 2 Preoperative and Operative Details

Variables		Healed, n=30 (46.2%)	Unhealed, n=35 (53.8%)	p value
Seton	Yes	12 (57.1%)	9 (42.9%)	0.08
	No	12 (33.3%)	24 (66.7%)	
Stoma	Yes	20 (51.3%)	19 (48.7%)	0.2
	No	8 (33.3%)	16 (66.7%)	
Crohn's activity	Yes	8 (40.0%)	12 (60.0%)	0.5
	No	22 (48.9%)	23 (51.1%)	
Type of current surgery	Mucosal advancement flap	20 (42.6%)	27 (57.4%)	0.6
	Colo-anal anastomosis	4 (57.1%)	3 (42.9%)	
	Episioproctotomy	5 (71.4%)	3 (28.6%)	
	Fibrin glue	1 (50.0%)	1 (50.0%)	
	Plug	0 (0%)	1 (100%)	
Number of repairs median (range)		2 (1–5)	2 (1–8)	0.5
Interval from last repair to current (months)[a]		7.6 (4.1–11.1)	9.7 (4.9–41.5)	0.1
Interval from seton to current repair (months)[a]		7.3 (5–8.9)	4.2 (3.6–8.2)	0.5
Interval from stoma to current repair (months)[a]		5.7 (0.6–7.8)	8 (0.9–22.9)	0.1

[a] Median interquartiles (IQR)

Discussion

Patients with Crohn's related RVF often have significant symptoms which affect their quality of life. When possible, this group of patients should be offered surgical repair in an attempt to improve symptoms. There is no ideal treatment option suitable for all patients, and many techniques have been reported with a wide range of success. Previous publications on Crohn's RVF repair from our institution and others have addressed short term outcomes. This is the first study to address long-term follow-up for this unique group of patients.

Published healing rates for Crohn's associated RVF in large studies have ranged from 40% to 60%.[4,13–18] Sonoda et al. reported 50% failure rate for Crohn's related RVF.[8] Hull et al. retrospectively reviewed 35 patients with low anovaginal fistulae in CD.[15] Overall, an initial healing rate of 54% was reported following primary surgical repair. Ultimately, 68% of patients healed their fistula with the use of additional repairs. Another study reported 60% of the Crohn's RVF were successfully repaired using a sleeve advancement flap.[19] In another report from our institution, six out of 12 patients (50%) with Crohn's related RVF healed after a total of 21 operations.[6]

In the present study, after variable numbers and types of repairs, 46.2% of RVF's healed. This is lower than the healing rate reported for non-Crohn's related RVF,[8] which reflects the complexities of the underlying disease process. This rate of healing is also lower than an earlier report from our group, which showed healing rates as high as 68%.[15] We believe that patients with Crohn's associated RVF initially may heal but with longer follow-up, higher failure rates may be seen. This likely reflects the recrudescent nature of Crohn's disease and the variable responses to

Table 3 Patient's Quality of Life

Variables		Healed, n=15 (51.7%)	Unhealed, n=14 (48.3%)	p value
FIQL		11.0±3.6	10.7±3.4	0.9
	Life style	2.9±1.1	3.1±0.8	0.7
	Coping	2.5±0.96	2.6±0.9	0.9
	Depression	2.85±0.8	2.7±0.9	0.6
	Embarrassment	2.69±1.1	2.5±0.9	0.5
IBD-QOL		53.7±33.2	42.4±27.1	0.4
SF-12	Physical health	44.7±11.8	42.6±11.0	0.6
	Mental health	44.3±11.9	42.6±16.3	0.7
Sexual activity		15 (50%)	13 (37.1%)	0.06
Dyspareunia		0 (0%)	9 (25.7%)	0.001

Table 4 Female Sexual Function Index (FSFI)

Variables		Healed, n=6 (37.5%)	Unhealed, n=10 (62.5%)	p value
FSFI	Desire	2.6±1.4	2.4±1.3	0.8
	Arousal	3.4±1.6	2.7±1.7	0.4
	Lubrication	2.7±1.1	3.6±1.8	0.3
	Orgasm	3.3±1.7	2.6±2.0	0.5
	Satisfaction	2.5±1.1	3.2±1.7	0.4
	Pain	2.9±1.3	3.4±2.1	0.5
Total FSFI		17.3±6.7	17.9±9.4	0.9

medical treatment. This fact is not fully appreciated in studies with shorter follow-up.

In our study, the use of immunomodulators was significantly associated with successful healing. The use of immunomodulators has also been reported to aid healing of Crohn's RVF in other studies.[20–23] The post hoc analysis of the ACCENT II trial by Sands et al.[20] examined 25 women with RVF treated with infliximab. They reported that 72.2% had healed RVF at 14 weeks. However, follow-up of this same group at 54 weeks found that healing had decreased to 44.4%. In our study, 61.5% of patients that were administered immunomodulators within 3 months of their definitive surgery were healed at a median follow-up significantly longer than the Sands study. Of note, healing of RVF in our study involved the use of immunomodulators as well as definitive surgical management. The Sands study involved immunomodulator use only. Another study by Topstad et al.[21] looked at using setons with infliximab in eight patients with RVF and showed only 13% healed after the setons were removed. We postulate that preoperative use of immunomodulators followed by curative surgical repair (as in this study) may provide better RVF closure rates than immunomodulators alone or immunomodulators combined with some element of seton drainage. However, direct comparison between our study and others is difficult.

In our study, smoking and use of steroids were associated with a higher rate of failure. Smoking has previously been shown to negatively affect the successful outcome of mucosal advancement flaps in patients with perianal fistulae presumably due to reduced rectal mucosal blood flow.[24,25] Likewise, other studies have found steroid use to be associated with a higher failure rate.[8]

It is unclear how the number of attempted repairs influence outcome. In this study, patients having four or five repairs had healing rates similar to the overall healing rate. This suggests that multiple surgical attempts may still offer a successful outcome. This is tempered by the finding that no patients having more than five repairs were healed at follow-up. Scarring from previous repairs may impede healing with five repairs being the limit in this study. Other reports evaluating all types of perineal fistulae, including RVF, have shown conflicting results on whether the number of repairs affects the eventual healing rate.[24,25] It is possible that our study, despite enrolling 65 patients, may have lacked the power to make a definitive statement.

Placement of a preoperative seton has previously been reported as a factor that improves the healing rate of perineal fistulas, including RVF.[8,26] The benefit has been speculated to result from drainage of sepsis and promotion of fibrosis in the tract. This study did not show a significant benefit, but shows a trend toward increased healing with seton use (p=0.08).

The response rate for mailed questionnaires was 45% for QOL and 57.1% for FSFI. This is consistent with typical response rates for mailed questionnaires in the literature, which ranges from 40% to 60%.[28]

Due to the systemic impact of Crohn's disease, QOL is generally lower in these patients versus unaffected individuals.[27] This may account for the modest QOL scores in the three QOL questionnaires used in our study. When comparing the group of women that had healed RVF versus non-healed, there was no significant difference in QOL overall or separately in any of the domains within the questionnaires. This may reflect that the systemic symptoms of Crohn's disease have a more overriding influence on QOL rather than any one individual complication of the disease.

Due to the sensitive nature of the topic, evaluation of female sexual function is difficult and has resulted in a paucity of data. Moody et al.[29] performed a structured interview of fifty CD patients and compared them to controls. They showed in the CD group that 24% of women had infrequent or no sexual intercourse compared with just 4% of controls. Reasons for sexual inactivity in Moody's study included abdominal pain (24%), diarrhea (20%), and fear of fecal incontinence (14%). In our study, nearly 67% of women abstained from sexual intercourse. Our higher abstinence rate may reflect that all women had a RVF, which may deter them from having sexual intercourse. In the Moody study, dyspareunia was significantly more common in women with CD compared to controls, and this was independent of the enteric site of disease. Interestingly, they found when women had only perianal disease or fistulae that there was no significant difference in

dyspareunia versus the control group. Similar to Moody's results, this study found that the FSFI scores were similar between the healed and non-healed RVF groups. In particular, subset analysis of dyspareunia with the FSFI found no difference between the two groups. These findings must be interpreted with caution due to the small number of people answering this questionnaire. When we specifically asked all 65 women about dyspareunia at the time of telephone interview, 30% of sexually active women in the unhealed group admitted to experiencing dyspareunia versus zero in the healed group. This may reflect the difficulty in assessing dyspareunia since we found apparent differences in questioning patients on paper versus specifically asking over the phone. We do believe however that an unhealed RVF does contribute to dyspareunia.

Conclusions

Crohn's related RVF continue to be difficult to treat. Healing increased when immunomodulators were used within 3 months prior to surgery. Further prospective trials are needed to help surgeons decide if and when to consider immunomodulators before surgical repair of Crohn's RVF. Smoking and steroids were predictors of repair failure. Regardless of successful healing, QOL and sexual function were similar. Dyspareunia appears to be higher for women with unhealed fistulas.

References

1. Heyen F, Winslet MC, Andrews H, et al. Vaginal fistulas in Crohn's disease. Dis Colon Rectum 1989;32:379–383.
2. Scott NA, Nair A, Hughes LE. Anovaginal and rectovaginal fistula in patients with Crohn's disease. Br J Surg 1992;79:1379–1380.
3. Schwartz DA, Loftus EV Jr, Tremaine WJ, et al. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. Gastroenterology 2002;122:875–880.
4. Radcliffe AG, Ritchie JK, Hawley PR, et al. Anovaginal and rectovaginal fistulas in Crohn's disease. Dis Colon Rectum 1988; 31:94–99.
5. Makowiec F, Jehle EC, Becker HD, et al. Clinical course after transanal advancement flap repair of perianal fistula in patients with Crohn's disease. Br J Surg 1995;82:603–606.
6. Halverson AL, Hull TL, Fazio VW, et al. Repair of recurrent rectovaginal fistulas. Surgery 2001;130:753–757. discussion 757-8.
7. Ozuner G, Hull TL, Cartmill J, et al. Long-term analysis of the use of transanal rectal advancement flaps for complicated anorectal/vaginal fistulas. Dis Colon Rectum 1996;39:10–14.
8. Sonoda T, Hull T, Piedmonte MR, et al. Outcomes of primary repair of anorectal and rectovaginal fistulas using the endorectal advancement flap. Dis Colon Rectum 2002;45:1622–1628.
9. Ware J Jr, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220–233.
10. Hahn BA, Kirchdoerfer LJ, Fullerton S, et al. Evaluation of a new quality of life questionnaire for patients with irritable bowel syndrome. Aliment Pharmacol Ther 1997;11:547–552.
11. Rockwood TH, Church JM, Fleshman JW, et al. Fecal incontinence quality of life scale: quality of life instrument for patients with fecal incontinence. Dis Colon Rectum 2000;43:9–16.
12. Rosen R, Brown C, Heiman J, et al. The female sexual function index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000;26:191–208.
13. Bandy LC, Addison A, Parker RT. Surgical management of rectovaginal fistulas in Crohn's disease. Am J Obstet Gynecol 1983;147:359–363.
14. Hesterberg R, Schmidt WU, Muller F, et al. Treatment of anovaginal fistulas with an anocutaneous flap in patients with Crohn's disease. Int J Colorectal Dis 1993;8:51–54.
15. Hull TL, Fazio VW. Surgical approaches to low anovaginal fistula in Crohn's disease. Am J Surg 1997;173:95–98.
16. Morrison JG, Gathright JB Jr, Ray JE, et al. Results of operation for rectovaginal fistula in Crohn's disease. Dis Colon Rectum 1989;32:497–499.
17. O'Leary DP, Milroy CE, Durdey P. Definitive repair of anovaginal fistula in Crohn's disease. Ann R Coll Surg Engl 1998;80:250–252.
18. Penninckx F, D'Hoore A, Filez L. Advancement flap plasty for the closure of anal and recto-vaginal fistulas in Crohn's disease. Acta Gastroenterol Belg 2001;64:223–226.
19. Marchesa P, Hull TL, Fazio VW. Advancement sleeve flaps for treatment of severe perianal Crohn's disease. Br J Surg 1998;85:1695–1698.
20. Sands BE, Blank MA, Patel K, et al. Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study. Clin Gastroenterol Hepatol 2004;2:912–920.
21. Topstad DR, Panaccione R, Heine JA, et al. Combined seton placement, infliximab infusion, and maintenance immunosuppressives improve healing rate in fistulizing anorectal Crohn's disease: a single center experience. Dis Colon Rectum 2003;46:577–583.
22. Present DH, Korelitz BI, Wisch N, et al. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. N Engl J Med 1980;302:981–987.
23. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340:1398–1405.
24. Ellis CN, Clark S. Effect of tobacco smoking on advancement flap repair of complex anal fistulas. Dis Colon Rectum 2007;50:459–463.
25. Zimmerman DD, Delemarre JB, Gosselink MP, et al. Smoking affects the outcome of transanal mucosal advancement flap repair of trans-sphincteric fistulas. Br J Surg 2003;90:351–354.
26. van der Hagen SJ, Baeten CG, Soeters PB, et al. Staged mucosal advancement flap for the treatment of complex anal fistulas: pretreatment with noncutting Setons and in case of recurrent multiple abscesses a diverting stoma. Colorectal Dis 2005;7:513–518.
27. Lix LM, Graff LA, Walker JR, et al. Longitudinal study of quality of life and psychological functioning for active, fluctuating, and inactive disease patterns in inflammatory bowel disease. Inflamm Bowel Dis 2008;14:1575–1584.
28. Brems C, Johnson ME, Warner T, Robert LW. Survey return rates as a function of priority versus first-class mailing. Psychol Rep 2006;99:496–501.
29. Moody G, Probert CS, Srivastava EM, et al. Sexual dysfunction amongst women with Crohn's disease: a hidden problem. Digestion 1992;52:179–183.

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ORIGINAL ARTICLE

Colorectal Surgeons: Gender Differences in Perceptions of a Career

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Abstract
Purpose The outlook of surgeons is changing. There has been recent interest in looking at job perception towards general surgery, which further has been divided into looking at gender differences.
Methods A questionnaire with nine sections/63 questions was mailed to all 1799 ASCRS members (244 women) who were on the ASCRS mailing list from the USA. The returned questionnaires were analyzed.
Results A total of 498/1,799 (28%) were returned; 109/498 were female (22%), which represented 109/244 (45%) of the ASCRS female membership vs.389/1,655 (23%) of the ASCRS male membership. The mean age was 49 years (females 42 years, males 51 years, $p<0.001$). Demographically significant findings were that more female colorectal surgeons (FCR) were single 12% vs. 2% ($p<0.001$). Male colorectal surgeons (MCR) overall earned more than their female counterparts ($p<0.001$) and 11% FCR's had a salary of >$350,000 vs. 33% MCR. More MCR found work atmosphere ($p<0.004$) and casemix ($p<0.001$) were satisfactory elements of their job. A majority of the colorectal surgeons polled, would not change their careers however more FCR (21%) than MCR (13%) would do so ($p=0.03$). When queried specifically, FCR also indicated they affected the OR in a positive way ($p<0.001$). FCR were more sensitive to their colleagues opinion of their capabilities ($p<0.001$), MCR however felt that their colleagues had a high impression of their capabilities ($p<0.001$). FCR agreed that women mentors were few because of lack of time ($p<0.001$) and also felt their views were not considered when executive decisions were made ($p<0.001$).
Conclusions Interestingly, proportionally more younger, single FCR than MCR returned the questionnaires. The significance of this finding is uncertain. Acknowledgment of these differences will promote more understanding and job satisfaction in both academic and private practice.

Keywords Colorectal surgeons · Gender · Income · Career · Disparity

Introduction

The last two decades have seen a trend towards diversity and changing expectations related to work schedules and work environment. The surgical specialties of yesteryears were predictably Caucasian and male dominated. The evolution from the white male stereotype towards a gender and racial diversity has changed the perception of a surgeon in the eyes of the administration, healthcare personnel, and patients. Today, female surgeons are more visible. In 2003 across the US, 51% of all medical school admissions were female and accounted for 46% of medical graduates and 41% of all residents.[1] Colon and rectal surgery had 18/60 women residents.[1] In spite of these numbers, gender disparity remains an important topic of modern times and may be more apparent in the surgical specialities.[2–5] The female resident is not expected to work less than her male counterpart, yet it has been shown that the female surgeon does more of the expected work at home than her male

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counterpart.[6] This inequality of everyday work has deterred some women from considering a surgical career. The ability of programs to continue to attract female medical graduates and then mentor them into community and academic positions is vital for this diversity to exist. Female role models in the surgical specialties are not plentiful [7] and the reasons are related to time and responsibilities at home and family [8] and are similar to those cited by other high-pressure careers across the world. With decreasing number of physicians in the USA, women are essential to adequately provide sufficient healthcare. It is essential to recognize women's perceptions in order to recruit and retain academic surgeons.[9] While some literature is emerging regarding gender differences in surgery no data examining gender differences in colorectal surgery exists. Since many colorectal surgeons may have practice patterns different from orthopedic, cardiothoracic, general, and other surgical practices, specific study of colorectal surgeons is needed to discover if issues exist. The aim of this study was to evaluate if gender disparity among colorectal surgeons towards the perception and expectations of their career exists, and study possible causes that lead to any disparity.

Methods

After IRB approval, all members of the American Society of Colon and Rectal Surgeons (ASCRS) practicing in the USA were mailed a questionnaire approved by ASCRS (See Questionnaire). Respondents who were in active practice at the time of the survey were included. Retired surgeons and surgeons not practicing in the USA were excluded. The questionnaire was received anonymously by the research section of the Department of Colon and Rectal Surgery of Cleveland Clinic Foundation, Cleveland, Ohio. The questionnaire was mailed to the entire group twice with a 2-month interval between the two mailings. The questionnaire was based on similar questionnaires of other surgical specialties and utilized questions with answers on a Likert scale.[10] The questionnaire was divided into ten headings each of which had three to four questions. The headings included demographics, time issues, gender issues, specialty issues, job satisfaction, vacation and time off, income, research and its funding, career advancement, and harassment at work. The answers were entered in a database and sent for statistical analysis.

Statistical Analysis

Male and female colorectal surgeons were compared with respect to categorical survey responses using Fisher's exact test, or a chi-square test if cross-tabulated expected cell counts were of sufficient size (≥5). Comparisons with respect to quantitative and ordinal survey variables were performed using Wilcoxon rank sum tests. Categorical survey responses were summarized by frequencies and percents, while means, standard deviations, and/or appropriate percentiles were used to summarize quantitative and ordinal responses. Analyses were performed using R version 2.3.1.

Results

Demographics

Five hundred and ten questionnaires out of 1,799 were received of which 498 (28%) were considered to be complete. One hundred and nine (29%) of these were female colorectal surgeons (FCR). The mean age of FCR was 42 years while that of the male colorectal surgeons (MCR) was 51 years. Significant demographic parameters were that more MCR were married (94% vs. 75% $p<0.001$) and were in practice significantly more years (17.5 vs. 8 $p<0.001$). MCR married earlier (27 years vs. 29 years $p<0.001$) and had children during residency training (55% vs. 15% FCR, $p<0.001$). A majority of FCR had their first child in the first 3 years of practice or later while a majority of MCR had their first child in residency ($p<0.001$). Forty-three percent of MCR spouses did not work outside the home compared with 10% of FCR spouses. Physician spouses were 35% among FCR and 16% among MCR. Forty-one percent of FCR spouses were in a non-healthcare profession compared with 15% MCR spouses. More FCR (75%) than MCR (68%) were board certified although this was not significant. An equal number of both groups were not practicing in the town they underwent their colorectal training. Significantly more FCR would change their career if they had a chance (22% vs. 13% MCR, $p=0.03$; Table 1).

Time Issues

There were no significant differences in time spent at work, on call, or taking weekend call. However, more FCR answered yes to the question of whether they felt that they had inadequate time to spend with their children (52% vs. 36%, $p=0.004$), time to spend on hobbies (77% vs. 57%, $p<0.001$) and time to spend on sports (79% vs. 57% $p<0.001$; Table 2).

Gender Issues

In general, FCR felt that gender impacted their job ($p<0.001$), especially in the manner the nurses and ancillary staff reacted to them ($p<0.001$). FCR also felt they affected the operating room in a positive way ($p<0.001$). When queried,

Table 1 Demographics

Variable	Overall (n=498)	FCR (n=109)	MCR (n=389)	p value
Age	48.97±10.40	41.98±6.61	50.89±10.43	<0.001
Sex				
Female	109 (21.9%)	109 (100%)	0 (0%)	<0.001
Male	389 (78.1%)	0 (0%)	389 (100%)	
Years in practice	15.44±10.56	8.04±6.51	17.50±10.55	<0.001
Type of practice				
Institutional	135 (28.1%)	40 (38.5%)	95 (25.2%)	0.008
Private practice	346 (71.9%)	64 (61.5%)	282 (74.8%)	
Income				
<K150	27 (5.5%)	11 (10.4%)	16 (4.2%)	<0.001
K150–K250	183 (37.4%)	56 (52.8%)	127 (33.2%)	
K250–K350	139 (28.4%)	27 (25.5%)	112 (29.2%)	
K350–K500	95 (19.4%)	10 (9.4%)	85 (22.2%)	
K500–K700	28 (5.7%)	2 (1.9%)	26 (6.8%)	
>K700	17 (3.5%)	0 (0%)	17 (4.4%)	
Age: when married	27.88±4.56	29.38±5.34	27.51±4.28	<0.001
Age: first childbirth	31.64±4.66	34.42±4.86	31.14±4.45	<0.001
Timing: first child				
Internship	31 (7.2%)	3 (4.3%)	28 (7.7%)	<0.001
Medical school	29 (6.7%)	3 (4.3%)	26 (7.2%)	
Residency	190 (44.1%)	11 (15.9%)	179 (49.4%)	
Fellowship	34 (7.9%)	5 (7.2%)	29 (8.0%)	
Practice: years 1–3	90 (20.9%)	25 (36.2%)	65 (18.0%)	
Practice: years>3	57 (13.2%)	22 (31.9%)	35 (9.7%)	

14% FCR were undecided if their colleagues valued their opinion (14% vs. 3%, p<0.001). Neither group felt overburdened by their job (p=0.06); however, when asked if colleagues of the opposite sex handled pressure better than them, more MCR disagreed or strongly disagreed that their female colleagues handled work pressure better than members of the opposite sex (84% vs.69%, p<0.001). More FCR (32%) than FCR agreed or strongly agreed that their views

Table 2 Work-Related Issues

Variable		Overall (n=498)	FCR (n=109)	MCR (n=389)	p value
Total working hours per week		59.40±18.14	58.66±15.69	59.60±18.79	0.28
Total days on call per month		11.67±9.21	10.02±7.95	12.14±9.49	0.07
Male surgeons do not like female mentors	(1): strongly agree	8 (1.6%)	3 (2.8%)	5 (1.3%)	0.025
	(2): agree	82 (16.8%)	23 (21.7%)	59 (15.4%)	
	(3): undecided	127 (26.0%)	34 (32.1%)	93 (24.3%)	
	(4): disagree	230 (47.1%)	36 (34.0%)	194 (50.8%)	
	(5): strongly disagree	41 (8.4%)	10 (9.4%)	31 (8.1%)	
Case mix does not reflect gender	(1): strongly agree	94 (19.1%)	9 (8.4%)	85 (22.1%)	<0.001
	(2): agree	276 (56.2%)	38 (35.5%)	238 (62.0%)	
	(3): undecided	32 (6.5%)	9 (8.4%)	23 (6.0%)	
	(4): disagree	73 (14.9%)	38 (35.5%)	35 (9.1%)	
	(5): strongly disagree	16 (3.3%)	13 (12.1%)	3 (0.78%)	
Recommend career to others	(1): strongly agree	170 (34.5%)	43 (39.4%)	127 (33.1%)	0.005
	(2): agree	277 (56.2%)	49 (45.0%)	228 (59.4%)	
	(3): undecided	26 (5.3%)	12 (11.0%)	14 (3.6%)	
	(4): disagree	13 (2.6%)	2 (1.8%)	11 (2.9%)	
	(5): strongly disagree	7 (1.4%)	3 (2.8%)	4 (1.0%)	

were not considered for executive decisions ($p<0.001$; Table 3).

Specialty Issues

FCR perceived that women patients tended to seek them out (86% vs. 24%, $p<0.001$), but did not feel that male patients had a preference. More FCR felt that HIV-positive patients tended to seek them out (24% vs. 1%) while MCR did not have this perception (60% vs. 23%, $p<0.001$). Further analyses show that surgeons over age 50 were more likely to express disagreement with the statement that HIV patients seek them out compared to surgeons 50 and younger (63% vs. 44%, $p<0.001$). Given the relationship between surgeon gender and age, it is reasonable to suspect that age of the surgeons is an explanatory factor for the observed association between surgeon gender and the perception of being sought out by HIV patients, in which we showed that females were less likely to disagree with the statement that HIV patients seek them out. A linear regression model for the numerically coded agreement level versus gender was fit, with age included as a covariate. The model results demonstrated that the association between the surgeon's gender and the perception of whether HIV patients seek them out is not reduced by the inclusion of age as a covariate (i.e., no reduction in the gender model parameter estimate, and continued strong significance with $p<0.001$). Therefore, the association between surgeon gender and perception is present even when surgeon age is taken into account. MCR also did not feel that women were better at handling healthcare issues specific to women patients (74% vs. 59%, $p<0.001$).

Job Satisfaction

When questioned about availability of existing opportunities to advance their careers both genders agreed that they had adequate chances in their practice ($p=0.35$). However, when asked if fewer opportunities existed for female colorectal surgeons to advance their careers, more FCR agreed (19% vs. 2%) and more MCR disagreed (83% vs. 62%; $p=<0.001$). FCR did not perceive that their fewer numbers caused them to feel restricted (78% vs. 66%). However, more FCR than MCR answered that female mentors were few due to time commitments at work and home (37% vs. 8% $p<0.001$). MCR did not feel that male residents disliked female mentors; however, FCR felt that this was a true statement ($p=0.02$). On the subject of type of cases both MCR and FCR were happy with the type of cases they saw. When asked if their casemix reflected their gender significantly fewer FCR than MCR agreed or strongly agreed (44% vs. 88%, $p<0.001$) implying that the FCR had a more mixed casemix and did not see only female patients. Overall, more MCR felt that they were supported by the FCR (89% vs. 67%, $p<0.001$) while more FCR were undecided (14% vs. 5%) or disagreed with this statement (19% vs. 6%). On the question of whether they would recommend their career to the female residents more FCR were undecided (11% vs. 4%, $p=0.005$).

Vacation and Time Off

Both MCR and FCR felt that they had adequate vacation and did not feel they took time off to catch up on research.

Table 3 Gender-Related Issues

Variable		Overall ($n=498$)	FCR ($n=109$)	MCR ($n=398$)	p value
Gender is an important factor in your job (agree)		25%	20%	42%	<0.001
Nurses react positively because of your gender (agree)		97%	96%	97%	0.63
Gender affects the OR atmosphere positively	(1): strongly agree	45 (9.1%)	20 (18.5%)	25 (6.5%)	<0.001
	(2): agree	151 (30.6%)	44 (40.7%)	107 (27.7%)	
	(3): undecided	139 (28.1%)	30 (27.8%)	109 (28.2%)	
	(4): disagree	133 (26.9%)	13 (12.0%)	120 (31.1%)	
	(5): strongly disagree	26 (5.3%)	1 (0.93%)	25 (6.5%)	
Residents approach you because of your gender	(1): strongly agree	17 (3.9%)	10 (10.8%)	7 (2.1%)	<0.001
	(2): agree	63 (14.6%)	28 (30.1%)	35 (10.3%)	
	(3): undecided	134 (31.0%)	30 (32.3%)	104 (30.7%)	
	(4): disagree	178 (41.2%)	24 (25.8%)	154 (45.4%)	
	(5): strongly disagree	40 (9.3%)	1 (1.1%)	39 (11.5%)	
Colleagues have a high opinion about you	(1): strongly agree	173 (35.1%)	33 (30.8%)	140 (36.3%)	<0.001
	(2): agree	282 (57.2%)	53 (49.5%)	229 (59.3%)	
	(3): undecided	27 (5.5%)	15 (14.0%)	12 (3.1%)	
	(4): disagree	7 (1.4%)	4 (3.7%)	3 (0.78%)	
	(5): strongly disagree	4 (0.81%)	2 (1.9%)	2 (0.52%)	

Both genders felt they took similar time off as their opposite gender counterpart to attend issues at home.

Income

Significantly more MCR had higher incomes than FCR (33% MCR earned >$350,000 vs. 11% FCR, 53% FCR earned between $150,000 and $250,000 vs. 33% MCR; $p<0.001$). Overall more MCR felt that they earned more or equal to others who practiced in their vicinity ($p<0.001$). Fifty-six percent of FCR indicated that they earned less than other colorectal surgeons in their area (vs. 31% MCR); while 13% of MCR felt that they earned more (compared with 4% FCR). Further analyses show some interesting relationships between income level and each of age and years of service. Among surgeons age 40 years and younger, 36% made over $250,000, and among surgeons over age 60, 51% made over $250,000. In the middle age range between 41 and 60, 67% made over $250,000, so the relationship between income is not linear, and income is maximized among surgeons toward the middle of the age spectrum. Similarly, only 33% of surgeons with five or fewer years of practice, and 56% of surgeons with over 25 years of experience made over $250,000, while 66% of surgeons in practice between 6 and 25 years made over $250,000. Given the relationships we had shown between surgeon gender and each of age and years of service, it is reasonable to suspect that age or years of practice are explanatory factors for the observed association between surgeon gender and income, in which females tended to make less than males. Linear regression models for the numerically coded income level versus gender were fit, with age and years of service included as covariates in separate models, including quadratic polynomial terms to account for the non-linear associations between income level and each of age and years of service. The model results demonstrated that the associations between surgeon gender and income level were only slightly reduced (i.e., reduction in the gender model parameter estimate by 26% when adjusting for age and 18% when adjusting for years of service, and continued strong significance with $p<0.001$). Therefore, the association between surgeon gender and income level is present even when surgeon age or years of practice is taken into account.

Research Funding and Grants

There were no differences between the responses of MCR and FCR with regard to research funding although more FCR cited inadequate mentoring as a reason for inadequate funding (22% vs. 11%, $p=0.03$). Interestingly, MCR reported publishing significantly more articles (17 vs. 10, $p=0.01$).

Career Advancement

An equal number of FCR and MCR agreed or disagreed with the concept whether their career was at a standstill. More MCR felt that they had more opportunities to advance their careers but this was not significant ($p=0.35$). However, more MCR than FCR (46% vs. 38%, $p=0.03$) did not want to reduce the hours at work as they preferred to advance their career. Significantly more MCR (90% vs.77%, $p=0.01$) indicated relocation was not dependent on the spouse's vocation. When asked if they were happy with their careers more FCR were undecided (19% vs. 10%) and more MCR were strongly positive towards their careers (79% vs. 65%, $p=0.004$).

Harassment at Work

Twenty-three percent of FCR felt strongly that their colleagues said insensitive things about them versus 3% MCR ($p<0.001$). Twenty-five percent FCR vs. 1% MCR observed that residents were more critical of the opinions of FCR than their male counterparts.

Discussion

Colorectal surgery focuses on treating a defined region of the body and disease entities that are characteristic to it. The patient profile is also different from the regular general surgery patient and patient issues can also be rather complex. To make this work environment easier to handle, a good working relationship within a practice is needed. In the last decade, more female surgeons have been looking towards colorectal surgery as a specialty. The success of women in academic surgery is dependent on the institution and the leadership development that are available to them.[11] This survey did show that gender disparity existed and the disparity was not related to workload or individual work ethics.

A comparison with other surveys is not easy but a comparison was made with surveys from pediatric surgery,[12] cardiothoracic surgery [2], and plastic surgery [13] and some results have been compared (Table 4).

An anonymous survey dealing with a sensitive issue like gender bias does carry a potential for bias. Surgeons both male or female and irrespective of their age or years in practice could be in practices that are not a good fit or work with colleagues where the relationships are not symbiotic. There is no good way to evaluate this or exclude it from a general survey. Non-responders to this survey may also have been the rather busy colorectal surgeon from the generation that dealt with their career as their sole commitment or the dissatisfied surgeon ready to move to a different field. Some of the issues that this survey brought

Table 4 Comparison of Some Responses Among Different Surgical Specialties

Variable	Colorectal		Plastic surgery [13]		Cardothoracic surgery [2]		Pediatric surgery [12]
Response rate							
Overall	29%		60%		51%		75%
Male	22%		57%		44%		
Female	45%		73%		61%		
Demographics							
Average age							
Male	51 years		46.5 years		48 years		44 years (41%)
Female	42 years		42.1 years		42 years		
Marriage							
Male	94%		88.6%		92%		61%
Female	75%		64.6%		51%		
Academic practice							
Male	28%		31%		52%		60%
Female	38%		26.2%		64%		
Salary	Male	Female	Male	Female	Male	Female	Female
>$350,000	33%	11%	45%	24%	36%	12%	8.5%
<$250,000	63%	37%	52%	61%	10%	4%	53%
Career satisfaction							
Male	Yes		Yes		Yes		Yes
Female	Yes		Yes		Yes		
Unfair promotion/discrimination by opposite sex							
Male	No		No		No		NA
Female	Yes		Yes (59%)		Yes		
Sexual harassment (training/career)							
Male	No		No		No		NA
Female	Yes		Yes		Yes		
Encouraged by same sex role models/same sex role models needed							
Male	Yes		No		No		NA
Female	Yes		Yes		Yes		

forward maybe the result of a generational difference and a difference in perception of careers and its implication on the personal and family lives of both genders.

The survey had a response rate of 27% which is fairly low; however, response rates of some surveys dealing with similar issues have been comparable (Troppmann et al [14]; 25.5%). This may be due to the sensitive nature of the questionnaires. Hence, we cannot exclude bias from extremely satisfied or unhappy surgeons who have participated or the surgeon who does not agree that surveys like this bring forward any issues that can be addressed and hence are non-responders.

Demographics and Gender Issues

Female physicians have often been scrutinized in requiring time off for childbirth and family matters. Although most female colorectal surgeons in this study had children after their training more women are having children during their residency[15] and hence need flexibility in their work schedules. Work environments should not ignore this trend. Application of certain environmental changes targeted by Baumgartner et al.[16] which include day care facilities, limiting important departmental functions that occur at times spent with the family, and parental leave policies will benefit both genders. One of the issues many female surgeons face is pregnancy and its effect on their careers.[15] In general, most female physicians seem to consider "after residency" to be the best time to become pregnant.[17] However, having more than one pregnancy will lead to a break in a women's career path. In our survey compared to men less women than men had children in residency probably due to the same reasons that affect other women surgeons, and most had children in the first 6 years of their career. This is the trend among women surgeons in other fields like pediatric surgery and cardiothoracic surgery. [2, 18]

Time Issues

It is apparent that today's colorectal surgeon may not have the same attitude toward work as their older peers. Today, work and family are not independent issues. Although vacation was not an issue with either gender in this study flexibility of work schedules may become an important factor. Work satisfaction

with a work atmosphere that allows flexibility in timing and a routine that allows for adequate time away from work is becoming a trend irrespective of the gender.

Research Funding and Grants and Mentorship

There are many male role models, but female role models although not scarce are few. In the UK, female pediatric surgeons cited insufficient research time over lack of mentorship that hindered development.[18] In vascular surgery however in the USA men and women rarely reported a female mentor, and that women lacked female vascular mentors in medical school.[19] In this survey female colorectal surgeons did feel that female mentors were few and few males had female mentors. In colorectal surgery female surgeons have been more attracted to the specialty in the last two decades. This may be the reason the survey may have generated the response about the lack of female mentors. It is however vital that mentoring should be an institutional practice and female mentors encouraged in order to spark interest of the young female medical students.[20] A recent study has shown that mentored surgical residency graduates were more likely to enter the same specialty as the mentor,[21] thus mentoring female colorectal surgeons could be an inspiration for the medical graduates and keep academic institutions diverse. As women account for almost 60% of current graduating class, recruitment or attracting women to surgical specialties is becoming increasingly important. Neurosurgery has a white paper on recruitment and retention[19] and identifies eliminating discriminatory practices in hiring and advancement, promoting women to leadership positions, and training competent female trainees as some of their goals. Hoover et al.[22] also state that institutions must identify barriers that prevent women from entering surgery and develop leadership skills among women and insure a 'buy in' from their male counterparts.

Job Satisfaction and Vacation/Time Off

Although vacation was not an issue with either gender in this study flexibility of work schedules may become an important factor. Work satisfaction with a work atmosphere that allows flexibility in timing and a routine that allows for adequate time away from work is becoming a trend irrespective of the gender. This would in turn address burnout issues [9] that are often ignored. Balancing work and home issues [23] is the key to achieving harmony in the life of surgeons irrespective of gender. Barnett et al. have correlated reduced working hours with stronger family relationships and professional outcomes and have shown direct relationship of career satisfaction and intention to leave with quality of home life in women physicians who work reduced hours.[24]

Income

Income disparity between male and female physicians has been historically noted,[25] although women physician's salaries have increased and the disparity is less compared to those 30 years ago. Even in fields like obstetrics and gynecology an income disparity is present.[26, 27] Among general surgeons gender was independently associated with a lower income. Race was also an independent factor leading to income disparity among men. The reason for this disparity is unclear considering despite that the fact that both genders train for the same amount of time and sign up for the same workload. Do income differences exist based on caseload or work hours? We did not ask this question but it may be an important factor. However, income equality should be a goal not determined by gender or race and income disparity should only be considered discriminatory if case volumes are equal or productivity is equal.

General Issues

Most female surgeons are quite happy with their career choice [13] and would not change their career; however, most cite unequal promotion and income are cited as reasons for discontentment. Burnout was not specifically addressed in this questionnaire. However, it is intuitive that increased family pressures and decreased research opportunity may contribute to burnout. Among surgical oncologists burnout was reported in 28% of their respondents and burnout was seen more in the age 50 and younger age group with respondents having lower physical quality of life.[4] Younger surgeons are more susceptible to burnout and a perceived imbalance between career family and personal growth has been reported more than caseload.[9] Anderson et al. [28] have identified a relationship between career development issues, fellowship training, and type of fellowship training. Attention to these or acknowledging deficits and helping to overcome them, may be helpful in career satisfaction and retaining both male and female surgeons in any type of practice.

Although disparity in home time commitment based on gender does exist, it is important to balance work and home issues to achieve satisfaction in the workplace. Since 42% of the MCR and 10% of FCR had spouses that did not work outside the home in this study, more FCR surgeons feel pressured managing home issues. Therefore, departmental attitudes towards sensitivity regarding these issues and creating a work environment to meet these needs may attract both men and women surgeons and retain them.[23] Frank et al.[29] found that women physicians are most often satisfied with their careers, correctable factors include work stress, harassment, and poor control over work environment.

Conclusions

Gender disparity exists amongst colorectal surgeons; however, it is not based on work load or case mix. Work environment, disparity in income, involvement in management positions, research time, and mentoring opportunity are some of the areas that have been identified by this survey. It is essential to recognize that perceptions of male and female surgeons are different and that the issues need to be addressed in order to recruit and retain surgeons. In the era where more women are graduating from medical schools and projections for future surgeons are expected to decrease, it is vital that hospitals examine their surgical departments making changes that will attract and retain both genders. In turn this will lead to diversity particularly among teaching institutions that will attract all incoming medical students.

A Questionnaire to Evaluate the Perceived Gender Differences of Surgeons In Colorectal Practice

Section I - Demographics

1. Age _____

2. Sex ☐ Male ☐ Female

3. Marital Status ☐ Single ☐ Married ☐ Separated ☐ Divorced ☐ Widowed ☐ Living with partner

4. Years in Practice _____

5. Board Certified ☐ General Surgery ☐ Colorectal Surgery

6. Type of Practice ☐ Private Practice ☐ Institutional Practice

7. Income ☐ <150,000 ☐ 350,000 – 500,000 ☐ 150,000 – 250,000 ☐ 500,000 – 700,000 ☐ 250-000 – 350,000 ☐ >700,000

8. Spouse Occupation
☐ Not employed ☐ Finance ☐ Pharmaceutical
☐ Physician ☐ Engineering ☐ Marketing/Sales
☐ Healthcare (Non-physician) ☐ Other _____

9. Age at Start of Surgical Residency: _____

10. Age at time of first/only marriage: _____

11. Age when 1st child was born _____

12. Any children before/during residency? ☐ Yes ☐ No ☐ No children

13. Time when first child was born:

☐Medical School ☐ Internship ☐ Residency
☐ Fellowship ☐ Clinical Practice, Years 1-3 ☐ Clinical Practice, Years >3

14. Colorectal surgery was my first career choice? ☐ Yes ☐ No

15. I would change my career choice if I had the opportunity? ☐ Yes ☐ No

16. My practice is in the town I did my surgical/colorectal training? ☐ Yes ☐ No

Section II - Time

1. Percentage of time spent on:
   a. Clinical work _____%
   b. Teaching _____%
   c. Research _____%
   d. Administration _____%
   e. Other _____%

2. Total hours spent at work per week: _____hrs

3. Total number of days on call per month: _____days

4. Number of weekends on call per quarter: _____

5. The time spent with family / children is: ☐ Adequate ☐ Inadequate

6. The time spent on hobbies is: ☐ Adequate ☐ Inadequate

7. The time involved in sports/outdoor activities is: ☐ Adequate ☐ Inadequate

Section III - Gender Issues

1. Gender is an important factor in performing my current job.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

2. My gender is important to the way the nurses and ancillary staff react to me.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

3. The nurses and ancillary staff react to me in a positive way most of the time.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

4. My gender affects the atmosphere in the OR in a positive way.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

5. Surgical residents approach me readily because of my gender.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

6. My colleagues have a high opinion of my capabilities.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

7. I feel overburdened by my workload.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

8. Colleagues of the opposite sex seem to handle work pressure better than I can.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐Disagree ☐ Strongly disagree

Section IV - Specialty Issues

1. In my specialty:

   a. Women patients tend to seek me out.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

   b. Male patients tend to seek me out.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

   c. HIV positive patients tend to seek women physicians.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

   d. Patients rely on their referring doctor for a choice of surgeon.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

2. "Colorectal Surgery" is male dominated and women have a limited role.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

3. Women are intimidated by the workload and work hours in Colorectal Surgery.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

4. Women are better off handling women's issues and problems in Colorectal Surgery.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

5. You are happy in your practice because of:

a. Salary	☐ Yes	☐ No
b. Case Mix	☐ Yes	☐ No
c. Workload	☐ Yes	☐ No
d. Part time Work Schedule	☐ Yes	☐ No
e. No Gender Bias	☐ Yes	☐ No
f. Relationship with colleagues	☐ Yes	☐ No
g. Work atmosphere	☐ Yes	☐ No
h. No academia	☐ Yes	☐ No
i. Research opportunities	☐ Yes	☐ No
j. Chances to progress	☐ Yes	☐ No
k. Opportunities to learn new techniques	☐ Yes	☐ No

6. You are unhappy in your practice because of

a. Salary	☐ Yes	☐ No
b. Case Mix	☐ Yes	☐ No
c. Workload	☐ Yes	☐ No
d. Part time Work Schedule	☐ Yes	☐ No
e. No Gender Bias	☐ Yes	☐ No
f. Relationship with colleagues	☐ Yes	☐ No
g. Work atmosphere	☐ Yes	☐ No
h. No academia	☐ Yes	☐ No
i. Research opportunities	☐ Yes	☐ No
j. Chances to progress	☐ Yes	☐ No
k. Opportunities to learn new techniques	☐ Yes	☐ No
l. No family life	☐ Yes	☐ No

Section V - Job Satisfaction

1. Career advancement opportunities are few in Colorectal Surgery for women.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

2. Women feel restricted in Colorectal Surgery because of their numbers and gender.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

3. Female mentors are few because women surgeons are too involved in their job and home to mentor.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

4. Male residents/surgeons do not like female mentors.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

5. In my practice my case mix does not reflect my gender.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

6. My colleagues support me fully in my daily activities.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

7. I would recommend Colorectal Surgery as a career to female residents.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

Section VI - Vacation and Time Off

1. My vacation time is adequate.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

2. I take more frequent vacations than my opposite gender colleagues.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

3. I take vacations to catch up on office and research work.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

4. I take more vacations than my partners due to issues at home (family illness, etc).
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

Section VII - Income

1. My income is
   ☐ **Comparable to** other colorectal surgeons in the area where I practice
   ☐ L**ess than** other colorectal surgeons in the area that I practice
   ☐ M**ore than** other colorectal surgeons in the area that I practice

2. I would work more hours and perform more surgery if it would mean a higher salary.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

3. I would cut down hours and sacrifice income to spend time with my family.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

4. My debts have kept me from cutting down on work hours/income.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

Section VIII - Research & Grant Funding

1. Approximate number of articles published _____

2. The number of articles I have published is approximate at this stage of my career.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

3. Have you received grant funding? ☐ Yes ☐ No

4. If grant funding was not received, it is because of:

   ☐ No time
   ☐ No available funding in my field of interest
   ☐ No interest
   ☐ No research time
   ☐ Inadequate mentoring

Section IX - Career Advancement

1. My career is at a standstill since the past few years.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

2. I have adequate career advancement opportunities in my practice.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

3. I cannot advance my career as I cannot make a location change due to my spouse's job.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

4. I would prefer to cut down hours to advancing my career.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

5. I am happy with my career at present.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

Section X - Harassment at work

1. Colleagues of the opposite gender say insensitive things to me.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

2. Residents are more critical of my opinion than that of my opposite gender colleagues.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

3. I sense my opinion is regarded considerably less for executive decision making within my department due to my gender.
   ☐ Strongly agree ☐ Agree ☐ Undecided ☐ Disagree ☐ Strongly disagree

References

1. Colleges. AOAM. Women in US Academic Medicine. Statistics and medical school benchmarkng 2004;1–40.
2. Dresler CM, Padgett DL, MacKinnon SE, Patterson GA. Experiences of women in cardiothoracic surgery. A gender comparison. Arch Surg 1996;131(11):1128–1134. discussion 1135
3. Ennker IC, Schwarz K, Ennker J. The disproportion of female and male surgeons in cardiothoracic surgery. Thorac Cardiovasc Surg 1999;47(2):131–135.
4. Kuerer HM, Eberlein TJ, Pollock RE, et al. Career satisfaction, practice patterns and burnout among surgical oncologists: report on the quality of life of members of the Society of Surgical Oncology. Ann Surg Oncol 2007;14(11):3043–3053.
5. Schroen AT, Brownstein MR, Sheldon GF. Women in academic general surgery. Acad Med 2004;79(4):310–318.
6. Sonnad SS, Colletti LM. Issues in the recruitment and success of women in academic surgery. Surgery 2002;132(2):415–419.
7. Neumayer L, Konishi G, L'Archeveque D, et al. Female surgeons in the 1990s. Academic role models. Arch Surg 1993;128(6):669–672.
8. Jonasson O. Women as leaders in organized surgery and surgical education. Has the time come? Arch Surg 1993;128(6):618–621.
9. Campbell DA Jr, Sonnad SS, Eckhauser FE, et al. Burnout among American surgeons. Surgery 2001;130(4):696–702. discussion 702–705
10. Wolfle D, Likert R, et al. Standards for appraising psychological research. Am Psychologist 1949;4:320–328.
11. Flannery AM. Success, women, and academic surgery. Surgery 2002;131(6):670–671.
12. Caniano DA, Sonnino RE, Paolo AM. Keys to career satisfaction: insights from a survey of women pediatric surgeons. J Pediatr Surg 2004;39(6):984–990.
13. Capek L, Edwards DE, Mackinnon SE. Plastic surgeons: a gender comparison. Plast Reconstr Surg 1997;99(2):289–299.
14. Troppmann KM, Palis BE, Goodnight JE, et al. Career and lifestyle satisfaction among surgeons: what really matters? The National Lifestyles in Surgery Today Survey. J Am Coll Surg 2009;209(2):160–169.
15. Potee RA, Gerber AJ, Ickovics JR. Medicine and motherhood: shifting trends among female physicians from 1922 to 1999. Acad Med 1999;74(8):911–919.
16. Baumgartner WA, Tseng EE, DeAngelis CD. Training women surgeons and their academic advancement. Ann Thorac Surg 2001;71(2 Suppl):S22–S24.
17. Sinal S, Weavil P, Camp MG. Survey of women physicians on issues relating to pregnancy during a medical career. J Med Educ 1988;63(7):531–538.
18. Smith NP, Dykes EH, Youngson GS, Losty PD. Is the grass greener? A survey of female pediatric surgeons in the United Kingdom. J Pediatr Surg 2006;41(11):1879–1881.
19. Benzil DL, Abosch A, Germano I, et al. The future of neurosurgery: a white paper on the recruitment and retention of women in neurosurgery. J Neurosurg 2008;109(3):378–386.
20. De Angelis CD. Women in academic medicine: new insights, same sad news. N Engl J Med 2000;342(6):426–427.
21. McCord JH, McDonald R, Sippel RS, et al. Surgical career choices: the vital impact of mentoring. J Surg Res 2008.
22. Hoover EL. Mentoring women in academic surgery: overcoming institutional barriers to success. J Natl Med Assoc 2006;98 (9):1542–1545.
23. Colletti LM, Mulholland MW, Sonnad SS. Perceived obstacles to career success for women in academic surgery. Arch Surg 2000;135(8):972–977.
24. Barnett RC, Gareis KC, Carr PL. Career satisfaction and retention of a sample of women physicians who work reduced hours. J Womens Health (Larchmt) 2005;14(2):146–153.
25. Wallace AE, Weeks WB. Differences in income between male and female primary care physicians. J Am Med Womens Assoc 2002;57(4):180–184.
26. Weeks WB, Wallace AE. The influence of physician race and gender on obstetrician-gynecologists' annual incomes. Obstet Gynecol 2006;108(3 Pt 1):603–611.
27. Yutzie JD, Shellito JL, Helmer SD, Chang FC. Gender differences in general surgical careers: results of a post-residency survey. Am J Surg 2005;190(6):955–959.
28. Anderson KD, Mavis BE. The relationship between career satisfaction and fellowship training in academic surgeons. Am J Surg 1995;169(3):329–333.
29. Frank E, McMurray JE, Linzer M, Elon L. Career satisfaction of US women physicians: results from the Women Physicians' Health Study. Society of General Internal Medicine Career Satisfaction Study Group. Arch Intern Med 1999;159(13):1417–1426

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ORIGINAL ARTICLE

Is the Use of T-tube Necessary after Laparoscopic Choledochotomy?

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Abstract
Background Traditionally, the common bile duct (CBD) is closed with T-tube drainage after choledochotomy and removal of CBD stones. However, the insertion of a T-tube is not without complication.
Aim of Work This randomized study was designed to compare the use of T-tube and primary closure of choledochotomy after laparoscopic choledochotomy to determine whether primary closure can be as safe as closure with T-tube drainage.
Methods Between February 2006 and June 2009, 122 consecutive patients with proven choledocholithiasis had laparoscopic choledochotomy. They were randomized into two equal groups: T-tube (n=61) and primary closure (n=61). Demographic data, intraoperative findings, postoperative complications, and postoperative stay were recorded.
Results There was no mortality in both groups. There were no differences in the demographic characteristics or clinical presentations between the two groups. Compared with the T-tube group, the operative time and postoperative stay were significantly shorter and the incidences of overall postoperative complications and biliary complications were statistically and significantly lower in the primary closure group.
Conclusion Laparoscopic common bile duct exploration with primary closure without external drainage after laparoscopic choledochotomy is feasible, safe, and cost-effective. After verification of ductal clearance, the CBD could be closed primarily without T-tube insertion.

Keywords T-tube · Common bile duct exploration · Choledochotomy · Laparoscopic · Primary closure

Introduction

Laparoscopic common bile duct exploration (LCBDE) for choledocholithiasis has become increasingly popular as prospective randomized studies have concluded that LCBDE, as a single-stage procedure, is feasible, safe, effective, and cost-effective compared to the two-stage procedure for the management of choledocholithiasis.[1–3]

The LCBDE can be performed either transcystically or through a choledochotomy according to specific indications.[4] Traditionally, the common bile duct (CBD) is closed with T-tube drainage after choledochotomy and removal of CBD stones. Laparoscopic choledochotomy carries a higher morbidity rate than the transcystic approach, mainly related to the T-tube insertion at the end of the procedure.[5,6] A study has highlighted the fact that the T-tube-related complication rate is approximately 15%, without any significant difference between open and laparoscopic CBD explorations.[7] This led several authors to perform laparoscopic primary duct closure after choledochotomy.[8–10]

The purpose of this randomized study is to answer the question: is it safe to close the CBD after laparoscopic choledochotomy without insertion of a T-tube?

Patients and Methods

Between February 2006 and June 2009, LCBDE was tried as a single-stage procedure in a total of 254 consecutive

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patients with proven choledocholithiasis. LCBDE was successfully completed in 232 cases and the remaining 22 cases required conversion to laparotomy. Of the 232 successfully completed cases, 98 underwent laparoscopic transcystic stone extraction and 134 required laparoscopic choledochotomy.

In our work, laparoscopic choledochotomy was indicated when the CBD was wider than 10 mm, stones were large (>10 mm), multiple (>4), proximal in location, or after failure of transcystic duct exploration.[11,12] Out of 134 patients with laparoscopic choledochotomy, four patients underwent laparoscopic choledochoduodenostomy due to markedly dilated CBD (>15 mm) or benign stricture at the lower end of CBD. Choledochotomy closure with an antegrade stent placed under fluoroscopic guidance was performed in six patients. Closure with leaving the retrograde stent placed at the previous endoscopic attempt was carried out in two patients.

The remaining 122 patients with laparoscopic choledochotomy—after fluoroscopic verification of complete CBD clearance—were randomly divided into two equal groups: the first group had extrahepatic biliary tree decompression at the end of the procedure by T-tube placement (T-tube group, n=61) and the second group had primary closure of choledochotomy using absorbable sutures without placement of a T-tube or biliary endoprosthesis (primary closure group, n=61).

All patients were subjected to history taking, clinical examination, biochemical workup, abdominal ultrasound examination, and medical fitness for anesthesia. Late in this work, magnetic resonance cholangiopancreatography (MRCP) was considered when the diagnosis of CBD stone was doubtful.

Patients were excluded when there was evidence of pancreatitis (abdominal pain, nausea/vomiting, and serum amylase more than triple the normal value) or evidence of cholangitis (upper abdominal pain, fever/rigors, and high leukocytic count). Additionally, postcholecystectomy patients and patients with a contraindication to laparoscopy (associated medical comorbidities, upper abdominal surgery, morbid obesity, or marked liver cirrhosis) were excluded.

All procedures, including obtaining written informed consent from the patient, were conducted in accordance with the recommendations of the Ethics Committee of the Faculty of Medicine, Mansoura University. Patients were randomly assigned to either primary closure or T-tube drainage by means of the closed envelope method.

Surgical Technique

The patient was positioned in the American position with head up and table tilt to the left. The surgeon stood to the left of the patient with the camera holder by his side and the first assistant to the right side of the patient. We used four port sites: 10–12 mm at the umbilicus for the 30° camera, 10–12 mm at the epigastrium, 5 mm at the midclavicular line close to the right costal margin, and 5 mm at the right anterior axillary line. A fifth port was used optionally to facilitate the introduction of basket, balloon, and guidewire.

The operation started by dissection at Calot's triangle exposing the cystic duct and artery. The cystic artery was divided between clips and the cystic duct was dissected for a sufficient length. The cystic duct was opened using scissors for intraoperative cholangiography. For all cases, operative cholangiography was performed using the Olsen/Reddich cholangiography forceps with a 4- or 5-Fr ureteric catheter. Dynamic fluoroscopic images were obtained with a mobile C-arm.

Choledochotomy was performed by first dissecting the peritoneal coverage of the anterior wall of the CBD. The actual wall of the CBD was opened longitudinally by scissors and the hole was extended by scissors or hook diathermy. The choledochotomy was located below the level of the cystic duct and close to the duodenum and it was made to equal the size of the largest stone.

Stones were removed by suction irrigation, forceps milking of the CBD, or basket and/or biliary balloon either blindly or under fluoroscopic guidance. Choledochoscope was not available at the time of our study so we did not use choledochoscopy in any case. Duct clearance was confirmed by routine completion cholangiography proximally and distally, using Fogarty balloon catheter.

After radiological verification of complete clearance of the CBD, patients were randomly assigned to either primary duct closure or T-tube drainage. In the primary closure group, the choledochotomy was closed primarily with 4/0 absorbable sutures (4/0 Vicryl; Ethicon, NJ) and intracorporeal knotting, whereas in the T-tube drainage group, a latex rubber T-tube of appropriate size (14–16 Fr) was inserted into the CBD incision. After the tube had been positioned in place, the CBD incision was closed using continuous sutures (4/0 Vicryl; Ethicon). Saline was flushed through the T-tube to rule out leakage and completion cholangiography was done to ensure ductal clearance and proper tube position.

At the end of the procedure, a subhepatic drain was placed and it was removed on the next morning when there was no evidence of leak. Patients with T-tube were discharged on the second postoperative day with the T-tube patent and connected to a drainage bag. Postoperative T-tube cholangiograms were obtained at the tenth day in the outpatient setting, and the tube was removed once clearance was verified. If there were retained stones, endoscopic retrograde cholangiopancreatography (ERCP) was ordered for removal of stones. Patients with primary closure were

Table 1 Characteristics of the Study

Parameter	T-tube (n=61)	Primary closure (n=61)	P value[a]
Sex (female/male)	45/16	39/22	0.468
Age in years, mean (range)	39 (20–71)	43 (20–67)	0.846
Indication			
Jaundice	52	48	0.063
Biliary colic without jaundice	9	13	0.574
Preoperative failed ERCP	5	4	0.138

[a] Student's t test

discharged once the peritoneal drain was removed. Follow-up assessment using liver function tests and ultrasound was carried out at 2 weeks and 2 months after surgery, with MRCP or ERCP used when indicated.

Statistical Analysis

All values were expressed as the mean (range). We compared the two groups of patients in terms of epidemiologic characteristics, intraoperative findings, and postoperative outcome. The statistical differences between the two groups were determined by Student's t test. Statistical significance was taken at $P<0.05$. All statistical calculations were performed using the SPSS statistical package (SPSS 12.0.1 for Windows; SPSS, Chicago, IL) software.

Results

There were no statistically significant differences in epidemiologic features, preoperative factors (Table 1), or intraoperative findings (Table 2) between the two groups. There was no statistically significant difference in CBD diameter, number of extracted stones, or stone number between the two groups, but the surgical time and postoperative hospital stay (and consequently hospital expenses) in the primary closure group were statistically lower than that of the T-tube drainage group (Table 2).

We did not experience any technical failure, either on T-tube or primary closure group and all operations were completed laparoscopically. There was no mortality in both groups. Postoperatively, six patients developed complications, five of whom were in the T-tube group. In the T-tube group, two patients developed biliary peritonitis on the second and third postoperative day due to leakage around the T-tube and was treated by laparotomy, peritoneal lavage, and T-tube replacement. One patient developed T-tube dislodgement, which was treated by open reoperation and T-tube replacement on the third postoperative day, with an excellent final outcome. One patient had evident internal hemorrhage and was treated by open exploration and control of the bleeder at the edge of choledochotomy. In a fifth patient, a subhepatic collection was successfully drained percutaneously. In the primary closure group, only one patient had bile leak in the surgical drain without peritonitis and he was treated conservatively with stoppage of leakage after 4 days.

Only one patient in the T-tube group had a retained stone diagnosed by postoperative T-tube cholangiogram and was successfully removed by endoscopic sphincterotomy. No other retained stones were detected at early (2 weeks) or late (2 months) follow-up in either group. The present results demonstrate a significantly shorter operative time, lower postoperative morbidity rate, and shorter postoperative hospital stay for the primary closure group compared to the T-tube group (Table 2).

Table 2 Intraoperative Findings and Postoperative Outcome

Parameter	T-tube (n=61)	Primary closure (n=61)	P value[a]
CBD diameter in IOC (mm)	11.6 (10–15.5)	11.2 (10–15)	0.0734
No. of extracted stones	2.3 (1–4)	1.9 (1–3)	0.0812
Operative time (min)	125.1 (100–150)	100.6 (90–120)	*0.022*
Postoperative complications related to the procedure	5	1	*0.035*
Retained stones	1	0	0.068
Postoperative hospital stay (days)	5.5 (4–11.25)	2.2 (1–5)	*0.005*

Significant values are in italics

CBD common bile duct, *IOC* intraoperative cholangiogram

[a] Student's t test

Discussion

The most recent advance in the management of CBD stones is LCBDE that can be performed either transcystically or through a choledochotomy according to specific indications. Laparoscopic choledochotomy is generally indicated in patients with a wide CBD (>9 mm in diameter) to avoid bile duct stricture,[11,13] large (>10 mm) stones, or multiple, impacted, and intrahepatic stones,[4,14] and also in cases of unfavorable cystic duct anatomy (e.g., too small, tortuous cystic duct, low cystic–CBD junction) or when the transcystic approach has failed.[9,15]

Because instrumentation of the CBD and maneuvers for stone extraction may cause edema to the papilla, leading to an increase in pressure inside the biliary tree,[16] temporary postoperative biliary drainage is usually required and T-tube placement has been historically chosen as the drainage method of choice.[17] The advocates of the use of a T-tube argue that it allows spasm or edema of sphincter to settle after the trauma of the exploration. Postoperative T-tube drainage has been used to prevent bile stasis, decompress the biliary tree, and minimize the risk of bile leakage. A T-tube has also provided an easy percutaneous access for cholangiography and extraction of retained stones.[18]

Despite these potential advantages, morbidity rates related to T-tube presence have been reported to be at a rate of 4% to 16.4% in the laparoscopic era.[2,11] The T-tube-related complications include accidental T-tube displacement leading to CBD obstruction,[19] bile leakage,[20] persistent biliary fistulas and excoriation of the skin,[21] cholangitis from exogenous sources through the T-tube, and dehydration and saline depletion.[22] Additionally, CBD stenosis has been reported as a long-term complication after T-tube removal. After discharge, indwelling T-tubes become uncomfortable, requiring continuous management, thus restricting patient activity because of the risk of dislodgement.[23] The 8.2% morbidity rate in the T-tube group of patients in the present study is comparable to those in published reports.[7,11]

For the above-mentioned disadvantages of T-tube use, a second option for choledochotomy closure, which is primary closure of choledochotomy with placement of biliary endoprosthesis, was proposed.[24,25] Biliary endoprosthesis, as with a T-tube, achieves biliary decompression, and published results have suggested that this leads to lower morbidity, shorter postoperative hospital stay, less postoperative discomfort, and earlier return to full activities, compared to T-tube placement.[15,26,27] Moreover, the presence of the endoprosthesis in the duodenal lumen makes postoperative ERCP easier, in the presence of residual CBD stones.[15,23] However, the use of biliary endoprosthesis is not devoid of complications such as duodenal erosion,[28] stent occlusion,[29] ampullary stenosis,[30] and distant stent migration, causing intestinal[31] or colonic[32] perforation. Moreover, removal of biliary endoprosthesis requires second-stage endoscopic extraction.

A third option for choledochotomy closure is primary closure without the use of T-tube or biliary endoprosthesis. Favorable short-term and long-term results have been published with this technique.[33] This option avoids the morbidities related to the use of T-tube or biliary stents. In this study, no postoperative mortality occurred in either group. The postoperative hospital stay and the operation time were shorter in the primary closure group than in the T-tube group. We did not calculate hospital expenses, but definitely, it is higher with longer operative time and hospital stay in the T-tube group. We have shown more complications in the T-tube group than in the primary closure group. Similar to the findings by other authors,[34] in our study, most complications in the T-tube group were related to the use of the T-tube.

However, our results do not match with those of some authors. A study noted higher complication and bile leakage rates after primary closure than those reported by this study,[9] and an experimental study addressed the issue of stenosis following primary closure without some form of drainage.[24] In this study, we found that the complication rate and bile leakage were lower after primary closure. We need studies with longer follow-up period for the evaluation of ductal stenosis.

At the end, according to the results of this randomized study, primary closure did not increase the risk of bile leakage after the operation. Postoperative hospital stay and operation time were shorter and the hospital expenses were lower in the primary closure group than in the T-tube group. Additionally, with primary closure, we could definitely avoid T-tube-related complications. Therefore, we can conclude that primary closure without external drainage after laparoscopic choledochotomy is feasible, safe, and cost-effective. After verification of ductal clearance, we can close the CBD primarily without the use of T-tube. However, randomized trials on a larger scale of patients and with a longer follow-up are awaited to address the issue of stenosis after primary closure.

References

1. Rhodes M, Sussman L, Cohen L, Lewis MP. Randomized trial of laparoscopic exploration of common bile duct versus postoperative endoscopic retrograde cholangiography for common bile duct stones. Lancet 1998;351:159–161.
2. Cuschieri A, Lezoche E, Morino M, et al. EAES multicenter prospective randomized trial comparing two-stage vs single-stage management of patients with gallstone disease and ductal calculi. Surg Endosc 1999;13:952–957.

3. Tranter SE, Thompson MH. Comparison of endoscopic sphincterotomy and laparoscopic exploration of the common bile duct. Br J Surg 2002;89:1495.
4. Memon MA, Hassaballa H, Memon MI. Laparoscopic common bile duct exploration: the past, the present, and the future. Am J Surg 2000;179:309–315.
5. Rhodes M, Nathanson L, O'Rourke N, Fielding G. Laparoscopic exploration of the common bile duct: lessons learned from 129 consecutive cases. Br J Surg 1995;82:666–668.
6. Franklin ME, Pharand D, Rosenthal D. Laparoscopic common bile duct exploration. Surg Laparosc Endosc 1994;4:119–124.
7. Wills VL, Gibson K, Karihaloo C, Jorgensen JO. Complications of biliary T-tubes after choledochotomy. ANZ J Surg 2002;72:177–180.
8. Ha JP, Tang CN, Siu WT, et al. Primary closure versus T-tube drainage after laparoscopic choledochotomy for common bile duct stones. Hepatogastroenterology 2004;51:1605.
9. Decker G, Borie F, Millat B, et al. One hundred laparoscopic choledochotomies with primary closure of the common bile duct. Surg Endosc 2003;17:12–18.
10. Zhang LD, Bie P, Chen P, et al. Primary duct closure versus T-tube drainage following laparoscopic choledochotomy. Zhonghua Waike Zazhi 2004;42:520
11. Martin IJ, Bailey IS, Rhodes M, et al. Towards T-tube-free laparoscopic bile duct exploration: a methodological evolution during 300 consecutive procedures. Ann Surg 1998;228:29–34.
12. Berthou JC, Dron B, Charbonneau PH, et al. Evaluation of laparoscopic treatment of common bile duct stones in a prospective series of 505 patients: indications and results. Surg Endosc 2007;21:1970.
13. Dion YM, Rattele R, Morin J, Gravel D. Common bile duct exploration: the place of laparoscopic choledochotomy. Surg Laparosc Endosc 1994;4:419–424.
14. Jacobs M, Verdeja JC, Goldstein HS. Laparoscopic choledochotomy. J Laparoendosc Surg 1991;1:79–81.
15. DePaula AL, Hashiba K, Bafutto M, Machado C, Ferrari A, Machado MM. Results of the routine use of a modified endoprosthesis to drain the common bile duct after laparoscopic choledochotomy. Surg Endosc 1998;12:933–935.
16. Holdsworth RJ, Sadek SA, Ambikar S, Cushieri A. Dynamics of bile flow through the human choledochal sphincter following exploration of the common bile duct. World J Surg 1989;13:300–306.
17. DeRoover D, Vanderveken M, Gerard Y. Choledochotomy: primary closure versus T-tube. A prospective trial. Acta Chir Belg 1989;89:320–324.
18. Paganini AM, Feliciotti F, Guerrieri M, et al. Laparoscopic common bile duct exploration. J Laparoendosc Adv Surg Tech A 2001;11:391–400.
19. Bernstein DE, Goldberg RI, Unger SW. Common bile duct obstruction following T-tube placement at laparoscopic cholecystectomy. Gastrointest Endosc 1994;40:362–365.
20. Kacker LK, Mittal BR, Sikora SS, et al. Bile leak after T-tube removal: a scintigraphic study. Hepatogastroenterology 1995;42:975–978.
21. Ortega Lopez D, Ortiz Oshiro E, La Pena Gutierrez L, Martinez Sarmiento J, Sobrino del Riego JA, Alvarez Fernandez-Represa J. Scintigraphic detection of biliary fistula after removal of a T-tube. Br J Surg 1995;82:82.
22. Lygidakis NJ. Choledochotomy for biliary lithiasis: T-tube drainage or primary closure. Effect on postoperative bacteremia and T-tube bile infection. Am J Surg 1983;146:254–256.
23. Gersin KS, Fanelli RD. Laparoscopic endobiliary stenting as an adjunct to common bile duct exploration. Surg Endosc 1998;12:301–304.
24. Wu JS, Soper NJ. Comparison of laparoscopic choledochotomy closure techniques. Surg Endosc 2002;16:1309–1313.
25. Riniatsos G, Arvounis E, Rbuckle J, Sla A. Cost-effective method for laparoscopic choledochotomy. ANZ J Surg 2005;75:35–38.
26. Sheen-chen S, Chou FF. Choledochotomy for biliary lithiasis: is routine drainage necessary? A prospective controlled trial. Acta Chir Scand 1990;156:387–390.
27. Sheridan WG, Williams HOL, Lewis MH. Morbidity and mortality of common bile duct exploration. Br J Surg 1987;74:1095–1099.
28. Lowe GM, Bernfield JB, Smith CS, Matalon TAS. Gastric neumatosis: sign of biliary stent-related perforation. Radiology 1990;174:1037–1038.
29. Yeoh KG, Zimmerman MJ, Cunningham JT, Cotton PB. Comparative costs of metal versus plastic biliary stent strategies for malignant obstructive jaundice by decision analysis. Gastrointest Endosc 1999;49:466–471.
30. Johanson JF, Schmalz MJ, Geenen JE. Incidence and risk factors for biliary and pancreatic stent migration. Gastrointest Endosc 1992;38:341–346.
31. Mofidi R, Ahmed K, Mofidi A, Joyce WP, Khan Z. Perforation of ileum: an unusual complication of distal biliary stent migration. Endoscopy 2000;32(11):S67.
32. Lenzo NP, Garas G. Biliary stent migration with colonic diverticular perforation. Gastrointest Endosc 1998;47:543–544.
33. Croce E, Golia M, Azzola M, et al. Laparoscopic choledochotomy with primary closure: follow-up (5–44 months) of 31 patients. Surg Endosc 1996;10:1064–1068.
34. Guillon F, Rodier JG, Fingerhut A. One hundred laparoscopic choledochotomies with primary closure of the common bile duct. Surg Endosc 2003;17:12.

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ORIGINAL ARTICLE

Influence of Body Mass Index on Complications and Oncologic Outcomes Following Hepatectomy for Malignancy

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Abstract
Background Following hepatectomy for malignancy, the effect of body mass index (BMI) on hepatic and oncologic outcomes is unknown.
Methods Two hundred seventy-nine post-hepatectomy patients with malignancy from our center were included in the cohort (1996–2006). BMI was categorized using World Health Organization criteria. The effect of BMI was evaluated using risk-adjusted Cox models for time to recurrence and overall survival.
Results Seventy-nine patients (28.3%) had primary hepatobiliary cancers, 134 (48.0%) had colorectal metastases, and 66 (25.3%) had other metastases. Thirty-five percent of patients were obese (BMI>30). Obese patients had more hepatic-specific perioperative complications (27.8% vs. 15.9%, p=0.018), bile leaks (18.6% vs. 9.9%, p=0.030), post-operative pneumonia (9.3% vs. 2.2%, p=0.0074), intra-abdominal abscesses (7.2% vs. 1.7%, p=0.017), acute renal failure (7.2% vs. 1.7%, p=0.017), urinary tract infections (16.4% vs. 7.7%, p=0.024), and longer lengths of stay (10.5 vs.8.6 days, p=0.029). Obese and non-obese patients had similar perioperative mortality, time to recurrence, and overall survival on univariate analysis. However, after adjusting for demographic, tumor, and operative characteristics, and complications, increasing BMI displayed improved recurrence-free (HR 0.90, 95% CI 0.86–0.95) and overall survival (HR 0.96, 95% CI 0.92–0.99).
Conclusions High BMI patients may have better oncologic outcomes despite higher perioperative morbidity and hepatic complications following hepatectomy. These findings have important clinical and biological implications.

Keywords Body mass index · Hepatic malignancy · Hepatectomy · Survival · Recurrence

Introduction

Obesity is an increasing public health problem in the USA. Nearly a third of the US population is considered obese, with more than 66% of individuals being overweight or obese.[1] Significant research has been devoted to studying the negative health effects of obesity, including cardiovascular disease, dyslipidemia, diabetes mellitus, and, recently, malignancy.[1,2] Several reports have emerged about the increased lifetime risk of certain types of cancer in obese patients, including breast, endometrial, prostate, renal cell, and colorectal cancers.[3,4]

Obesity, to varying extents, has been shown recently to be a risk factor for surgical complications following general surgical operations.[5–8] Indeed, hepatic steatosis incidence is higher for obese patients (~25%) with subsequent higher complication rates following hepatic surgery.[9,10] Steatosis is not always quantifiable pre-operatively and is not universal in its occurrence in patients with a high body mass index (BMI). The prognostic value of pre-operative BMI to predict hepatic complications following liver resection is less defined. Further, the role of BMI in oncologic outcomes for solid organ malignancies is controversial,

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particularly with regard to hepatobiliary and pancreatic cancers. Recent data suggest that obesity is correlated with node-positive disease and worse survival for patients with pancreatic adenocarcinoma.[11,12] With regard to oncologic outcomes for patients with hepatic malignancies, this relationship has been largely unexplored. Two large meta-analyses suggest that obesity is associated with increased risk of hepatobiliary malignancy,[13,14] but the influence of BMI on oncologic outcomes following hepatectomy for primary liver tumors and hepatic metastases is unknown. With the increasing rates of obesity in the US coupled with the increasing volume of hepatobiliary cancer cases, the need to further understand this influence is imperative to understanding biologic determinants of tumor recurrence as well as tailoring future therapies.

We therefore queried whether patients with high BMIs would have greater perioperative and hepatic-specific complications with inferior overall survival and shorter time to recurrence following hepatic resection. Within this context, we retrospectively reviewed 279 hepatectomy cases for primary and metastatic hepatic malignancies at our center to further understand the relationship between BMI and oncologic outcomes. In this study, we show that while perioperative and hepatic-specific complications are increased in obese patients following hepatectomy, risk-adjusted oncologic outcomes improved, rather than worsened, in the presence of high BMI.

Material and Methods

Patient Cohort

We reviewed all patients who underwent hepatectomy at our center from July 5, 1995 to March 17, 2006. We defined obesity by adapting the World Health Organization (WHO) definition, as determined by BMI: underweight less than 18.5, normal weight 18.5–24.9, overweight 25.0–29.9, class I obese 30.0–34.9, class II obese 35.0–39.9, and class III obese greater than 40.0. Obese was defined as BMI greater than or equal to 30 for this study. BMI was identified during electronic medical record review and was considered valid if recorded before the date of hepatectomy. Three hundred sixty-four patients were identified with adequate BMI and clinical data for review. Eighty-five patients were excluded due to the presence of a benign diagnosis. Patient diagnoses, demographics, co-morbidities, operative details, radiographic results, laboratory results, tumor pathology, complications, and dates of death and recurrence were recorded via comprehensive medical record review. Dates of death were further confirmed using the Social Security Death Master File. The study was performed under local institutional review board approval.

Diagnostic Classifications and Definitions of Outcomes

Malignant diagnoses included metastatic colorectal cancer, primary hepatobiliary malignancies (hepatocellular carcinoma, gallbladder adenocarcinoma, and cholangiocarcinoma), and other metastases (neuroendocrine, melanoma, and sarcoma). Major hepatic resections were defined as lobectomy, extended lobectomy, or resections of greater than three Couinaud segments. Minor resections were defined as less than three segments. Patients were included in the cohort if surgical treatment had the intention of cure by clinical and stage criteria. Patients who had palliative operations were excluded. Post-operative complications were defined as hepatic and non-hepatic. Hepatic complications included development of ascites, biliary leak, cholangitis, and hepatic dysfunction. Hepatic dysfunction between obese and non-obese was measured based on peak post-operative laboratory values of the international normalized ratio (INR), aspartate transaminase (AST), alanine transaminase (ALT), and total bilirubin. Non-hepatic complications included renal failure, pneumonia, urinary tract infections, and intra-abdominal abscess. Disease recurrence was determined based on pathologic or radiographic confirmation locally or systemically.

Statistical Analysis

The primary outcomes of interest were time to recurrence and overall survival. Secondary outcomes were differences in perioperative complication rates and 30-day post-operative mortality. Our primary exposure variable was BMI as a continuous variable. Separate analyses were also performed with BMI as a categorical variable to identify the specific risk for patients based on WHO obesity class for long-term outcomes. Patient demographics, diagnoses, medical co-morbidities, operative details, and perioperative complications were compared based on obese or non-obese status using Student's t test or chi-square test where appropriate. For perioperative survival, multivariable logistic regression techniques were used to assess the effect of BMI. For both recurrence and overall survival, the Kaplan–Meier method was used to estimate event rates over time. The log-rank test was used to compare survival between BMI categories, as well as between diagnosis groups. In order to evaluate the specific effect of obesity on oncologic outcomes in the context of other clinical variables, two multivariable Cox proportional-hazards models were constructed, one for time to recurrence and the other for overall survival, with BMI as the primary exposure. The recurrence model specifically estimated the time to recurrence, censored for death or the end of follow-up. The overall survival model estimated the time to death, censored at the end of follow-up. Disease recurrence was treated as a time-

varying covariate in the overall survival model. All models were adjusted for patient demographics (age, gender), co-morbidities (history of diabetes, viral hepatitis, cirrhosis, or other chronic liver disease), tumor characteristics (tumor size and number), extent of surgical resection (major or minor), surgical margin status, the presence of various perioperative complications, use of adjuvant chemotherapy, and peak post-operative INR, transaminases, and total bilirubin. The Cox models were also stratified by cancer diagnosis, given the intrinsic clinical and biological differences that affect survival and disease recurrence based on varying tumor biology. Stratified Cox proportional-hazards models assume varying hazard functions for death within each stratum, which, in this context, represented the different cancers for which hepatectomy was required. We assumed that patients with colorectal metastases, hepatocellular carcinoma (HCC), cholangiocarcinoma, gallbladder adenocarcinoma, metastatic neuroendocrine tumors to the liver, sarcoma metastases to the liver, and metastatic melanoma to the liver had intrinsic clinical differences that affected their potential survival and recurrence, and specifically how BMI affected their long-term outcomes. For example, patients who undergo hepatectomy for early HCC have an inherently different mortality risk than those who require it for colorectal metastases, due to differences in tumor biology, specific treatments received based on the diagnosis pre-operatively, as well as other unknown factors. The varying survival assumption was assessed graphically. Using this method, the effect of BMI was essentially tested for each cancer type, and their effects on the hazard of death were summarized in a single hazard ratio, without loss of statistical power that occurs when dividing up the cohort by each individual diagnosis.

STATA version 10.0 (College Station, TX) was used to complete all statistical analyses. Statistical significance was defined at a p-value of <0.05.

Results

Baseline Characteristics and Perioperative Outcomes

The study cohort was comprised of 279 patients who were surgically treated for hepatic malignancy and had BMI data for analysis. The distribution of these patients with respect to obesity status and malignant diagnosis is displayed in Fig. 1. Thirty-five percent of patients who underwent hepatectomy for primary or metastatic liver malignancies were obese. Forty-eight percent of the cohort carried colorectal metastases as the diagnosis ($n=134$), 28.3% had malignant tumors of primary hepatobiliary origin ($n=79$), and 23.7% had other metastases ($n=66$). No significant differences were noted in the mean BMI by diagnosis, but some trends were noteworthy in the distribution of obesity ($p=0.187$). The primary hepatobiliary patients had a higher proportion of obese patients (41.8%) than those with colorectal (34.3%) or other metastases (27.3%). Underweight patients made up less than 3% of the cohort.

Obese and non-obese patients had some differences with regards to baseline demographic, clinical, and perioperative characteristics after univariate analysis (Table 1). The overall average BMI for the cohort was 28.5±6.3, with a range of 14.8–52.5. Non-obese patients had an average BMI that was the upper limit of the WHO normal weight classification, and the average obese patient had class II obesity (BMI 35–40). The obese group also had 14% more males. Following hepatectomy, obese patients had significantly longer lengths of stay, higher post-operative peak transaminases, and higher post-operative peak bilirubin levels compared to the non-obese.

Following hepatectomy, patients with a BMI greater than 30 had significantly greater perioperative morbidity compared to the non-obese (Fig. 2) by univariate analysis. These patients had nearly two-fold greater liver-specific complications compared to the non-obese, with an overall rate of 20.1%. The biliary leak rate for the cohort was 12.9%. Obese patients had a nearly two-fold higher biliary leak rate (obese 18.6% vs. non-obese 9.9%). Obese patients also had significantly higher rates of urosepsis (16.5% vs. 7.7%), pneumonia (9.3% vs. 2.2%), acute renal failure (7.2% vs. 1.7%), and intra-abdominal abscess (7.2% vs. 1.7%). While there was no statistical difference with regards to post-operative liver failure by BMI, 5.2% of obese patients had liver failure vs. 1.7% of non-obese patients. Additionally, there was no significant difference between obese and non-obese patients with regards to post-operative ileus, surgical site infection, ascites, or cholangitis. Neither BMI nor obesity class was associated with a 30-day perioperative mortality in a multivariable logistic regression model (data not shown).

Influence of Obesity on Oncologic Outcomes Following Hepatectomy

Median follow-up for the cohort was 31 months, with a range of 0–143 months. On univariate analysis, obese patients trended toward a lower cumulative recurrence rate over time, but this did not reach statistical significance (Fig. 3). Median survival for the entire cohort was 41 months, with median survival of 48 months for obese patients and 37.3 months for non-obese patients. No significant differences were identified in overall survival or cancer recurrence by obesity status in these unadjusted analyses. When compared by diagnosis, patients with colorectal metastases trended toward lower recurrence rates over time compared to the other groups, particularly in the

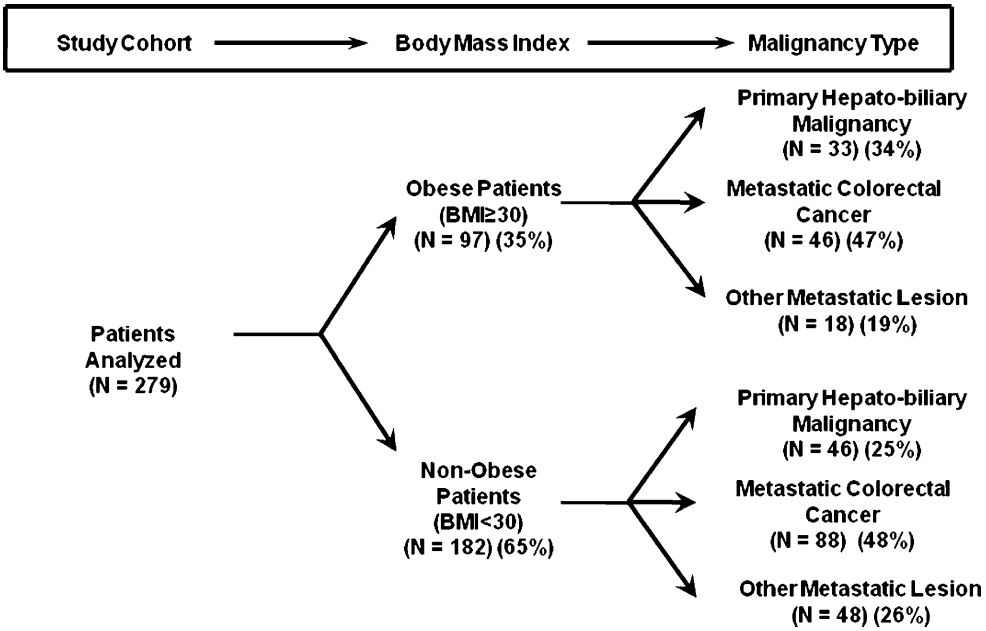

Figure 1 Body mass index and malignancy status of hepatectomy patients. The clinical distribution of the study cohort is summarized here with respect to obesity and diagnosis. More than one third of patients had a BMI in the obese range.

first four years of follow-up, which was nearly statistically significant (p=0.059; Fig. 4). Three-year unadjusted survival following hepatectomy was 66.4% for colorectal metastases patients, 54.4% for patients with primary hepatobiliary cancers, and 63.6% for patients with other metastases. These differences were not statistically significant likely due to the low sample size in each diagnostic cohort.

The notable covariates identified in the stratified multivariate Cox models for time to recurrence and overall

Table 1 Clinical and Perioperative Characteristics of 279 Patients Undergoing Hepatectomy for Malignancy

Variable	Non-obese (n = 182)	Obese (n=97)	p-value
Age (years) (SD)	58.8 (12.2)	59.5 (12.6)	0.651
Gender (% male)	48.9	62.9	0.026*
Mean BMI (kg/m^2)	24.9 (3.2)	35.3(4.7)	<0.001*
Diagnosis			
Colorectal metastases (%) (n = 134)	48.4	47.4	0.883
Primary hepatobiliary (%) (n=79)	25.2	34.0	0.123
Other hepatic metastases (%) (n=66)	26.4	18.6	0.145
History of diabetes mellitus (%)	13.7	20.6	0.138
History of hepatitis (%)	7.1	6.2	0.763
History of other chronic liver disease (%)	1.6	5.2	0.09
History of cirrhosis (%)	9.9	10.3	0.912
Mean tumor diameter (cm) (SD)	4.70 (3.76)	4.69 (3.12)	0.977
Mean number of tumors			0.206
1 (%)	52.8	58.8	
2 (%)	21.4	24.7	
≥3 (%)	25.8	16.5	
Positive surgical margins (%)	12.7	9.8	0.481
Major resections (%)	40.1	43.8	0.560
Mean length of stay (days)	8.63 (4.96)	10.54 (9.57)	0.029*
Peak post-operative labs			
Mean INR	1.33	1.31	0.581
Mean AST (U/ml)	521	966	0.026*
Mean ALT (U/ml)	442	704	0.002*
Mean total bilirubin (U/ml)	1.98	3.14	0.024*

*p-value < 0.05

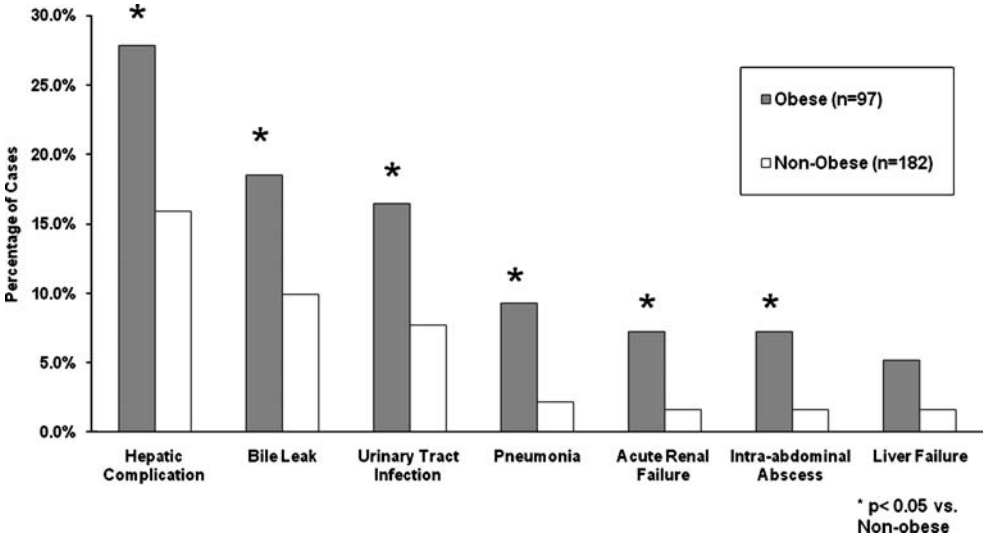

Figure 2 Perioperative complication rates by obesity status. Univariate analysis of obese (n=97) vs. non-obese patients (n=182) for the rates of indicated complications following hepatectomy for malignancy.

survival are presented in Tables 2 and 3. For each unit increase in BMI, the relative risk of disease recurrence decreased by 10%. After adjusting for BMI and other factors, male gender more than doubled the risk of recurrence. With regards to overall survival, BMI decreased the overall mortality risk by 3.9% for each point increase. Post-operative peak ALT and longer length of hospital stay was also associated with higher overall mortality (Table 3). As expected, disease recurrence was also associated with increased overall mortality. When BMI was analyzed categorically, class II and III obesity were significant predictors of improved recurrence-free survival compared to being in the normal range (class II=HR 0.286, 95% CI 0.0926–0.889, p=0.031; class III=HR 0.095, 95% CI 0.023–0.393, p=0.001). No specific obesity class was associated with overall survival. Due to the number of patients in each group, BMI was not a statistically significant predictor of outcome when testing the patients within each diagnostic group.

Discussion

For patients requiring a hepatectomy related to a primary or metastatic liver tumor, obesity is increasingly common and has significant implications for perioperative and long-term prognosis. More than one third of patients in our analysis had a BMI greater than 30. Obese patients had significantly more perioperative complications than non-obese patients with regard to hepatic and non-hepatic complications. With

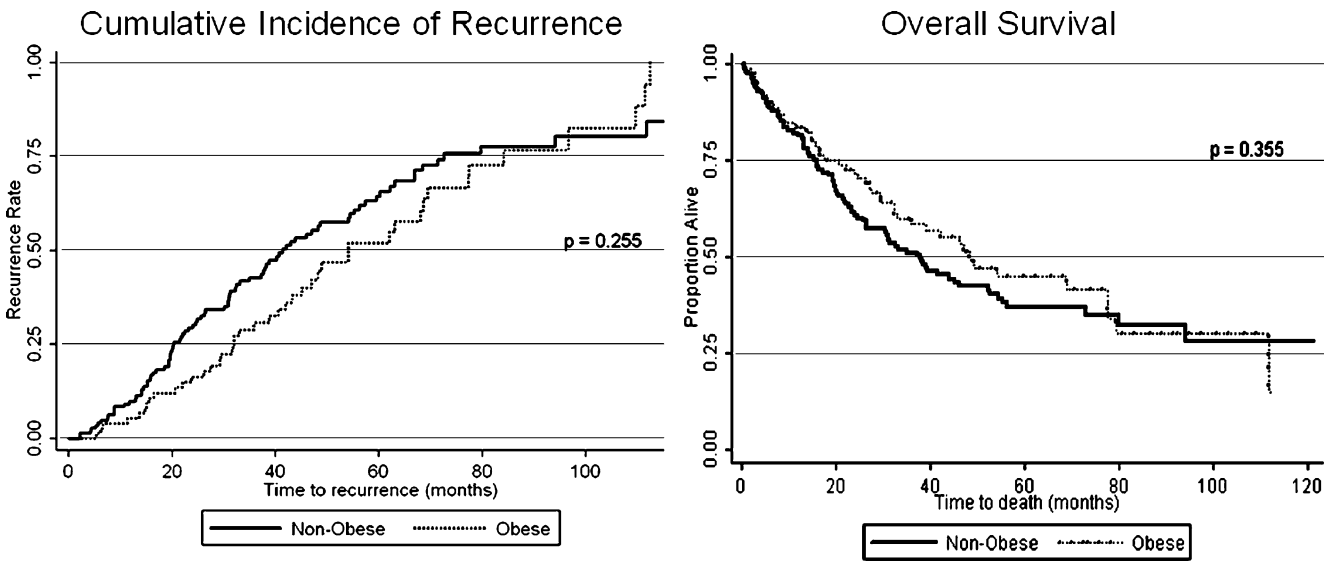

Figure 3 Time to recurrence and overall survival by obesity status. Kaplan–Meier curves for cumulative incidence of recurrence (*left*) and overall survival (*right*) of obese (n=97) vs. non-obese patients (n=182) following hepatectomy for malignancy. Obese and non-obese patients had similar recurrence and survival rates on univariate analysis.

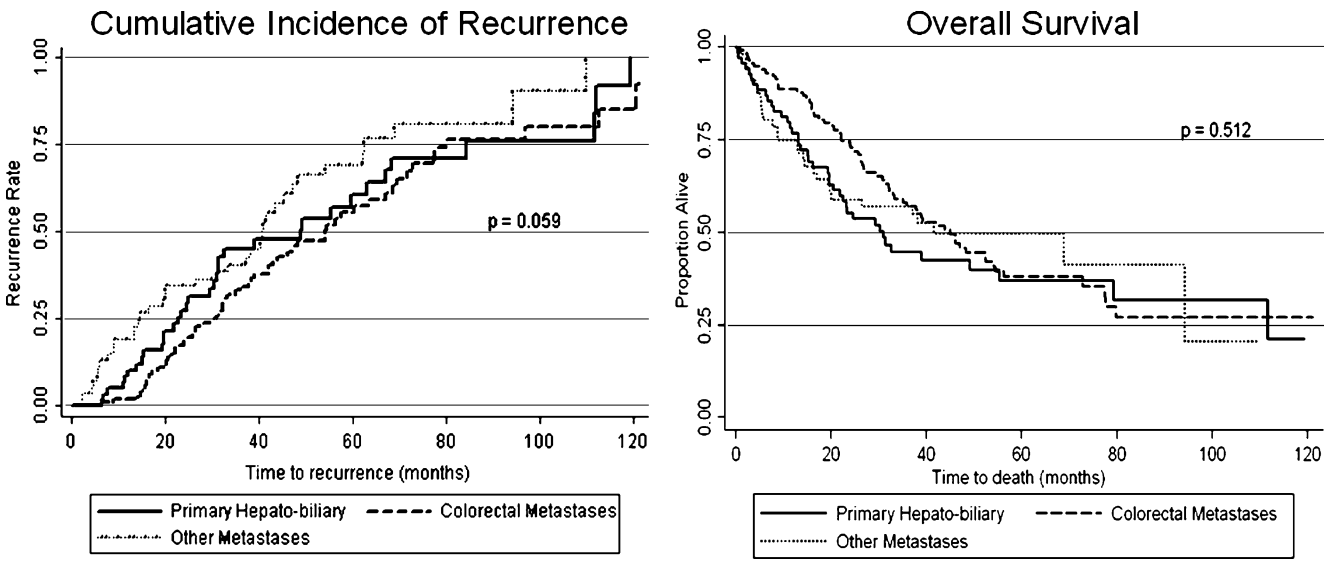

Figure 4 Time to recurrence and overall survival by diagnosis. Kaplan–Meier curves for cumulative incidence of recurrence (*left*) and overall survival (*right*) for patients with primary hepatobiliary cancers (n=79), colorectal metastases (n=134), and other metastases to the liver (n=66). On univariate analysis, patients with other metastases had more rapid recurrence rates than the other groups, and those with colorectal metastases had the best survival at 40 months.

reasonable long-term follow-up, patients had improved time to recurrence and overall survival with increasing BMI. Time to recurrence appeared most improved among those specifically with class II and class III obesity.

Obesity has been found to be associated with significant perioperative morbidity following major abdominal surgery for cancer.[8] In studies of pancreas and liver resection, obesity and steatosis were independent predictors of

Table 2 Covariates in Time-to-Recurrence Model Following Hepatectomy for Primary and Metastatic Liver Malignancies

Time to recurrence				
		95% confidence interval		
Variable	Hazard ratio	Lower limit	Upper limit	p-value
Body mass index	0.901	0.860	0.945	<0.001
Male	2.15	1.33	3.49	0.002
Length of stay	1.05	1.01	1.09	0.02
Age	1.00	0.98	1.02	0.71
Major resection	1.05	0.62	1.77	0.86
Positive surgical margin	1.38	0.71	2.71	0.343
Tumor size (cm)	0.97	0.91	1.04	0.365
Tumor number				
1	ref	Ref	Ref	Ref
2	1.56	0.897	2.73	0.115
≥3	1.56	0.901	2.70	0.112
Post-operative hepatic failure	3.64	0.36	37.3	0.276
Biliary complication	0.152	0.01	3.08	0.220
Cholangitis	1.03	0.07	16.0	0.981
Ascites	0.51	0.03	9.60	0.653
Diabetes mellitus	1.36	0.71	2.64	0.362
Peak INR	0.90	0.29	2.79	0.850
Peak AST	1.00	0.99	1.01	0.298
Peak ALT	1.01	1.00	1.02	0.075
Peak total bilirubin	1.07	0.90	1.27	0.460

Table 3 Covariates in Overall Mortality Model Following Hepatectomy for Primary and Metastatic Liver Malignancies

Overall mortality				
		95% confidence interval		
Variable	Hazard ratio	Lower limit	Upper limit	*p*-value
Body mass index	0.961	0.923	0.999	0.050
Peak post-operative ALT	1.01	1.00	1.02	0.050
Length of stay	1.04	1.00	1.09	0.050
Disease recurrence	1.03	1.01	1.05	0.003
Diabetes mellitus	1.70	0.931	3.10	0.08
Age	1.00	0.98	1.02	0.89
Major resection	0.80	0.48	1.31	0.384
Positive surgical margin	1.56	0.84	2.92	0.162
Tumor size (cm)	1.00	0.94	1.06	0.99
Tumor number				
1	Ref	Ref	Ref	Ref
2	0.99	0.56	1.73	0.972
≥3	1.06	0.59	1.90	0.907
Post-operative hepatic failure	2.15	0.29	16.1	0.461
Biliary complication	1.10	0.97	1.25	0.125
Cholangitis	3.02	0.26	35.7	0.380
Ascites	0.919	0.21	4.00	0.911
Post-operative renal failure	1.58	0.34	7.34	0.555
Post-operative pneumonia	1.78	0.57	5.53	0.317
Peak AST	0.99	0.98	1.00	0.088
Peak total bilirubin	1.10	0.97	1.25	0.125

perioperative morbidity.[2,5,12,15,16] Kooby et al. have shown that, while steatosis is associated with greater perioperative complications, BMI itself was only associated with complication rates on univariate analysis.[10] The morbidity in these studies included greater intraoperative blood transfusion requirements, longer operative times, and worse post-operative complications including wound infections, pancreatic fistula, impaired hepatic regeneration, and respiratory and cardiovascular compromise, resulting in longer lengths of stay. Our findings concur with previous work regarding the deleterious effect of obesity on perioperative morbidity, but our study expands the current literature regarding the prognosis of BMI on liver-specific complications and oncologic outcomes.

Notably, obesity has been found to influence oncologic outcomes, but with variable effects in different types of cancer. Several major reports have evaluated obesity in the context of oncologic outcomes after curative resections for pancreatic cancer and renal cell carcinoma.[12,17,18] Obese patients who have undergone pancreatic resection had poorer recurrence-free and overall survival than non-obese patients.[12] In contrast, renal cell carcinoma risk increases with obesity, but higher BMI was associated with improved tumor-specific survival in the renal cell cancer population.[17,18] The mechanisms of this heterogeneous relationship between obesity and tumor recurrence are unknown, but host–tumor interactions have been suggested as a potential contributor in translational studies.[19,20] Analogous studies have not been performed with regard to hepatic malignancies, likely related to the heterogeneity of tumors for which hepatic resection is indicated. To our knowledge, this is the first report describing improved time to recurrence and overall survival with increasing BMI following resection for hepatic malignancy.

Our analysis indicates a potential favorable effect of BMI on oncologic outcomes, but must be considered in a broader context. The negative effects of obesity on overall health outcomes are profound, especially in the context of perioperative general surgical and hepatic-specific complications. However, the favorable effect of increasing BMI on oncologic outcomes observed in this study may speak to a larger issue of patient frailty and possibly the ability to tolerate adjuvant therapy.[21–25] Patients with relatively higher BMI may have more physiologic reserve than lower BMI patients, and may thus withstand the various effects of hepatic resection coupled with other therapies.

Another interesting finding in our analysis was related to the negative independent effect of post-operative ALT on survival. This most likely is related to the degree of ischemic/reperfusion injury that occurs in hepatic resections

with temporary occlusion of the porta hepatis. Given the numerous covariates in the model relative to our sample size, it may have been driven by significant elevations of ALT, as occurs in post-operative liver failure, in a limited number of patients who had died early after surgery. This data suggests that limiting the period of portal vascular occlusion or the use of ischemic pre-conditioning techniques has acute benefits with regards to acute mortality risk. Strategies to limit hepatic ischemic/reperfusion injury in both obese and non-obese patients are clearly important but may be of greatest utility in those with steatosis. Steatosis may portend a greater risk for ischemia–reperfusion injury,[26,27] which has led to broader basic efforts to further understand this theory. Further understanding of this relationship will have important clinical implications in hepatic surgery and transplantation, and the assessment of patient risk.

As a retrospective study, our analysis is subject to some limitations. The study design aimed to evaluate BMI and oncologic outcomes in a single-center heterogeneous patient population. We attempted to test the effect of BMI within each diagnosis but did not have the statistical power to observe an effect secondary to limited patient numbers for each individual diagnosis. This is a possible explanation why no difference in overall survival or recurrence rates between tumor types was noted on the unadjusted analyses as well. In addition, the effect of adjuvant therapy was not directly incorporated into our statistical models, given the differences in utilization between our center and other centers which may have provided this care to the patients in the cohort following surgery. However, stratification of the recurrence and mortality models should account for those differences. Our study also spans a significant amount of time, and therefore we cannot completely exclude an era effect secondary to changes in practice patterns. No specific data was obtained on weight loss or gain leading up to the initial evaluation or after the operation. BMI changes over time were therefore not accounted for in the analysis. Further, the effect of BMI is observed in a highly selected group of patients who were considered to be good operative candidates with resectable tumors that could expect reasonable post-operative outcome. The effect of BMI observed in this study may not extend to patients who were considered too high risk for resection, based on other co-morbidities or more aggressive tumors.

In the context of the current literature on this topic, one potential limitation is related to the relationship between BMI, steatosis, and long-term oncologic outcomes. Steatosis was not recorded in our study, as it was not specifically noted in the pathological evaluation of the surgical specimens. Steatosis is of particular clinical concern in hepatobiliary surgery.[2,10,28–32] However, based on current literature, the relationship between the degree of hepatic steatosis and morbidity may not always be linear. El-Badry and colleagues have recently shown that the quantification of hepatic macro- and micro-steatosis is highly variable, plagued by low inter-rater reliability even between highly trained pathologists.[32] Studies evaluating the relationship between steatosis, complications, or long-term outcomes may not be readily generalizable as a result. Therefore, if surgeons are unable to depend on this unreliable pathological determinant of hepatic fat content, more intuitive clinical metrics to estimate risk may be more appropriate. The quantification of obesity by BMI is clinically intuitive, reliably determined, and is considered a global marker of potential perioperative risk across surgical specialties. In order to estimate the effect of obesity on longer term outcomes, it may therefore be more useful to concentrate on BMI.

The improved overall survival and time to recurrence for patients with high BMI is certainly significant and has implications for clinical practice and future research. Our findings should certainly be considered in the context arising from a referral population to a large academic center with an extensive experience in hepatobiliary surgery. Our data suggests that, for patients with higher BMIs and hepatic malignancies, surgeons should carefully select appropriate candidates for hepatectomy but should maintain an aggressive approach to resecting these patients. If patients are carefully managed in this context, higher perioperative complication rates may still be expected, but long-term outcomes appear to be reasonable. It remains to be determined whether our findings may be related to the physiological resilience of patients with higher BMIs, despite suffering from higher complication rates. The results of this analysis also allude to the significant interplay between tumor and patient, which has significant oncologic research implications. For example, Ogino et al. have identified a cellular molecule, STMN1, which has a poor prognosis in obese patients with colorectal cancer.[19] Tumor factors such as these may partly explain some of our findings for high BMI patients. High BMI may predispose patients to develop a hepatic tumor microenvironment that retards tumor growth. The relationship identified in this study is important and is certainly worthy of more clinical and translational research.

In summary, BMI has significant implications in the perioperative setting following hepatic resection for malignancy, with general and hepatic complications being more frequent among the obese. However, relatively higher BMI displayed a favorable prognosis on oncologic outcomes. These findings highlight the potential interactions between BMI and the biology of tumor recurrence and carry implications toward the design of future therapies. Additional translational research to evaluate these interactions is certainly warranted for the future.

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References

1. Ogden CL, Yanovski SZ, Carroll MD, Flegal KM. The epidemiology of obesity. Gastroenterology 2007;132(6):2087–2102.
2. Pitt HA. Hepato-pancreato-biliary fat: the good, the bad and the ugly. HPB (Oxford) 2007;9(2):92–97.
3. Renehan AG, Roberts DL, Dive C. Obesity and cancer: pathophysiological and biological mechanisms. Arch Physiol Biochem 2008;114(1):71–83.
4. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371(9612):569–578.
5. Gedaly R, McHugh PP, Johnston TD, Jeon H, Ranjan D, Davenport DL. Obesity, diabetes, and smoking are important determinants of resource utilization in liver resection: a multicenter analysis of 1029 patients. Ann Surg 2009;249(3):414–419.
6. Benns M, Woodall C, Scoggins C, McMasters K, Martin R. The Impact of Obesity on Outcomes Following Pancreatectomy for Malignancy. Ann Surg Oncol 2009;16(9):2565–2569.
7. Utsunomiya T, Okamoto M, Kameyama T, Matsuyama A, Yamamoto M, Fujiwara M et al. Impact of obesity on the surgical outcome following repeat hepatic resection in Japanese patients with recurrent hepatocellular carcinoma. World J Gastroenterol 2008;14(10):1553–1558.
8. Mullen JT, Davenport DL, Hutter MM, Hosokawa PW, Henderson WG, Khuri SF et al. Impact of body mass index on perioperative outcomes in patients undergoing major intra-abdominal cancer surgery. Ann Surg Oncol 2008;15(8):2164–2172.
9. Ryan CK, Johnson LA, Germin BI, Marcos A. One hundred consecutive hepatic biopsies in the workup of living donors for right lobe liver transplantation. Liver Transpl 2002;8(12):1114–1122.
10. Kooby DA, Fong Y, Suriawinata A, Gonen M, Allen PJ, Klimstra DS et al. Impact of steatosis on perioperative outcome following hepatic resection. J Gastrointest Surg 2003;7(8):1034–1044.
11. Mathur A, Zyromski NJ, Pitt HA, Al-Azzawi H, Walker JJ, Saxena R et al. Pancreatic steatosis promotes dissemination and lethality of pancreatic cancer. J Am Coll Surg 2009;208(5):989–994; discussion 994–986.
12. Fleming JB, Gonzalez RJ, Petzel MQ, Lin E, Morris JS, Gomez H et al. Influence of obesity on cancer-related outcomes after pancreatectomy to treat pancreatic adenocarcinoma. Arch Surg 2009;144(3):216–221.
13. Larsson SC, Wolk A. Overweight, obesity and risk of liver cancer: a meta-analysis of cohort studies. Br J Cancer 2007;97(7):1005–1008.
14. Larsson SC, Wolk A. Obesity and the risk of gallbladder cancer: a meta-analysis. Br J Cancer 2007;96(9):1457–1461.
15. House MG, Fong Y, Arnaoutakis DJ, Sharma R, Winston CB, Protic M et al. Preoperative predictors for complications after pancreaticoduodenectomy: impact of BMI and body fat distribution. J Gastrointest Surg 2008;12(2):270–278.
16. Behrns KE, Tsiotos GG, DeSouza NF, Krishna MK, Ludwig J, Nagorney DM. Hepatic steatosis as a potential risk factor for major hepatic resection. J Gastrointest Surg 1998;2(3):292–298.
17. Schrader AJ, Rustemeier J, Rustemeier JC, Timmesfeld N, Varga Z, Hegele A et al. Overweight is associated with improved cancer-specific survival in patients with organ-confined renal cell carcinoma. J Cancer Res Clin Oncol 2009.
18. Haferkamp A, Pritsch M, Bedke J, Wagener N, Pfitzenmaier J, Buse S et al. The influence of body mass index on the long-term survival of patients with renal cell carcinoma after tumour nephrectomy. BJU Int 2008;101(10):1243–1246.
19. Ogino S, Nosho K, Baba Y, Kure S, Shima K, Irahara N et al. A Cohort Study of STMN1 Expression in Colorectal Cancer: Body Mass Index and Prognosis. Am J Gastroenterol 2009.
20. Ogino S, Shima K, Nosho K, Irahara N, Baba Y, Wolpin BM et al. A cohort study of p27 localization in colon cancer, body mass index, and patient survival. Cancer Epidemiol Biomarkers Prev 2009;18(6):1849–1858.
21. Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, Nelson H et al. Impact of body mass index and weight change after treatment on cancer recurrence and survival in patients with stage III colon cancer: findings from Cancer and Leukemia Group B 89803. J Clin Oncol 2008;26(25):4109–4115.
22. Meyerhardt JA, Tepper JE, Niedzwiecki D, Hollis DR, McCollum AD, Brady D et al. Impact of body mass index on outcomes and treatment-related toxicity in patients with stage II and III rectal cancer: findings from Intergroup Trial 0114. J Clin Oncol 2004;22(4):648–657.
23. Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Benson AB, 3rd, Macdonald JS et al. Influence of body mass index on outcomes and treatment-related toxicity in patients with colon carcinoma. Cancer 2003;98(3):484–495.
24. Dignam JJ, Polite BN, Yothers G, Raich P, Colangelo L, O'Connell MJ et al. Body mass index and outcomes in patients who receive adjuvant chemotherapy for colon cancer. J Natl Cancer Inst 2006;98(22):1647–1654.
25. Miyake K, Hayakawa K, Nishino M, Morimoto T, Mukaihara S. Effects of oral 5-fluorouracil drugs on hepatic fat content in patients with colon cancer. Acad Radiol 2005;12(6):722–727.
26. He S, Atkinson C, Evans Z, Ellett JD, Southwood M, Elvington A et al. A role for complement in the enhanced susceptibility of steatotic livers to ischemia and reperfusion injury. J Immunol 2009;183(7):4764–4772.
27. He S, Atkinson C, Qiao F, Cianflone K, Chen X, Tomlinson S. A complement-dependent balance between hepatic ischemia/reperfusion injury and liver regeneration in mice. J Clin Invest 2009;119(8):2304–2316.
28. Gao F, Xu X, Ling Q, Wu J, Zhou L, Xie HY et al. Efficacy and safety of moderately steatotic donor liver in transplantation. Hepatobiliary Pancreat Dis Int 2009;8(1):29–33.
29. Gomez D, Malik HZ, Bonney GK, Wong V, Toogood GJ, Lodge JP et al. Steatosis predicts postoperative morbidity following hepatic resection for colorectal metastasis. Br J Surg 2007;94(11):1395–1402.
30. Vetelainen R, Bennink RJ, van Vliet AK, van Gulik TM. Mild steatosis impairs functional recovery after liver resection in an experimental model. Br J Surg 2007;94(8):1002–1008.
31. Aloia T, Sebagh M, Plasse M, Karam V, Levi F, Giacchetti S et al. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. J Clin Oncol 2006;24(31):4983–4990.
32. El-Badry AM, Breitenstein S, Jochum W, Washington K, Paradis V, Rubbia-Brandt L et al. Assessment of Hepatic Steatosis by Expert Pathologists: The End of a Gold Standard. Ann Surg 2009;250(5);691–697.

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ORIGINAL ARTICLE

Dose Delivery Estimated by Bremsstrahlung Imaging and Partition Model Correlated with Response Following Intra-arterial Radioembolization with ^{32}P-Glass Microspheres for the Treatment of Hepatocellular Carcinoma

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Abstract
Rationale The objective of this study was to retrospectively evaluate the efficacy of a combination of ^{32}P-glass microsphere-mediated intra-arterial internal radiation and chemoembolization for the treatment of hepatocellular carcinoma.
Methods Twenty-five consecutive patients with primary hepatocellular carcinoma referred for radiation therapy were treated with intra-arterial infusion of ^{32}P-glass microspheres followed by chemoembolization. β-bremsstrahlung imaging was performed to monitor microsphere distribution. A partition model and a radiation dose equation were used for determination of radiation exposure in various tissues. Clinical response was evaluated using computed axial tomography scans.
Results The mean estimated absorption dose in tumor tissue was 137.42±56.69 Gy. A receiver operating characteristic curve was used to establish 90.65 Gy as the cutoff absorption dose with the best sensitivity and specificity for predicting response. The overall tumor response rate was 92%, while response in patients with radiation doses >90.65 Gy was 100%. Overall median patient survival was 15 months.
Conclusion β-bremsstrahlung imaging following intra-arterial infusion of ^{32}P-glass microspheres and chemoembolization incorporates effective treatment with convenient dosimetry monitoring and manageable adverse events using a single surgical procedure. This approach is a safe and effective method for ameliorating hepatocellular carcinoma.

Keywords β-bremsstrahlung SPECT · Hepatic cancer · Internal radiation therapy · ^{32}P-glass microspheres · Radioembolization

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Introduction

Hepatocellular carcinoma is the sixth most common cancer worldwide and causes more than 500,000 global deaths annually.[1] Despite improvements in cancer diagnosis, the prognosis for patients with this disease remains poor. Radioembolization has been evaluated as a novel strategy for local effective treatment of liver tumors. More recent versions of this radio-therapeutic treatment have typically involved the use of radio-isotope (yttrium-90 or phosphorus-32) glass microspheres for the intra-arterial delivery of radiation directly to tumors, thus providing localized, regional treatment of unresectable malignant lesions.[2,3] This approach is particularly applicable to hepatic tumors, since the tumor blood supply is primarily derived from the hepatic artery, whereas normal liver tissue is predominantly supplied with blood through the portal vein.[4–8] A recent review concluded that radioembolization with 90-yttrium glass microspheres for the treatment of patients with advanced hepatocellular carcinoma resulted in significant

antitumor effects and that this promising new approach for targeted radiation delivery could effectively ameliorate this malignancy.[9]

Similar to external radiotherapy, the therapeutic response of patients receiving internal radiation is closely related to the absorption of radiation doses within the tumor. Until a partition model was established,[10] it was impossible to estimate the radiation doses within tumor and non-tumor liver tissues without the use of laparotomy, which involves surgical intervention. Indeed, because ^{32}P-glass microspheres applied during intra-arterial infusion distribute inhomogeneously in the liver, absorbed radiation doses differ between tumor and non-tumor liver tissues.[8] Due to the limited availability of tools for evaluating the radiation dose–effect relationship, it was necessary to use absorbed radiation doses of all liver tissue when evaluating treatment efficacy, rather than differentiating between tumor versus non-tumor liver and lung tissues.[11,12]

Using the partition method,[10] the percentage of radioactivity shunted to the lung and the tumor-to-normal liver tissue ratio (T/N) are obtained using technetium-99m-labeled macroaggregate albumin (^{99m}Tc-MAA scan). Although with this conventional approach ^{99m}Tc-MAA is easily detectable outside of the body, facilitating the deduction of the radioactive partition in tumor-to-normal tissue, it requires selective hepatic angiography prior to radiation therapy, subjecting the patient to two operations at a greater expense and the clinician to an expanded workload. This approach was also recently reported as not being ideal in cases involving microsphere-mediated treatments.[13]

An alternative approach incorporating β-bremsstrahlung imaging[14,15] is recognized as a powerful method for determining the distribution of weak ^{32}P radiation emanating from radio-isotopes in tumor versus non-tumor liver tissues during treatment. This technique can be used to observe the distribution of ^{32}P glass microspheres. Indeed, in a case of hepatic metastasis, an injection of yttrium-90 microspheres was followed in the liver using β-bremsstrahlung imaging and showed that the microspheres were primarily localized in the tumor tissue within the liver.[16] This observation was confirmed using histopathological methods. Thus this report demonstrated that the injected, radiolabeled microspheres exhibited very little circulation in the healthy liver tissues and mainly accumulated in the tumor tissue.[16] ^{32}P glass microsphere-mediated radioembolization was recently shown to suppress growth of human hepatocellular carcinoma xenografts implanted in nude mice[17] and to prevent hepatocellular carcinoma recurrence following hepatectomy in patients with massive hepatocellular carcinomas.[8]

Here, we investigated a novel and effective method for treating patients with hepatocellular carcinoma using intra-arterial ^{32}P-glass microspheres and chemoembolization. Using β-bremsstrahlung imaging of ^{32}P radiation and a partition model for assessing glass bead distribution, we estimated the radiation doses within tumor tissue, non-tumor liver tissue, and non-tumor lung tissue during treatment and evaluated patient clinical outcomes and possible adverse treatment effects following combined radio- and chemoembolization.

Patients and Methods

Patients

A total of 25 patients (22 males and three females) with hepatocellular carcinoma treated between March 2001 and June 2003 were included in this retrospective review of a prospectively set database study. The mean patient age was 55 years (range, 41 to 73 years). The patient cohort consisted of 14 patients with Child-Pugh Grade A and 11 patients with Child-Pugh Grade B.[18] All patients were diagnosed with hepatic cancer based on clinical features, past history of chronic hepatitis and cirrhosis of the liver, abdominal enhanced computed tomography (CT) and AFP, cranial computed tomography scans, sternite, and bone scan with single photon emission computed tomography (SPECT) to exclude extrahepatic disease. CT scans were obtained using the parameters of 10-mm slice thickness, 130 kV, and 85 mA. While positron emission tomography is a typical method of choice,[19] its application was not feasible in the present study, which was carried out in the People's Republic of China. All patients either had unresectable tumors or were unwilling to undergo surgery. The high cost of liver transplantation eliminated this procedure as a possibility for the vast majority of patients. Because this study used a procedure similar to transcatheter arterial chemoembolization (TACE) with lipiodol, patients with Child-Pugh Grade C were excluded due to an elevated risk of serious hepatic damage as a result of treatment.[18] All patients signed their informed consent prior to voluntary participation in the study. All treatment protocols and procedures were approved by the local Institutional Internal Review Board.

Preparation of ^{32}P-Glass Microspheres

^{32}P is a pure β-particle emitter with a half-life of 14.28± 0.02 days. Its average penetration in tissue is 3.2 mm, with a maximum penetration depth of 8 mm, depending on the tissue type and composition. The average ^{32}P energy is 0.695 MeV, with a maximum of 1.711 MeV. ^{32}P-glass microspheres (Chengdu Gaotong Isotope Corporation, Chengdu, China) are solid microspheres with diameter of 46–76 μm and a density of 2.0–2.5 g/cm^3. The radioactivity

inside the microspheres is higher than 99% and the releasing rate of ^{32}P from the microspheres is less than 0.1% per month per manufacturer instructions. The ^{32}P glass microsphere suspension (10 to 15 mCi depending on the tumor size, Table 1) was mixed with 10-mL lipiodol ultra fluid and 10 mg pirarubicin (THP) in 1 mL iopromide immediately prior to use.

Interventional Therapy

The femoral artery was punctured using the Seldinger technique[16] and hepatic arteriography was performed in order to observe the tumor vascular system and tumor staining, which facilitates superselective catheterization. In cases where the tumor was not well displayed, additional approaches were applied, including angiography of the superior mesenteric artery, inferior phrenic artery, and right renal artery to identify other arteries supplying blood flow to the tumor. The suspension of ^{32}P glass microspheres described above was infused via a catheter. Following this infusion, 1,000 mg 5-fluorouracil, 2.0 g ifosfamide, and 10 mg THP were infused sequentially.

To the best of our knowledge, there is no standard or commonly accepted chemotherapy plan for the treatment of hepatocellular carcinoma. The chemotherapeutical approach utilized in the present study was based on the collective experience of physicians in our hospital (data not shown). Hepatocellular carcinomas are highly dependent on a rich blood supply. Embolization alone is an effective treatment, but application of gel foam can be used to enforce treatment efficacy.[8] Therefore, when rich blood supplies were observed following infusion, 1×1-mm gel foam granules were used during the embolization. Six patients were embolized via hepatic segmental artery, nine

Table 1 Patient Clinical Characteristics

Patient	Tumor type	Tumor size[a] (%)	Tumor absorption dose (Gy)	Absorption dose T/N ratio	Tumor response	Follow up[b] (months)
1	Nodules	>75	98.1	3.4	PD	***7***
2	Large mass	<25	146	3.5	PR	22
3	Large mass	<25	245	4.2	PR	***19***
4	Nodules	>75	88.5	2	SD	***8***
5	Large mass	<25	169	3.5	MR	***12***
6	Large mass	<25	176	4.7	PR	***21***
7	Large mass	<25	160	3.1	MR	20
8	Nodules	>75	63.7	1.9	SD	***14***
9	Nodules	50–75	115	2.5	PR	***13***
10	Nodules	25–55	89.3	2.7	PD	***3***
11	Nodules	25–55	180	3.4	PR	19
12	Large mass	25–55	75.4	3.16	MR	18
13	Large mass	<25	211	4.3	PR	19
14	Large mass	25–55	147	3.5	MR	18
15	Large mass	<25	238	3.6	PR	23
16	Diffuse	50–75	80.1	2	SD	***9***
17	Nodules	50–75	65.2	2.9	SD	***12***
18	Nodules	25–55	98.3	3.4	SD	***10***
19	Large mass	<25	194	3	PR	19
20	Nodules	50–75	92.2	2	MR	***13***
21	Large mass	<25	194	4	PR	16
22	Nodules	50–75	92	2.8	SD	***9***
23	Nodules	25–55	78.8	3.2	MR	***12***
24	Large mass	<25	208	5.8	PR	18
25	Large mass	25–55	131	4	MR	***15***

Large mass diameter of a single tumor >5 cm, *nodules* diameter of a single tumor <5 cm, *diffuse* diameter of a single tumor <3 cm with multiple tumors, *PR* partial response, *MR* minor response, *SD* static disease, *PD* progressive disease

[a] Tumor size is presented as a percentage of liver volume

[b] Survival at the time of final follow-up is indicated in bold and italic font

via the hepatic left or right artery, and ten via the hepatic proper artery. β-bremsstrahlung imaging was performed to determine the ratio of activity in tumor/normal tissue (T/N ratio) and L% (the percentage of activity shunted to the lung) 2 days after treatment. CT scans were performed monthly to determine residual tumor volume.

Estimation of the Radiation Dose

Based on the principle of Medical Internal Radiation Dose,[17–19] the formula to calculate the radiation dose with ^{32}P as radionucleotide was as follows:

$$D_t = 34.6 \times T \times C_0 \times \sum_{i=1}^{i} \Delta_i \left\{ 1 - e^{\frac{-0.693t}{T}} \right\}$$

where $\Delta_i = 1.4799\ \mathrm{g \cdot rad/\mu Ci \cdot h}$, T=14.3 d, assuming that all ^{32}P was absorbed at the original site, and 34.6 is a constant in the formula. The formula was further simplified as $D(\mathrm{rad}) = 732.22 \times C_0(\mu\mathrm{Ci/g})$, and transformed using the formula:

$$D(\mathrm{Gy}) = \frac{0.1979 \times A_0(\mathrm{Bq})}{M(\mathrm{g})} \quad (1)$$

where D (Gy) represents radiation doses received by tissue; A_0 (mCi) represents radioactivity of radionuclide in tissue; M (g) represents the mass of the tissue.

Two formulas were acquired as follows based on partition modeling[10]:

$$A \times (1 - L\%) = A_T + A_N \quad (2)$$

$$T/N = \frac{D_T}{D_N} = r = \frac{A_T/M_T}{A_N/M_N} \quad (3)$$

where L% represents the lung shunt percentage, A represents the radioactivity of infused radionuclide, A_T and A_N represent radioactivity of radionuclide in tumor tissue and non-tumor liver tissue, D_T and D_N represent the radiation doses of tumor tissue and non-tumor liver tissue, respectively, and M_T and M_N represent the mass of tumor tissue and non-tumor liver tissue, respectively.

CT examination and manual segmentation were performed to determine liver or tumor volume using the following formula: $\mathrm{Volume(mm^3)} = \pi/6 \times a \times b^2$, where a is the long radius and b is the short radius. Then, the mass of tumor and non-tumor liver tissue was estimated following the formula $M(\mathrm{g}) = \mathrm{volume(cm^3)} \times 1.03$. T/N ratio and L% were measured using bremsstrahlung imaging, which incorporated SPECT with low-energy general purpose collimators. The voltage for these measurements was 140 keV and the anteroposterior image was acquired at counts of 800 K. The values obtained were used in Eqs. 1, 2, and 3 mentioned above and the radiation doses in tumor tissue, non-tumor liver tissue, and lung tissue were acquired. The tumor lesions identified in CT images and hepatic arterial angiograms corresponded with those observed in the bremsstrahlung images.

Treatment Efficacy

The results of the therapeutic interventions were classified based on the World Health Organization criteria as follows: complete response, the visible tumor disappeared completely for at least 4 weeks; partial response, the tumor size decreased more than 50% for at least 4 weeks; minor response, the tumor size decreased 25% to 50% for at least 4 weeks; static disease, the tumor size decreased less than 25% or increased less than 25%; progressive disease, the tumor size increased at least 25% or new lesions appeared.

Statistical Analysis

The receiver operating characteristic curve was used to determine the cutoff absorption dose with the best sensitivity and specificity for predicting response. Patient survival status was compared using the Kaplan–Meier method, and Fisher's exact test was used to compare response and dosage. Data were analyzed using SAS 9.0 (SAS Institute, Inc., Cary, NC, USA) and a p value <0.05 was considered to be statistically significant.

Results

Estimated Absorption Dose

Patient and tumor characteristics are listed in Table 1. T/N ratios ranged from 1.9 to 5.8 (mean 3.30±0.91) and the corresponding L% ranged from 1.8% to 11.6% (mean 4.6%). Estimated absorption doses in tumor tissue ranged from 63.70 to 245.00 Gy (mean 137.42±56.69 Gy).

Clinical Response

The total treatment response rate was 92%, with ten partial responses, seven minor responses, six patients with stable disease, and two patients with progressive disease (Table 1). In Fig. 1, a liver CT scan is shown of patient case 3 (Table 1), demonstrating the presence of a liver tumor. The liver tumor was injected with ^{32}P glass microspheres, the radioactivity of which was primarily included in the tumor tissue. After 4 weeks of treatment, the tumor size had substantially decreased (Fig. 1).

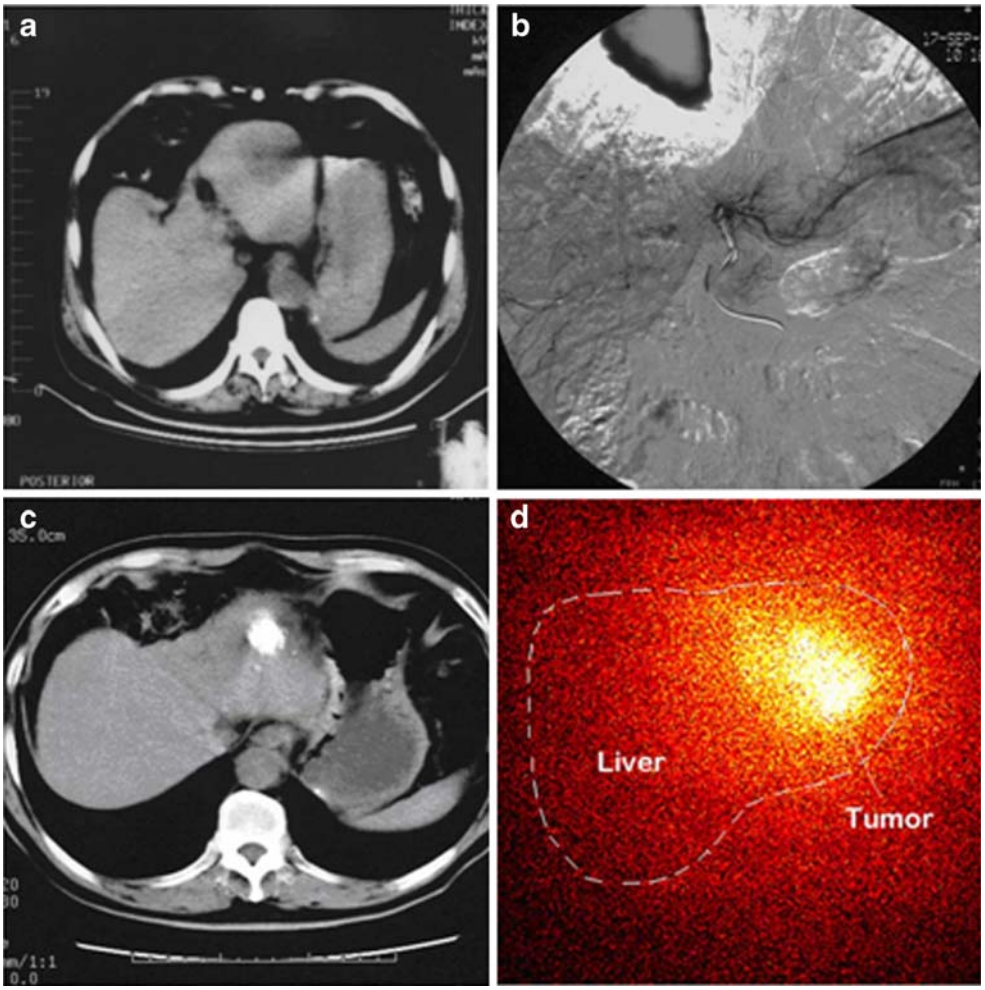

Figure 1 Images of a 66-year-old male with a hepatocellular carcinoma. **a** CT scan of the liver of patient case 3 (documented history of chronic type B hepatitis, alpha-fetoprotein= 183.25 ng/mL) demonstrating the presence of a tumor (round low-density area in the left lateral lobe). **b** Image from left lateral lobar arteriography demonstrating the presence of thick and tortuous tumor vessels, with tumor staining observed in the venous phases. **c** CT scan of the patient's liver after 4 weeks of treatment demonstrating that tumor size was significantly decreased. **d** β-bremsstrahlung gamma camera image showing that the ^{32}P-glass microsphere distribution was primarily in the tumor tissue.

In 13 patients, the tumor tissue radiation dose was greater than 120 Gy, the cutoff point established from conventional radiation therapy. Among this group, nine patients had a partial response and four patients showed a minor response. Stable disease and progressive disease were not observed within this subgroup. Thus, the cumulative response rate for this group was 100% (Table 2). In the 12 patients with tumor radiation doses of less than 120 Gy, partial response was observed in one patient, minor response in three, no change in six, and progressive disease in two patients. The response rate for this group was 48% (Table 2).

Using a cutoff point determined by receiver operating characteristic curve analysis, where the area under curve is 0.70 with a sensitivity of 73.91 and a specificity of 50.00, 18 patients had tumor radiation doses greater than 90.65 Gy. Among this subgroup, partial response was observed in 10 patients, minor response in five, stable disease in two, and progressive disease in one. The response rate for this group was 100% (Table 2). Seven

Table 2 Patient Responses in Patients Receiving Different Tumor Radiation Doses

Tumor radiation dose (Gy)	Partial response	Minor response	Static disease	Progressive disease	Response rate (%)
<120	1	3	6	2	48*
>120	9	4	0	0	100
<90.65	0	2	4	1	28**
>90.65	10	5	2	1	100

*p=0.0007 versus >120 GY, Fisher's exact test; **p=0.0122 versus >90.65 GY, Fisher's exact test

patients had tumor radiation doses of less than 90.65 Gy, with two patients with minor responses, four with static disease, and one with progressive disease. The response rate for this group was 28% (Table 2). Thus, there was a clear correlation between dosage and outcome using 90.65 Gy as a cutoff point.

All estimated absorption doses in normal tissues were less than 20 Gy, with values ranging from 22.35 to 68.64 Gy (mean 36.55±12.41 Gy) in non-cancerous liver and from 2.1 to 16.3 Gy (mean 7.2±5.6 Gy) in healthy lung tissue.

Patient Survival

All study patients were followed for 3 to 23 months following treatment and Kaplan–Meier survival analysis was performed (Figs. 2 and 3). Patient survival at 6, 12, and 18 months was 96%, 76%, and 48%, respectively, with a median survival period of 15 months. The median survival period was 21 months in the 13 patients who received tumor radiation doses of >120 Gy and 10 months in the 12 patients who received tumor radiation doses of <120 Gy. Using the receiver operating characteristic curve cutoff point, median survival period was 21 months in the 18 patients who received a tumor radiation dose of >90.65 Gy and 12 months in the seven patients who received tumor radiation doses of <90.65 Gy.

Adverse Events

All patients received a combined radioembolization and chemoembolizaiton treatment and experienced adverse events. These events included fever with temperatures of 38.2±0.9°C, abdominal pain, and abdominal distension, typically caused by intestinal gas accumulation. These symptoms were observed for 3 to 4 days following treatment. Symptoms of abdominal pain and abdominal distension also occurred in five patients. Different degrees of impairment in liver function observed within 5 to 10 days following interventional therapy. Liver function returned to pre-surgery levels after 2 weeks in 27 patients, but irreversible deteriorations in liver function were apparent in three patients who had Child-Pugh Grade B disease. No respiratory system symptoms, radiation-mediated pneumonitis, or gastric or duodenal ulcer development was observed.

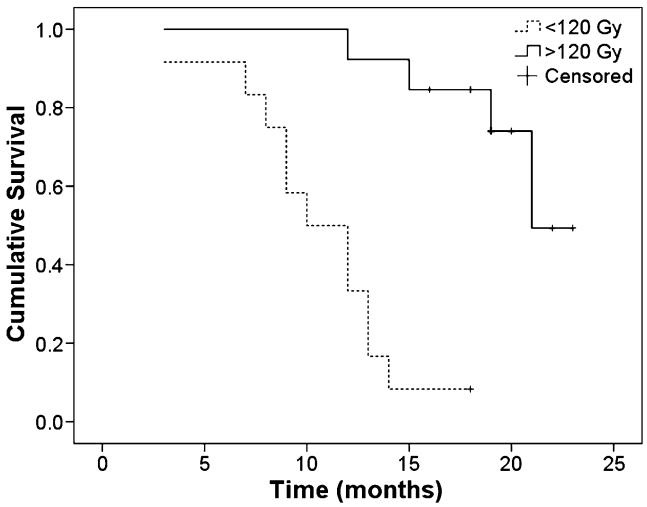

Figure 2 Kaplan–Meier analysis of patient survival. Tumor radiation doses were greater than 120 Gy in 13 patients and lower than 120 Gy in the other 12 patients (log-rank test, $p<0.0001$).

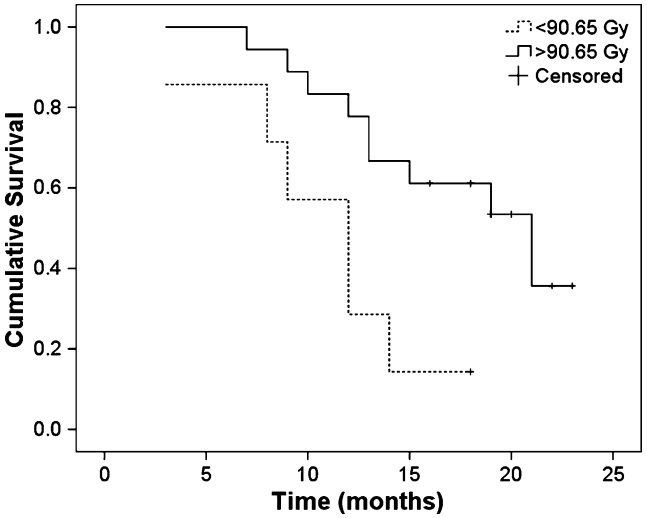

Figure 3 Kaplan–Meier curve of patient survival following treatment. The receiver operating characteristic (ROC) curve was used to determine the cutoff absorption dose with the best sensitivity and specificity in predicting patient response to treatment. The radiation doses in tumor tissue were greater than 90.65 Gy in 18 patients and lower than 90.65 Gy in the remaining seven patients. The ROC curve had an area under the curve of 0.7469, a sensitivity of 73.91, and a specificity of 50.00 (log-rank test, $p=0.0019$).

Threshold Dose for Tumor Response Based on the Clinical Outcome

Based on the estimated radiation doses in the respective tumors, the cumulative response rate of patients who received radiation doses of >90.65 Gy (100%) was significantly higher than the response rate in patients who received radiation doses of <90.65 Gy (28%, $p=0.0122$). Although one patient had an estimated absorption dose in normal liver tissue higher than 60 Gy (68.64 Gy), no hepatocirrhosis was observed. In three patients with irreversible impairment of liver functions, the estimated radiation doses in non-tumor liver tissues were 34.63, 38.94, and 63.69 Gy, respectively. No respiratory system symptoms or radiation-mediated pneumonitis were ob-

served and the estimated absorption dose in lung tissue was less than 20 Gy in all patients. Furthermore, no gastric or duodenal ulcer formation occurred, and no radioactivity was detected within the gastroduodenal region based on β-bremsstrahlung-mediated imaging.

Discussion

The present study establishes and validates a more convenient method of monitoring effective therapeutic radiation dosage for the treatment of hepatocellular carcinoma. Patients were treated with intra-arterial ^{32}P-glass microspheres followed by chemoembolization. The weak ^{32}P radiation was monitored outside of the body using bremsstrahlung imaging during treatment, with dosage deduced by calculating the doses delivered to the tumor and to the surrounding organ, checks of radiopharmaceutical distribution, and follow-up measurements of this distribution over time. Subsequent statistical analyses showed a clear dosage–outcome correlation. A unique tumor radiation cutoff dosage was also established which compared favorably with the conventional method.

One significant result of the present study is that this new methodology incorporates monitoring of the radiation dosage delivered to the tumor during treatment, facilitating repeat treatment as applicable if the optimal dosage is not achieved in the first treatment without the requirement of a repeat surgery. Also, by controlling the dosage, treatment complications and the potential side effects of overdose and bystander effects resulting in damage to normal tissue are much easier to avoid. β-bremsstrahlung-mediated imaging demonstrated that most of the ^{32}P was localized within the tumor tissue and radiation exposure outside of the body was also very limited. All of the adverse effects that were observed after combined radioembolization and chemoembolization treatment were manageable.

Another important aspect of this study was that the radioactivity is specifically localized in the tumor tissues, eliciting a maximum antitumor effect. Although 120 Gy is often the target for the treatment of HCC with radioembolization, a lower radiation dose could be applied due to possible synergistic effects of the combined radioembolization and chemoembolization treatment, potentially increasing efficacy while reducing patient risk. Considering potential synergistic effect of this combined treatment, we identified a cutoff of 90.65 Gy, which was derived from retrospective survival curve analysis. This lower value might reflect the possible beneficial synergistic effects of the combined treatment approach used in the present study.

Cases have been reported in which clinical response and adverse effects were investigated without assessing the possible contribution of radioactivity present in other non-target tissues into account.[9,20–23] Because infused radioactive microspheres distribute inhomogeneously in the liver, absorbed radiation doses in tumor and non-tumor liver tissues are different.[24] Moreover, microspheres could possibly be shunted to lung tissues, so the tolerance of normal liver tissues and the occurrence of radiation-mediated pneumonitis are also directly related to the radiation doses of normal liver tissue and lung tissue, respectively. Using the partition model combined with β-bremsstrahlung imaging, *L*% and *T*/*N* ratios were calculated by estimating the radiation doses following treatment with intra-arterial ^{32}P glass microspheres. Our observations are in accordance with those reported by Lau et al.[24] where the radiation doses of tumor tissue were measured using a β-probe during an operation.

Recommendations for tolerable radiation doses in normal liver tissue are generally in the range of 30 Gy.[25] However, Gray et al.[26] reported that patients treated with yttrium-90 received radiation doses in non-tumor liver tissues as high as 138.9 Gy without the occurrence of radiation-mediated hepatitis. Therefore, a safe radiation dose of non-tumor liver tissues was recommended to be in the range of 80 Gy.[26] In the present study, the radiation doses of non-tumor liver tissue ranged from 22.35 to 68.64 Gy. The liver functions of three patients with Child-Pugh Grade B were irreversibly deteriorated. Among this group, one patient had a radiation dose in non-tumor liver tissue greater than 60 Gy, while exposure in the two other patients was greater than 40 Gy. The liver function of one patient with Child-Pugh Grade A who received radiation doses of non-tumor liver tissue of 68.64 Gy gradually recovered following surgical intervention. Thus, in the present study, the radiation tolerance of non-tumor liver tissue was not only related to the radiation dose, but also to basic liver function or the incidence of hepatocirrhosis.

Furthermore, we observed that the estimated radiation dose of lung tissue could predict the occurrence of radiation pneumonitis. Ho et al.[27] reported that with the use of yttrium-90 glass microspheres to treat hepatic cancer, among three patients whose estimated radiation doses in lung tissue were higher than 30 Gy, there was one occurrence of radiation pneumonitis. In contrast, no patients with a radiation dose in lung tissue lower than 30 Gy were diagnosed with pneumonitis due to radiation. As a result, the report recommended that the safe level of radiation dose in lung tissue was below 30 Gy[27] following internal radiotherapy. In the present study, the radiation dose of lung tissue was below 20 Gy in all patients and radiation pneumonitis was not observed.

The procedure described in this report provides a favorable method of estimating radiation doses for intra-arterial internal radiation with ^{32}P-glass microspheres for treatment of hepatic cancer. The median survival of

15 months achieved by this group of patients is also encouraging. However, this survival rate is lower than 40–86% 5-year survival achieved with hepatic resection, depending on the tumor size, extent of disease, vascular involvement, surgical margins, and presence of confounding factors such as viral infection or cirrhosis.[28] The patients enrolled in this retrospective review of a prospective clinical study only represent approximately 30% of all the patients with hepatocellular carcinoma seen at our institution during the period of study. Comparison with surgical outcomes following resection for eligible patients would also be appropriate. Thus, assessment of the impact of this form of treatment on survival will require a larger patient cohort participating in a randomized, controlled trial.

The results of this trial were further influenced by the chemotherapy and embolization of lipiodol and were not precluded by previous nonradioactive embolization procedures. In addition, due to economic restrictions, follow-up antitumor therapy (including TACE) was not possible for some patients, which may have impacted patient survival time. We postulated that the combined treatment using radioembolization and chemoembolization would be more effective than radioembolization alone; however, this approach may also have limitations stemming from the possible enhancement of the hepatotoxic effects of both the radiation and chemotherapeutic agents. The latter might explain the irreversible deterioration of liver function observed in three patients.

Furthermore, lipiodol has the ability to selectively deposit in tumor tissues and was shown to decrease the hepatocellular carcinoma recurrence rate in patients after hepatectomy, thereby improving patient survival.[8] Its viscosity is higher than that of contrast agents, allowing the microspheres to be efficiently carried to the tumor. Lipiodol is an X-ray radiopaque and thus functions well as a contrast agent. Embolization was achieved through superselective catheterization downstream of the opening of the gastroduodenal artery and right gastric artery. To avoid back flow, embolization should be performed under X-rays. However, additional studies are required which incorporate a more extensive group of patients with hepatic cancer who are observed over a more extended period of time. Besides providing a more robust approach and additional safety data pertaining to radioembolization and chemoembolization, this potential future clinical study will also facilitate the investigation of whether the more uncommon adverse effects observed in the present study are more or less frequent in a larger population.

In conclusion, β-bremsstrahlung imaging following intra-arterial infusion of ^{32}P-glass microspheres and chemoembolization incorporates effective treatment with convenient dosimetry monitoring with manageable adverse events using a single surgical procedure. This approach resulted in an overall median patient survival period of 15 months and is a safe and effective method for ameliorating hepatocellular carcinoma.

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References

1. Farazi PA, DePinho RA. Hepatocellular carcinoma pathogeneis: from genes to environment. Nat Rev Cancer 2006;6:674–687.
2. Bult W, Vente MA, Zonnenberg BA, Van Het Schip AD, Nijsen JF. Microsphere radioembolization of liver malignancies: current developments. Q J Nucl Med Mol Imag 2009;53:325–335.
3. Vente MA, Hobbelink MG, van Het Schip AD, Zonnenberg BA, Nijsen JF. Radionuclide liver cancer therapies: from concept to current clinical status. Anticancer Agents Med Chem 2007;7:441–459.
4. Cao X, He N, Sun J, Tan J, Zhang C, Yang J et al. Hepatic radioembolization with Yttrium-90 glass microspheres for treatment of primary liver cancer. Chin Med J (Engl) 1999;112:430–432.
5. Stubbs RS, Cannan RJ, Mitchell AW. Selective internal radiation therapy (SIRT) with 90Yttrium microspheres for extensive colorectal liver metastases. Hepatogastroenterology 2001;48:333–337.
6. Lim L, Gibbs P, Yip D, Shapiro JD, Dowling R, Smith D et al. Prospective study of treatment with selective internal radiation therapy spheres in patients with unresectable primary or secondary hepatic malignancies. Intern Med J 2005;35:222–227.
7. Popperl G, Helmberger T, Munzing W, Schmid R, Jacob TF, Tatsch K. Selective internal radiation therapy with SIR-spheres in patients with nonresectable liver tumors. Cancer Biother Radiopharm 2005;20:200–208.
8. Wang XM, Yin ZY, Yu RX, Peng YY, Liu PG, Wu GY. Preventive effect of regional radiotherapy with phosphorus-32 glass microspheres in hepatocellular carcinoma recurrence after hepatectomy. World J Gastroenterol 2008;28:518–523.
9. Ibrahim SM, Lewandowski RJ, Sato KT, Gates VL, Kulik L, Mulcahy MF et al. Radioembolization for the treatment of unresectable hepatocellular carcinoma: a clinical review. World J Gastroenterol 2008;14:1664–1669.
10. Ho S, Lau WY, Leung TW, Chan M, Ngar YK, Johnson PJ et al. Partition model for estimating radiation doses from yttrium-90 microspheres in treating hepatic tumours. Eur J Nucl Med 1996;23:947–952.
11. Shepherd FA, Rotstein LE, Yip TC, Paul K, Swiderman KW. A phaseI dose escalation trial of yttrium-90 microspheres in the treatment of primary hepatocellular carcinoma. Cancer 1992;70:2250–2254.
12. Andrews JC, Walker SC, Ackermann RJ, Cotton LA, Ensminger WD, Shapiro B. Hepatic Radioembolization with yttrium-90 containing glass microspheres: preliminary results and clinical follow-up. J Nucl Med 1994;35:1637–1644.
13. Selwyn RG, Avila-Rodriguez MA, Converse AK, Hampel JA, Jaskowiak CJ, McDermott JC et al. ^{18}F-labeled resin microspheres as surrogates for 90Y resin microspheres used in the treatment of

hepatic tumors: a radiolabeling and PET validation study. Phys Med Biol 2007;52:7397–7408.
14. Petri B, Nance R, Hanada J, Stevens J. P-32 Bremsstrahlung SPECT helps assess intracavitary therapy. Clin Nucl Med 1992;17:709–710.
15. Siegel JA, Khan SH. Body contour determination and validation for bremsstrahlung SPECT imaging. J Nucl Med 1996;37:495–497.
16. Tehranipour N, AL-Nahhas A, Canelo R. Concordant F-18 FDG PET and Y-90 Bremsstrahlung scans depict selective delivery of Y-90-microspheres to liver tumors: confirmation with histopathology. Clin Nucl Med 2007;32:371–374.
17. Zhang K, Loong SL, Connor S, Yu SW, Tan SY, Ng RT et al. Complete tumor response following intertumoral ^{32}P BioSilicon on human hepatocellular and pancreatic carcinoma xenografts in nude mice. Clin Cancer Res 2005;11:7532–7537.
18. Interventional Radiology Group of the Chinese Journal of Radiology, Chinese Medical Association. Standardized protocol of interventional therapy of hepatic cancer. Chin J Radiol (Chinese) 2001;35:887–891.
19. Coldwell DM, Kennedy AS, Nutting CW. Use of yttrium-90 microspheres in the treatment of unresectable hepatic metastases from breast cancer. Int J Radiat Oncol Biol Phys 2007;69:800–804.
20. Mancini R, Carpanese L, Sciuto R, Pizzi G, Golfien R, Giampalma L et al. A multicentric phase II clinical trial on intra-arterial hepatic radiotherapy with 90yttrium SIR-spheres in unresectable, colorectal liver metastases refractory to i.v. chemotherapy: preliminary results on toxicity and response rates. In Vivo 2006;20:711–714.
21. Jakobs TF, Hoffmann RT, Poepperl G, Schmitz A, Lutz J, Koch W et al. Mid-term results in otherwise treatment refractory primary or secondary liver confined tumours treated with selective internal radiation therapy (SIRT) using (90)Yttrium resin-microspheres. Eur Radiol 2007;17:1320–1330.
22. Szyszko T, Al-Nahhas A, Canelo R, Habib N, Jiao L, Wasan H et al. Assessment of response to treatment of unresectable liver tumours with 90Y microspheres: value of FDG PET versus computed tomography. Nucl Med Commun 2007;28:15–20.
23. Szyszko T, Al-Nahhas A, Tait P, Rubello D, Canelo R, Habib N et al. Management and prevention of adverse effects related to treatment of liver tumors with 90Y microspheres. Nucl Med Commun 2007;28:21–24.
24. Lau WY, Leung WT, Ho S, Leung NW, Chan M, Lin J et al. Treatment of inoperable hepatocellular carcinoma with intrahepatic arterial yttrium-90 microspheres: a phase I and II study. Br J Cancer 1994;70:994–999.
25. Ingold JA, Reed GB, Kaplan HS, Bagshaw MA. Radiation hepatitis. Am J Roentgenol Radium Ther Nucl Med 1965;93:200–208.
26. Gray BN, Burton MA, Kelleher D, Kemp P, Matz L. Tolerance of the liver to the effects of yttrium-90 radiation. Int J Radiat Oncol Biol Phys 1990;18:619–623.
27. Ho S, Lau WY, Leung TW, Chan M, Johnson PJ, Li AK. Clinical evaluation of the partition model for estimating radiation doses from yttrium-90 microspheres in the treatment of hepatic cancer. Eur J Nucl Med 1997;24:293–298.
28. Rampone B, Schiavone B, Martino A, Viviano C, Confuorto G. Current management strategy of hepatocellular carcinoma. World J Gastroenterol 2009;15:3210–3216.

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ORIGINAL ARTICLE

4-Dimensional Intravital Microscopy: A New Model for Studies of Leukocyte Recruitment and Migration in Hepatocellular Cancer in Mice

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Abstract
Introduction Although it is accepted that the immune system plays a role in the prognosis of hepatocellular carcinoma (HCC), the exact mechanisms of leukocyte recruitment into HCC are poorly understood. Progress in the study of this aspect has been hindered by technical limitations.
Materials and Methods In the present study, we describe the use of 4D intravital microscopy which represents an advantageous technology for the investigation of the microvascular system and leukocyte migration in HCC. To establish 4D intravital microscopy, we used a HCC tumor model in transgenic mice expressing enhanced green fluorescent protein in specific leukocyte subpopulations and combined digital time-lapse recording, laser scanning confocal microscopy, and 3D reconstruction. Using this technology, we studied the intra- and extravascular leukocyte adhesion and migration in HCC in vivo at the single-cell level.
Results We showed that although vessel density in HCC was lower than in normal liver, tumor tissue was moderately infiltrated with leukocytes of lymphoid and myeloid origin. Most tumor-infiltrating leukocytes migrated in a random manner frequently changing direction of migration in the tumor tissue. The migration velocity of myeloid and lymphoid leukocytes in HCC tissue was not different.
Discussion These results demonstrated that 4D intravital microscopy has potential to be a powerful tool in the study of mechanisms of leukocyte recruitment and intratumoral migration in HCC.

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Keywords Hepatocellular cancer · Leukocyte recruitment · Model · 4D · Time-lapse intravital microscopy

Abbreviations

HCC	Hepatocellular carcinoma
EGFP	Enhanced green fluorescent protein
4D	4-Dimensional
TRITC	Tetramethylrhodamine isothiocyanate

Introduction

There is increasing evidence that the immune response to hepatocellular cancer (HCC) may impact on the development and progression of HCC. It has been shown that

marked T-cell infiltration was associated with better prognosis in HCC patients.[1] HCC is characterized by different immunosuppressive mechanisms such as overproduction of interleukin-10,[2,3] decreased functional activity of dendritic cells,[4] and activation of regulatory T cells in tumor tissue.[5,6] In fact, the intratumoral balance between regulatory and cytotoxic T cells predicts recurrence and survival in HCC.[6,7] Recent studies also described an increase in myeloid-derived suppressor cells in the blood and in tumor tissue of HCC patients. This heterogeneous leukocyte population exerts effective immunosuppression through induction of CD4+CD25+Foxp3+regulatory T cells.[8]

Circulating leukocytes are considered a constituent part of the blood with the potential to leave the vasculature and migrate into tissue to fulfill their role as anticancer immune cells. The term "leukocyte recruitment" encompasses all events that bring circulating leukocytes into inflamed tissue. According to the current paradigm, leukocyte recruitment represents an important step of the antitumor immune response which follows a well-defined cascade of events,[9] starting with the capture of free-flowing leukocytes and leukocyte rolling along the endothelium. Triggered by chemotactic signals, leukocytes then attach to the vascular endothelium and prepare for their migration into the tissue.[9] Recent findings recognized that post-arrest leukocyte activation is a complex and extremely dynamic process which includes intraluminal leukocyte migration (crawling) and paracellular/transcellular migration.[9] In the final step, leukocytes exit the vascular basement membrane through regions of low matrix protein expression.[10]

Although a modulatory role of the immune system in HCC is accepted, exact mechanisms of leukocyte recruitment into HCC tissue have been poorly investigated. In almost all previous studies, the leukocyte–endothelium interaction was documented in real-time mode and was considered the major functional parameter to assess the capacity of the tumor endothelium in leukocyte recruitment. The dynamic investigation of leukocyte penetration into the tissue was not studied because of technical limitations.

Based on the current progress in digital and in microscopic technologies, we established a novel technique of multicolor 4D intravital microscopy (3D+time-lapse) to visualize and analyze the dynamic interactions of leukocytes, tumor cells, and the microvascular system (including intravascular, transendothelial, and extravascular migration) in tumor tissue over long time periods. We have previously utilized this technology to investigate intravascular, transendothelial, and extravascular leukocyte migration in the pancreas.[11] In the present study, we evaluated 4D intravital microscopy for study of leukocyte recruitment and migration in HCC tissue in mice.

Materials and Methods

HCC Cell Line

The HCC cell line, Hep55.1C, was used. This cell line was established from primary HCC in C57BL/6J mice.[12] Tumor cells were grown in Iscove's medium supplemented with penicillin (10,000 IU), streptomycin (10 mg/mL), L-glutamine (200 mM), and 10% heat-inactivated fetal calf serum (CCPro, Oberdorla, Germany). Cells were cultured for 4 days prior to inoculation.

Leukocyte Visualization

Leukocytes of both myeloid and lymphoid immune systems participate in the infiltration of HCC tissue. Therefore, differential visualization of myeloid and lymphoid leukocytes was performed. Thus, two strains of transgenic mice expressing enhanced green fluorescent protein (EGFP)-labeled leukocytes were used. The first strain was CD2-EGFP$^+$ mice.[13] This knock-in mouse strain expresses EGFP under the CD2 promoter leading to excellent visualization of lymphoid cells by fluorescence microscopy. The second strain, lys-EGFP-ki, expresses EGFP under the lysozyme M promoter and allows microscopic identification of leukocytes of myeloid origin, in particular neutrophils and monocytes.[14]

Tumor Inoculation

All animal experiments were approved by the local committee of animal care, Regierungspräsidium Karlsruhe. For tumor inoculation, six animals of every strain were used. Each animal was anesthetized using intraperitoneal injection of xylazine (10 mg/kg, Rompun®, Bayer, Leverkusen, Germany) and ketamine (40 mg/kg, KetanestS®, Parke Davis, Berlin, Germany). After midline incision, HCC was induced by an orthotopic inoculation of tumor cells (10 μL of tumor cell suspension containing 5×10^6 cells) into the liver using a 20-μL microsyringe (Hamilton, Reno, USA). After a defined period of growth (12–14 days), inoculated cells formed solid well-vascularized tumors of up to 10 mm at the implantation site.

4D Intravital Microscopy

For intravital microscopy, animals were anesthetized as described above. A small polyethylene catheter was inserted into the right internal jugular vein for venous access. Attention was paid to preserve sterile conditions during the surgical preparation and during intravital microscopy. After midline incision, tumors were identified macroscopically. The tumor-bearing liver lobe was slightly

exteriorized through the incision, placed on the cover slide in a flat position, and examined under the microscope system (C1si confocal on Nikon Eclipse Ti-inverted microscope, Nikon GmbH, Düsseldorf, Germany). The flat position allowed the exteriorized tissue to be kept still during any movement caused by breathing. Attention was also given to avoidance of any tension in the exteriorized tissue. Capillary perfusion was visualized using intravenous injection of tetramethylrhodamine isothiocyanate (TRITC)-labeled albumin (50 mg/kg, Sigma Aldrich, Deisenhofen, Germany). Two lasers (488 and 561 nm) allowed simultaneous multicolor imaging of fluorescence-labeled blood vessels and leukocytes. Capillary perfusion and leukocytes were recorded by parallel photomultipliers for 30 min/field. Digital images were saved on a personal computer in time-lapse mode as a line of consecutive 4D images (*x*–*y*–*z*-time axes). For every animal, images from two different tumor fields were recorded. The surface of one field was 0.4 mm^2. The images were superimposed and processed to video sequences. These sequences showed microperfusion and the 3D leukocyte movement with optional acceleration. Measurements were performed using software (NIS Elements, Nikon). Measured parameters were: density of perfused blood vessels, density and velocity of migrating leukocytes. Migration velocity of 10 migrating leukocytes/field was measured and expressed in micrometers per minute.

Statistics

Results were expressed as the mean ± SD. Analysis was performed using the Mann–Whitney *U* test. A p value <0.05 was considered to be significant.

Results

Inoculated hepatoma cells formed a solid tumor which had a clear border with the normal liver and no adhesions with surrounding organs. Intravenous injection of TRITC-labeled albumin led to excellent visualization of perfused blood vessels in the normal liver (Fig. 1a), in tissue surrounding the tumor (Fig. 1b), and in the HCC (Fig. 1c and d). The microvascular system of normal liver showed a dense and regular network of hepatic sinusoids and

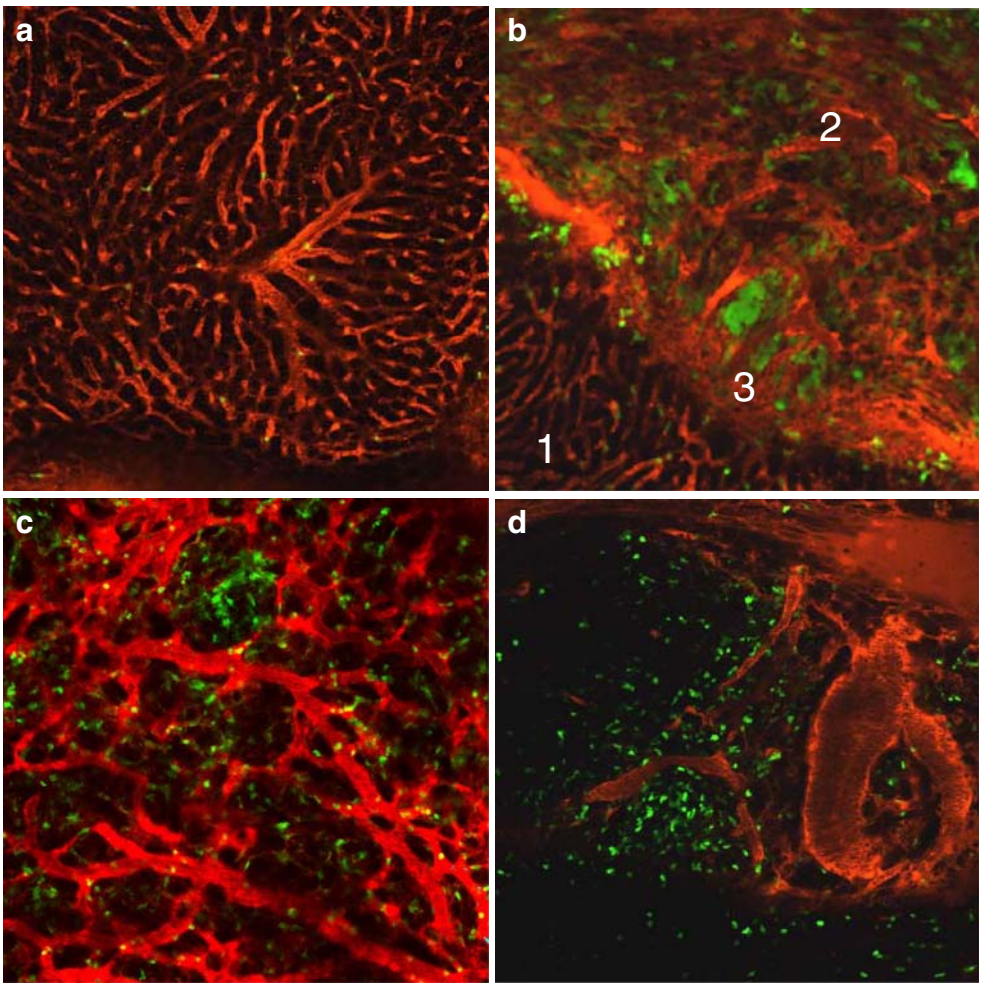

Figure 1 Representative images of intravital microscopy. Blood vessels were labeled using intravenous injection of TRITC-labeled albumin and appear in red. EGFP-fluorescent leukocytes are *green*. **a** Dense network of sinusoids in normal liver. **b** Simultaneous imaging of the normal liver,[1] tumor tissue,[2] and tumor border area.[3] HCC showed regions with high (**c**) and low (**d**) vessel density.

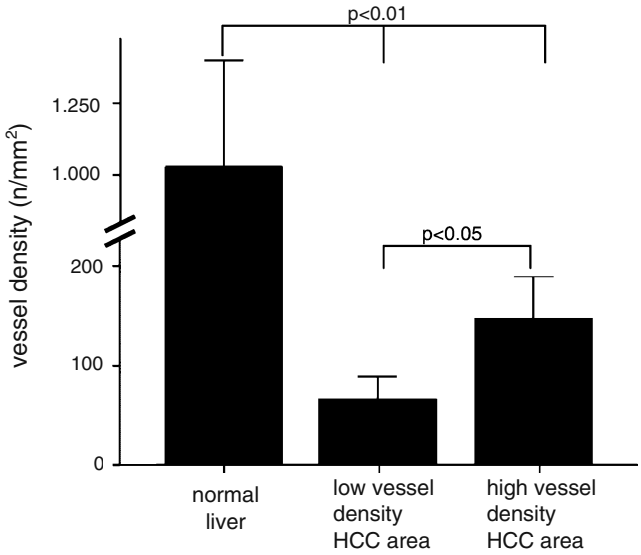

Figure 2 Vessel density in normal liver and in HCC: Vessel density in normal liver was significantly higher than in HCC. The vessel density of 100 vessels per square millimeters was determined as a cutoff between low and high vessel density areas in HCC.

collecting venules. The tumor border and normal liver tissue were clearly distinguishable. In contrast to normal liver, HCC blood vessels showed an irregular angioarchitecture. The vessel density in HCC was significantly lower than in normal liver ($p<0.01$, Fig. 2). The vessel distribution in HCC was heterogeneous: there were areas with high and low vessel density (Fig. 1c, d, Fig. 2). The density of 100 vessels per square millimeters was identified as a cutoff between low and high vessel density areas in tumor tissue (Fig. 2). There was no significant difference in vessel density between HCC in CD2-EGFP$^+$ and in lys-EGFP-ki mice (81.3±30.5 and 110.4±38.8 vessels per square millimeters, respectively). EGFP fluorescence allowed excellent visualization and quantification of the movement of intravascular and extravascular leukocytes. Surprisingly, peritumoral blood vessels were the major site of leukocyte recruitment, whereas low extravasation rates of single leukocytes in intratumoral blood vessels were found. Once recruited into the peritumoral tissues, extravasated leukocytes penetrated the tumor tissue, migrated actively, and disseminated within HCC tumor tissues. The density of lymphoid leukocytes (CD2-EGFP$^+$ mice) was significantly higher than the density of myeloid leukocytes (lys-EGFP-ki mice; Fig. 3a). Most intratumoral leukocytes migrated randomly and changed direction of migration many times during the observation period of 30 min (Suppl. Movie 1, 2). The mean velocities of myeloid and lymphoid leukocytes were not significantly different (Fig. 3b).

Discussion

In the present study, a new method of 4D intravital microscopy was used to analyze the microvascular system and leukocyte migration in HCC. The current progress in digital and microscopic technologies allows leukocyte imaging in living animals in tumor models. Recently, the first employment of 4D intravital imaging for studies of dynamic interactions between leukocytes, tumor blood vessels, and tumor tissue was reported.[15,16] It was described in a model of malignant thymoma and showed that antigen expression by tumor cells determines both T-cell motility and T-cell infiltration.[15] In the present study, digital time-lapse imaging and transgenic technologies were combined with laser scanning confocal imaging to analyze leukocyte recruitment and migration in HCC in vivo. Using the intravenous injection of TRITC-labeled albumin, blood vessels and EGFP-expressing leukocytes were observed in different fluorescence spectra.

In the present study, 4D microscopy was utilized for Hep-55.1C hepatoma cells which were orthotopically inoculated into the liver. This model has shown several

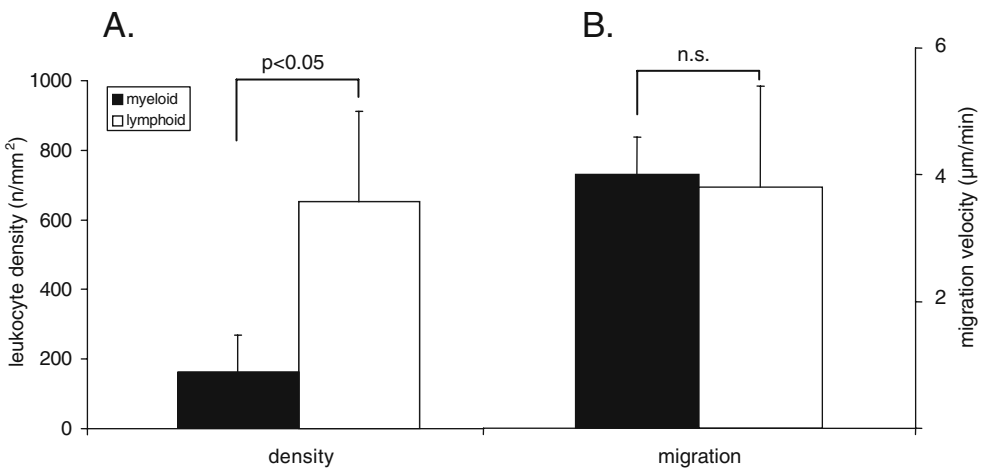

Figure 3 Density and migration velocity of myeloid and lymphoid leukocytes in HCC. The density of lymphoid leukocytes was significantly higher than the density of myeloid leukocytes (**a**) whereas no difference in leukocyte migration velocities was found (**b**).

important immunological features. It showed a baseline infiltration of tumor tissue by both lymphoid and myeloid leukocytes. This infiltration may be considered as a moderate cellular immune response against HCC which may allow the study of leukocyte recruitment under basic conditions with no requirement for additional immunological stimulation. Despite this moderate immune response, stable tumor progression was observed.

Conventional fluorescence microscopy displays a signal from the tissue, but its depth cannot be exactly defined. It does not allow differentiation between extravascular and intravascular leukocytes if they migrate along the blood vessel or in the projection of the blood vessel. In contrast to conventional microscopy, laser scanning confocal microscopy provides a signal from a thin tissue layer of less than 1 μm and allows identification of the exact position of single leukocytes in the microvascular lumen. In combination with 3D reconstruction and time-lapse recording, this method allowed the exact assessment of several important parameters such as the direction, distance, time, and velocity of leukocyte movement. Furthermore, the method allowed analysis of leukocyte migration in relation to its spatial distribution which is divided into the intra-, trans-, and extravascular space.

The Hep55.1C hepatoma showed heterogeneous and partial high vascularization. It may, in general, be identified as a well-vascularized tumor, although the vessel density in the normal liver was significantly higher than in HCC. Heterogeneous vessel density in HCC corresponds well with results of previous studies.[17,18] As expected, tumor angiogenesis was not altered by EGFP-transgenic leukocytes since no significant differences in vessel density between lys-EGFP-ki and CD2-EGFP$^+$ mice were found.

Using transgenic mice, we achieved a differential visualization of lymphoid (in CD2-EGFP$^+$ mice) and myeloid (in lysEGFP-ki mice) leukocytes. It is the first model which demonstrated that leukocytes can also be recruited in peritumoral blood vessel and became to tumor-infiltrating cells after active penetration of tumor tissue. Furthermore, intratumoral leukocytes of both lymphoid and myeloid origin showed an active non-altered migration in the tumor interstitium. This can be relevant to human situations and reflects the dynamic properties of leukocytes. Conventional analysis of leukocyte status is based on static assessment of leukocyte infiltration in histological sections. The present model demonstrated that leukocytes seen on histological slides are actually migrating cells before tissue removal, fixation, and staining. Interestingly, the velocity of intratumoral migration between these leukocyte populations did not differ. It indicates that mechanisms of leukocyte migration in the tumor interstitium are likely to be similar.

In conclusion, 4D intravital microscopy represents an advantageous technology for the investigation of dynamic interactions between the tumor microvascular system and leukocytes in HCC. This method may represent a powerful tool for the study of mechanisms of leukocyte recruitment in this type of tumor.

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References

1. Wada Y, Nakashima O, Kutami R, Yamamoto O, Kojiro M. Clinicopathological study on hepatocellular carcinoma with lymphocytic infiltration. Hepatology 1998;27:407–414.
2. Chau GY, Wu CW, Lui WY, Chang TJ, Kao HL, Wu LH, King KL, Loong CC, Hsia CY, Chi CW. Serum interleukin-10 but not interleukin-6 is related to clinical outcome in patients with resectable hepatocellular carcinoma. Ann Surg 2000;231:552–558.
3. Hsia CY, Huo TI, Chiang SY, Lu MF, Sun CL, Wu JC, Lee PC, Chi CW, Lui WY, Lee SD. Evaluation of interleukin-6, interleukin-10 and human hepatocyte growth factor as tumor markers for hepatocellular carcinoma. Eur J Surg Oncol 2007;33:208–212.
4. Kakumu S, Ito S, Ishikawa T, Mita Y, Tagaya T, Fukuzawa Y, Yoshioka K. Decreased function of peripheral blood dendritic cells in patients with hepatocellular carcinoma with hepatitis B and C virus infection. J Gastroenterol Hepatol 2000;15:431–436.
5. Yang XH, Yamagiwa S, Ichida T, Matsuda Y, Sugahara S, Watanabe H, Sato Y, Abo T, Horwitz DA, Aoyagi Y. Increase of CD4+ CD25+ regulatory T-cells in the liver of patients with hepatocellular carcinoma. J Hepatol 2006;45:254–262.
6. Fu J, Xu D, Liu Z, Shi M, Zhao P, Fu B, Zhang Z, Yang H, Zhang H, Zhou C, Yao J, Jin L, Wang H, Yang Y, Fu YX, Wang FS. Increased regulatory T cells correlate with CD8 T-cell impairment and poor survival in hepatocellular carcinoma patients. Gastroenterology 2007;132:2328–2339.
7. Gao Q, Qiu SJ, Fan J, Zhou J, Wang XY, Xiao YS, Xu Y, Li YW, Tang ZY. Intratumoral balance of regulatory and cytotoxic T cells is associated with prognosis of hepatocellular carcinoma after resection. J Clin Oncol 2007;25:2586–2593.
8. Hoechst B, Ormandy LA, Ballmaier M, Lehner F, Krüger C, Manns MP, Greten TF, Korangy F. A new population of myeloid-derived suppressor cells in hepatocellular carcinoma patients induces CD4(+)CD25(+)Foxp3(+) T cells. Gastroenterology 2008;135:234–243.
9. Ley K, Laudanna C, Cybulsky MI, Nourshargh S. Getting to the site of inflammation: the leukocyte adhesion cascade updated. Nat Rev Immunol 2007;7:678–689.
10. Wang S, Voisin MB, Larbi KY, Dangerfield J, Scheiermann C, Tran M, Maxwell PH, Sorokin L, Nourshargh S. Venular basement membranes contain specific matrix protein low expression regions that act as exit points for emigrating neutrophils. J Exp Med 2006;203:1519–1532.
11. Ryschich E, Kerkadze V, Deduchovas O, Salnikova O, Parseliunas S, Märten A, Hartwig W, Sperandio M, Schmidt J. Intracapillary leucocyte accumulation as a novel antihaemorrhagic mechanism in acute pancreatitis in mice. Gut 2009;58:1508–1516.
12. Kress S, König J, Schweizer J, Löhrke H, Bauer-Hofmann R, Schwarz M. p53 mutations are absent from carcinogen-induced

mouse liver tumors but occur in cell lines established from these tumors. Mol Carcinog 1992;6:148–158.
13. Singbartl K, Thatte J, Smith ML, Wethmar K, Day K, Ley K. A CD2-green fluorescence protein-transgenic mouse reveals very late antigen-4-dependent CD8+ lymphocyte rolling in inflamed venules. J Immunol 2001;166:7520–7526.
14. Faust N, Varas F, Kelly LM, Heck S, Graf T. Insertion of enhanced green fluorescent protein into the lysozyme gene creates mice with green fluorescent granulocytes and macrophages. Blood 2000;96:719–726.
15. Boissonnas A, Fetler L, Zeelenberg IS, Hugues S, Amigorena S. In vivo imaging of cytotoxic T cell infiltration and elimination of a solid tumor. J Exp Med 2007;204:345–356.
16. Hugues S, Scholer A, Boissonnas A, Nussbaum A, Combadière C, Amigorena S, Fetler L. Dynamic imaging of chemokine-dependent CD8+ T cell help for CD8+ T cell responses. Nat Immunol 2007;8:921–930.
17. Ikeguchi M, Oi K, Hirooka Y, Kaibara N. CD8+ lymphocyte infiltration and apoptosis in hepatocellular carcinoma. Eur J Surg Oncol 2004;30:53–57.
18. Ryschich E, Lizdenis P, Ittrich C, Benner A, Stahl S, Hamann A, Schmidt J, Knolle P, Arnold B, Hämmerling GJ, Ganss R. Molecular fingerprinting and autocrine growth regulation of endothelial cells in a murine model of hepatocellular carcinoma. Cancer Res 2006;66:198–211.

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ORIGINAL ARTICLE

Pterostilbene Inhibits Pancreatic Cancer In Vitro

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Abstract
Introduction Stilbenes are phenolic compounds present in grapes and blueberries. Resveratrol, a naturally occurring compound present in grapes, has been shown to have potent antioxidant properties as well as an ability to induce apoptosis. Resveratrol has also been reported to have significant inhibitory effects against a variety of primary tumors including breast, colon, and prostate. Pterostilbene, a naturally occurring analogue of resveratrol found in blueberries, also has antioxidant and antiproliferative properties. It is also substantially more bioavailable orally than resveratrol. These effects have not been studied in pancreatic cancer. We hypothesized that pterostilbene would inhibit pancreatic cancer cell growth in vitro.
Materials and Methods Two pancreatic cancer cell lines (MIA PaCa and PANC-1) were cultured using standard techniques. Cells were treated with graduated doses of pterostilbene ranging from 10 to 100 μM. Cell viability was measured by MTT at 24, 48, and 72 h.
Results Pterostilbene decreases cell viability in both cancer cell lines in a concentration- and time-dependent manner. Higher doses (75–100 μM) caused a significant reduction in cell viability at 24 and 48 h. However, by 72 h, all tested concentrations of pterostilbene (10 to 100 μM) resulted in significantly reduced cell viability in both pancreatic cancer cell lines in a dose-dependent fashion. Pterostilbene caused a dose-dependent 10–63% inhibition in MIA PaCa-2 cells and 10–75% inhibition in PANC-1 cells.
Discussion Treatment of pancreatic cancer cells in vitro with Pterostilbene leads to inhibition of cell proliferation and/or cell death, cell cycle arrrest, mitochondrial membrane depolarization, and activation of effector caspases. This naturally occurring agent may have a role in treating pancreatic cancer.
Conclusions Pterostilbene inhibits the growth of pancreatic cancer in vitro. Further, in vitro mechanistic studies and in vivo experiments are warranted to determine its potential for the treatment of pancreatic cancer.

Keywords Pterostilbene · Pancreatic cancer · Phytochemical · Resveratrol

Introduction

Pancreatic adenocarcinoma is the fourth leading cause of cancer-related death in the USA with an overall 5-year survival of less than 5%. Jemal et al. estimate 21,050 new cases for men and 21,420 new cases for women in 2009 with 6% of all cancer deaths for both sexes being attributable to pancreatic cancer.[1] This poor prognosis is attributed to the late presentation of pancreatic cancer, aggressive local invasion, early metastases, and poor response to conventional chemotherapy and radiotherapy. Despite advances in surgery, radiotherapy, and chemotherapy, greater than 90% of patients with pancreatic cancer die of chemotherapy insensitive disease. The nucleoside analogue gemcitabine is currently the most effective drug available for pancreatic cancer, yet it is only able to induce a 5% response rate.[2] Its effects are mostly palliative, with the majority of patients succumbing to their disease within

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6 months. Development of novel chemopreventive and/or chemotherapeutic agents and adjuncts is clearly warranted to improve the prognosis of this devastating disease.

Resistance to apoptosis is a commonly observed phenomenon in many cancers. Neoplastic cells are able to overcome apoptotic cell signaling and avoid natural selection for elimination. Because many therapeutic modalities principally act by promoting apoptosis, alterations in the intracellular signaling cascade can render neoplastic cancer cells resistant to therapy. In pancreatic cancer, various survival mechanisms act to prevent cell death, resulting in promotion of tumor growth and metastasis. Resistance of pancreatic cancer to apoptosis is a major factor preventing response to therapies. Strategies designed to attenuate this resistance to apoptosis-inducing stimuli may result in sensitization of the tumor to conventional modalities of cancer therapy.

Epidemiologic studies have suggested that a diet rich in fruits and vegetables is associated with a reduced risk for a number of common cancers. Case–control studies suggest that a higher intake of fruits and vegetables may decrease risk of pancreatic cancer.[3,4] Phytochemicals are non-nutritive chemicals found in plants that have protective or disease preventive properties. Stilbenes are one class of phytochemicals that have been shown to have antioxidant and antiproliferative properties. Resveratrol, a stilbene found in grapes, has been shown to inhibit a variety of primary tumors.[5–9] Pterostilbene, an analogue of resveratrol found in blueberries, has been shown to inhibit gastric, colon, and breast cancer as well as leukemia and melanoma in various in vitro and animal model systems.[10–15] Furthermore, its molecular structure makes it substantially more bioavailable than resveratrol upon oral ingestion. Little is known about its effects on cancer of the pancreas. We tested the hypothesis that pterostilbene would inhibit the growth of pancreatic tumor cells, in vitro.

Materials and Methods

Chemicals

Pterostilbene (3,5-dimethoxy-4-hydroxystilbene) and MTT, a tetrazolium dye (thiazolyl Blue tetrazolium bromide), were purchased from Sigma-Aldrich (St. Louis, MO, USA). 5-[(*S*)-(+)-2-(Methoxymethyl)pyrrolidino]sulfonylisatin, a reversible inhibitor of caspase-3 and caspase-7, as well as an irreversible pan-caspase inhibitor (Z-VAD-fmk), were obtained from Calbiochem (La Jolla, CA, USA). Compounds were dissolved in dimethyl sulfoxide (DMSO) and further diluted in sterile culture medium immediately prior to use. Cyclosporin A was obtained from BioMol (Plymouth Meeting, PA, USA).

Cell Culture

Pancreatic cancer cell lines (MIA PaCa-2 and PANC-1) were purchased from the American Type Culture Collection (Manassas, VA, USA). Cells were maintained as monolayers in T-25 flasks in Dulbecco's modification Eagle's medium (Mediatech, Inc., Herndon, VA, USA) supplemented with 10% fetal bovine serum (HyClone, Logan, UT, USA), and 1% penicillin streptomycin (Mediatech, Inc.). Flasks were kept at 37°C in a water-jacketed 5% CO_2 incubator (Fischer Scientific, Houston, TX, USA). For experiments, cells were harvested from culture monolayers at 80–90% confluency. Cells were rinsed with sterile phosphate-buffered saline (PBS; Mediatech, Inc.), and live cells were detached using 0.25% trypsin in 0.1% EDTA (Mediatech, Inc). Cells were then centrifuged at 1,000 rpm for 5 min and resuspended in growth medium. Cells were then plated and treated as described in each of the following sections.

Growth Inhibition

Cells were added to 24-well plates at 10^4 cells/well and incubated to allow for adherence. After 24 h, half of the media was changed, and cells were treated with pterostilbene or DMSO (vehicle control in all experiments is DMSO equal to the highest concentration of pterostilbene) at 20–100 μM for 24, 48, and 72 h. Cells were then harvested and counted by hemocytometer. The growth of treated cells was expressed as a percentage of untreated control cells. The concentration of pterostilbene that decreased cell count by 50% (IC_{50}) was calculated by nonlinear least-squares curve fitting of experimental data utilizing Graphpad Software (San Diego, CA, USA).

Cell Viability Assay

Cells were seeded at 10^4 cells per well in 96-well plates and allowed to attach overnight. Cells were then exposed to various doses of pterostilbene (10–100 μM) or DMSO. The MTT colorimetric assay was performed to detect cell viability after 24, 48, and 72 h of exposure to pterostilbene (10–100 μM). Culture media were removed, and MTT diluted in culture media was added to each well. Plates were incubated at 37°C in the CO_2 incubator for 1 h. Mitochondrial dehydrogenase activity reduced the yellow MTT dye to a purple formazan, which was solubilized in DMSO (Sigma), and absorbance was read at 540 nm on an ELISA plate reader.

DNA Fragmentation Assay

The Cell Death Detection ELISA kit (Roche, Mannheim, Germany), a sandwich enzyme immunoassay-based method,

was used to detect the occurrence of nuclear DNA fragmentation. This kit employs mouse monoclonal antibodies directed against DNA and histones. This allows the specific determination of mono- and oligonuclecleosomes in the cytoplasm fraction of cell lysates. Cells were plated 10^4 cells per well into 96-well plates and allowed to adhere for 24 h. Cells were then exposed to various doses of pterostilbene and DMSO control. After18 h, adherent cells were lysed, and lysates were then centrifuged to produce a nucleosome-containing supernatant to test for apoptosis. Samples were transferred to a streptavidin-coated microplate and incubated with anti-histone and anti-DNA antibodies followed by a peroxidase substrate resulting in color change. Color development was proportional to the amount of nucleosomes captured in the antibody sandwich and was measured spectrophotometrically at 405 nm.

Caspase Activity Assay

Cells were seeded at 10^4 cells per well into 96-well plates with opaque sidewalls. After an allotted 24 h for cell adherence, half of the media was replaced, and cells were exposed to pterostilbene (75 μM) or DMSO for 24 h. The Apo-ONE^{TM} homogeneous caspase-3/7 assay substrate (Promega, Madison, WI, USA) was utilized to evaluate the activities of caspase-3 and caspase-7. The caspase-3/7 substrate rhodamine 110,bis-(*N*-CBZ-L-aspartyl-L-glutamyl-L-valyl-L-aspartic acid amide; Z-DEVD-R110) is acted upon by caspase-3 and caspase-7 resulting in a fluorescent leaving group. The amount of fluorescent product generated is proportional to the amount of caspase-3/7 cleavage activity present in the sample. Caspase-3/7 substrate was added to each well and incubated at room temperature for 1–2 h. A spectrofluorometer was used to measure fluorescence (excitation wavelength 485±20 nm, emission wavelength 528±20 nm).

Caspase Inhibition

Cells were plated 10^4 cells per well into 96-well plates and allowed to adhere for 24 h. Cells were then pretreated for 30 min with 50 μM of caspase-3/7 inhibitor or with a pan-caspase inhibitor or with an equal concentration of DMSO. Next, cells were treated with DMSO and 50 or 75 μM pterostilbene for 24 to 48 h. Cell viability was assayed using MTT assay as described previously.

Mitochondrial Depolarization

Cells were seeded at 3×10^5 cells per well into a six-well plate. After 24 h for cell adherence, 2 μM of JC-1 (Molecular Probes, Eugene, OR, USA) was added to each well for 20 min at 37°C. Cells were washed with PBS and treated with DMSO control or pterostilbene (25, 50, 75, or 100 μM) for an additional 30 min. Cells were then trypsinized, resuspended in PBS, and run on a Coulter Elite Flow Cytometer. The excitation peak of JC-1 is 488 nm. The approximate emission peaks of monometric and J-aggregate forms are 529 and 590 nm, respectively.

Cell Cycle

Cells were seeded at 3×10^5 cells per well into a six-well plate. The next day, cells were treated with DMSO or pterostilbene for 24 h then washed in PBS, trypsinized, and fixed in cold ethanol for 2 h. Cells were then washed and resuspended in PBS + 0.1% Triton x-100 + 100 μg/mL RNase A (Sigma, St. Louis, MO, USA) + 40 μg/mL propidium iodide (MP Biomedicals Solon, OH) for 30 min at 37°C in the dark. Cells were run on a Coulter Elite Flow Cytometer. Propidium iodide, when bound to nucleic acids, has an excitation maximum at 535 nm and emission maximum at 617 nm. Cell populations were analyzed and categorized into cell cycle phases using Modfit LT 3.0 software.

Cell Viability Assay with Cyclosporin Pretreatment

Cells were seeded at 10^4 cells per well in 96-well plates and allowed to adhere for 24 h. The cells were then pretreated with 25 μM cyclosporine A or DMSO for 30 min, followed by 24 h of DMSO or 75 μM pterostilbene. The remainder of the MTT assay was performed according to the sequence outlined previously.

Statistical Analysis

Data were presented as mean values ± standard error. Statistical comparisons among groups were performed by Student's *t* test or analysis of variance (ANOVA) followed by Bonferonni post-tests for multiple comparisons.

Results

In Vitro Antitumor Activity of Pterostilbene

Pterostilbene induced a significant concentration- and time-dependent decrease in MIA PaCa-2 and PANC-1 cell viability (Fig. 1). The values of the inhibitory concentration at 50% effect level (IC_{50}) shown in Table 1 indicate the antitumor potency of this agent in both pancreatic cell lines. Potency was similar in both cell lines. Pterostilbene treatment for 24, 48, and 72 h required concentrations of 72, 51, and 32 μM, respectively, to inhibit cancer cell growth by 50% of control values in MIA PaCa-2, and 84, 33, and 29 μM for PANC-1.

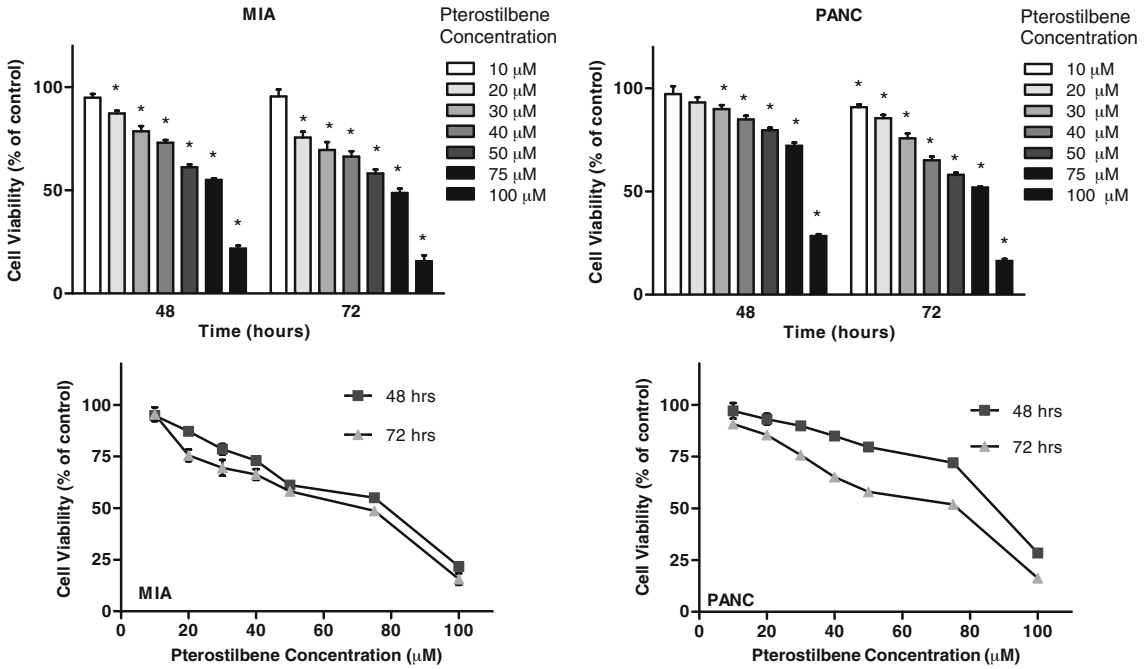

Figure 1 Cell viability assay. Pterostilbene treatment (10–100 μM) resulted in a significant concentration and time-dependent decrease in cell viability in both pancreatic cancer cell lines (ANOVA $p<0.001$). Data shown as means with SEM ($n=6$: *$p<0.001$ versus control). Representative data from experiments run in triplicate.

Pterostilbene Induces Apoptosis in MIA PaCa-2 Cancer Cells

Programmed cell death is characterized by chromatin condensation, membrane blebbing, inter-nucleosomal degradation of DNA, and apoptotic body formation. To investigate whether cytotoxic effects of pterostilbene were due to necrosis or apoptosis, an assay looking at released nucleosomes was performed (Fig. 2). There was a statistically significant 4.04±2.17-fold increase in released nucleosomes in MIA PaCa-2 cells exposed to pterostilbene. This trend was not seen in PANC-1 cells.

Caspase Activity Following Pterostilbene

To ascertain whether the biologic activity of pterostilbene could involve effector caspases, an assay was performed looking at the activity of two enzymes involved in the effector phase of apoptosis: caspase-3 and caspase-7. After treatment with 75 μM pterostilbene, both MIA PaCa-2 and PANC-1 cells were shown to have a significant increase in caspase-3/7 activity compared with vehicle-alone treated controls (Fig. 3). Caspase-3/7 activity in MIA PaCa-2 cells (3.21±0.90-fold increase versus vehicle-alone treated controls, $p<0.01$) was slightly greater than the activity in PANC-1 cells (1.81±0.36) fold increase versus vehicle-alone treated controls, $p<0.01$.

Table 1 Pterostilbene-Mediated Cell Growth Inhibition After 24, 48, and 72 h

	IC50 (μM), mean ± SEM	
	MIA PaCa-2	PANC
24 h	72±10.6	84±25.2
48 h	51±31.1	33±2.5
72 h	32±9	29±6.1

Experiments were performed in triplicate and values expressed as means ± SEM

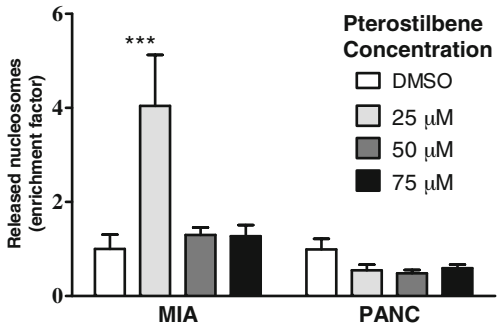

Figure 2 Cell death assay. MIA PaCa-2 cells exposed to DMSO or pterostilbene (25 μM) for 18 h have significantly increased released nucleosomes compared to control (vehicle-alone) treated cells, indicative of increased apoptosis. PANC-1 cells did not increase released nucleosomes with pterostilbene treatment. Data are represented as means plus SEM ($n=3$: Student's t test: *$p<0.05$).

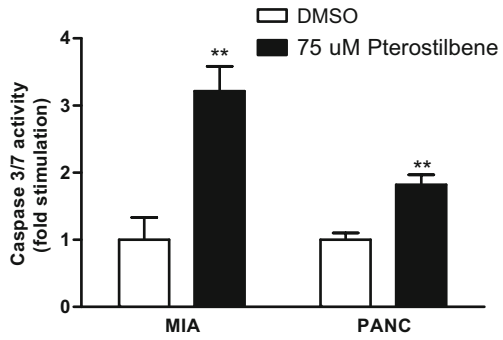

Figure 3 Caspase-3/7 activity. Pterostilbene treatment (75 μM) significantly increased caspase-3/7 activity in both pancreatic cancer cell lines when compared to vehicle-only treated controls. Data are represented as means plus SEM (n=6: Student's t test: *p<0.01).

Caspase Inhibition

To evaluate the effect of pterostilbene on caspase dependent pathways, both a caspase-3/7 inhibitor and pan-caspase inhibitor were utilized in an MTT assay. The results were mixed with the caspase-3/7 inhibitor demonstrating no ability to prevent pterostilbene-induced cell death, but the pan-caspase inhibitor blocking a larger proportion of cell death due to pterostilbene in the MIA but not in the PANC cells. Our results show that a pan-caspase inhibitor does save MIA cells from pterostilbene-induced cell death, while the PANC cells were not saved by the pan-caspase inhibitor (Fig. 4).

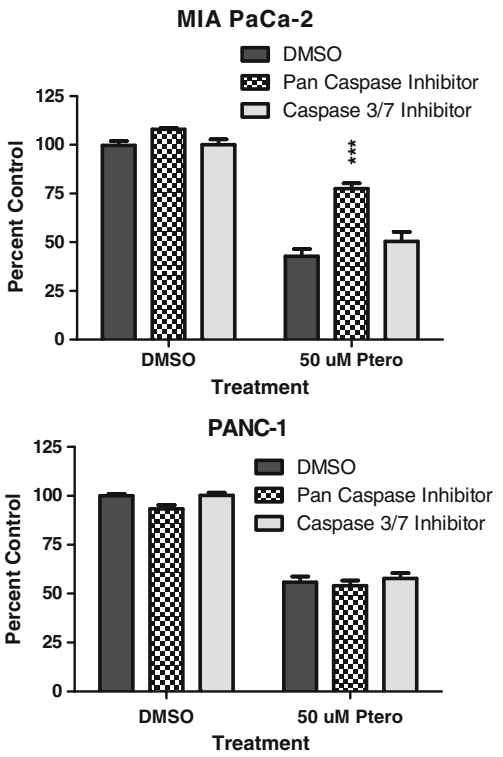

Figure 4 Caspase inhibition. Cells were pretreated with 50 μM of either a caspase-3/7 or a pan-caspase inhibitor for 30 min, then treated with pterostilbene for 24 h. DMSO controls were equal concentration to treatment. MIA cell viability was significantly increased when pretreated with the pan-caspase inhibitor. Data are represented as means plus SEM (n=6: Student's t test, *p<0.01).

Mitochondrial Depolarization

Both the MIA and PANC cells treated with pterostilbene were found to have rapidly depolarizing mitochondrial membranes (within 20 min of treatment with JC-1) (Table 2). The depolarization was found to be linearly related to the increasing dose of pterostilbene within the cell culture. The amount of depolarization was found to be more pronounced, or the amount of pterostilbene needed was less, in the PANC-1 versus MIA cells.

Cell Cycle

The cell cycle analysis of MIA and PANC-1 treated with pterostilbene shows the MIA cells arrested in the S phase when treated with 25 and 50 μM of pterostilbene. At a higher concentration (75 μM), MIA cells underwent G0/G1 arrest. The PANC cells were found to have S phase arrest at all doses of pterostilbene (Table 3).

Cyclosporin A Prevents Pterostilbene-Induced Cell Death

In both pancreatic cell lines, pretreatment with 25 μM cyclosporine A significantly protected cells from pterostilbene-induced death. Cyclosporin A (CsA) inhibits cyclophilin D and is a potent inhibitor of the mitochondrial permeability transition pore.[19] This stabilization of the mitochondrial membrane may stop ROS formation and/or pro-apoptotic proteins from reaching the cytosol, therefore preventing cell death (Fig. 5).

Table 2 Mitochondrial Depolarization with Pterostilbene

	Red/green ratio	
	MIA PaCa-2	PANC-1
DMSO	2.45	2.03
50 μM pterostilbene	1.00	0.36
75 μM pterostilbene	0.18	0.41
100 μM pterostilbene	0.08	0.08

JC-1 labeled cells after 20 min DMSO or pterostilbene treatment were run on a flow cytometer, and the percent red (normal mitochondria) and green (depolarized mitochondria) were evaluated. Mitochondrial depolarization is indicated by a decrease in the red/green ratio

Table 3 Cell Cycle Analysis

	Cell cycle analysis (%)		
	G0/G1	S	G2/M
MIA PaCa-2			
DMSO	53	23	24
25 μM Pterostilbene	37	46	17
50 μM Pterostilbene	52	34	16
75 μM Pterostilbene	64	20	16
PANC-1			
DMSO	52	28	20
25 μM Pterostilbene	49	34	17
50 μM Pterostilbene	52	34	16
75 μM Pterostilbene	44	39	17

MIA or PANC cells were treated with DMSO or pterostilbene for 24 h, then treated with propidium iodide, and run on the flow cytometer. Cell cycle phases were analyzed using Modfit LT 3.0 Software

Discussion

The present study demonstrates the in vitro anticancer activity of pterostilbene on two different pancreatic cancer cell lines, MIA PaCa-2 and PANC-1. Treatment with pterostilbene leads to inhibition of cell proliferation and/or cell death, cell cycle arrest, mitochondrial membrane depolarization, and activation of effector caspases.

Initially we hypothesized that the anticancer effect of pterostilbene may be mediated via the induction of apoptosis. During our study, when looking at inter-nucleosomal fragmentation as a feature indicative of apoptosis, pterostilbene induced apoptotic inter-nucleosomal fragmentation in MIA PaCa-2 cells but not PANC-1 cells. To follow up on this observation, we assessed whether caspase-3/7, two enzymes involved in the effector phase of apoptosis, were activated in either cell line. Our results demonstrated an increase in caspase-3/7 activity in both cell groups, indicating that pterostilbene interacts with caspase pathways in both pancreatic cancer cell lines, although perhaps at a higher rate in the MIA cells versus the PANC cells. However, the addition of the pan-caspase inhibitor rescued MIA cells treated with pterostilbene but were unable to reverse cellular death in similarly treated PANC cells. It appears that pterostilbene may achieve cellular demise that is unrelated to caspase pathways in certain cell types.

Mitochondria are emerging as promising targets for intervention and treatment of cancer.[16,17] Pan et al. [18] used transcript profiling techniques to identify cellular pathways targeted by pterostilbene and found that it up-regulated the expression of genes involved in mitochondrial functions. Our data show that pterostilbene causes pancreatic cancer cell mitochondrial depolarization early (within 20 min) and in a dose-dependent manner.

CsA is a transient modulator of mitochondrial membrane permeabilization. CsA inhibits cyclophilin D and is a potent inhibitor of the permeability transition pore.[19] Our data show that cells pretreated with 25 μM CsA are saved from pterostilbene-induced cell death. This stabilization of the mitochondrial membrane may stop ROS formation and/or pro-apoptotic proteins from reaching the cytosol, therefore preventing cell death.

Another area that will need to be further researched if the mechanism of pterostilbene is to be elucidated is the cessation of the cell cycle in cells treated with the compound. Inhibition of cell cycle progression is one possible target for chemopreventive agents. The cell cycle is regulated by cyclins and cyclin-dependent kinases.[20] The effect of resveratrol on the cell cycle of many tumor cells focuses on the S phase. A cell cycle arrest in the S phase has been reported for various cell types but appears to be cell line dependent.[18,21] We previously reported that pterostilbene treatment leads to an S phase arrest in the breast cancer line MCF7, but no such change in cell cycle was seen with MDA cells.[22] Opipari et al. [23] reported that

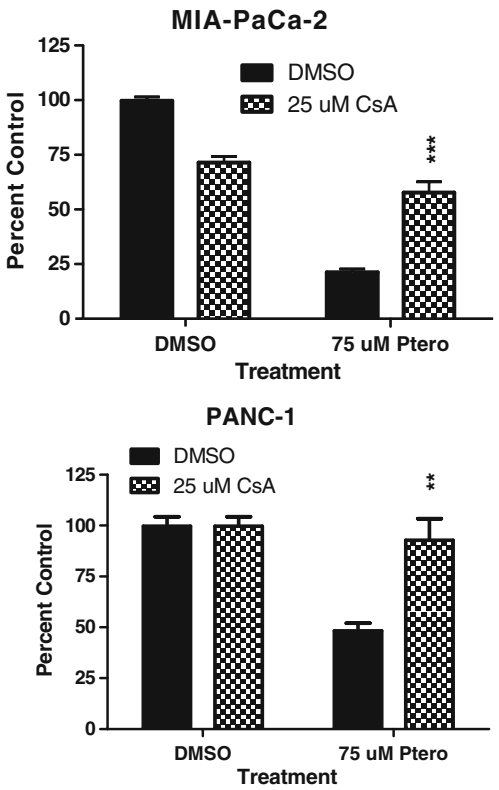

Figure 5 Cyclosporin A protects against pterostilbene-induced cell death. Cells were pretreated with 25 μM cyclosporin A for 30 min then 75 μM pterostilbene for 24 h (*$p<0.01$). Portions of this work were presented at the 4th Annual Academic Surgical Conference in Fort Meyers, Florida in February 2009.

resveratrol at a concentration of 50 μM accumulated ovarian cancer cells in S phase, but at 100 μM, the cells instead accumulated in the G0–G1 phase. This is similar to what our study shows with MIA cells: an S phase arrest with lower concentration (25 and 50 μM) of pterostilbene and G0/G1 arrest with higher concentrations. Low concentrations of pterostilbene often initially induce cells to proliferate before their numbers are reduced over time. Since PANC cells exhibited S phase arrest at all concentrations of pterostilbene, while the MIA cells demonstrated cell cycle arrest in the G0/G1 phase at a higher dose, pterostilbene may act via different pathways in each cell line.

In conclusion, our data indicate that pterostilbene induces cell death in pancreatic cancer cells. However, apoptosis is an inherently complex signaling cascade with multiple triggers and unique interactions that eventually lead to cellular demise. Further insights into pterostilbene's molecular mechanism of action is warranted in order to judge whether this naturally occurring compound could play a role as a chemopreventative agent or more importantly as an adjunct to help sensitize resistant pancreatic cancer cells to currently available chemotherapy regimens. Additionally, pterostilbene's effect in vivo is promising, and future studies in animals are warranted given the abundance of data to support its in vitro effectiveness.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin 2009;59(4):225-249.
2. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15(6):2403-2413.
3. Chan JM, Wang F, Holly EA. Vegetable and fruit intake and pancreatic cancer in a population-based case-control study in the San Francisco bay area. Cancer Epidemiol Biomarkers Prev. 2005;14(9):2093-2097.
4. Nkondjock A, Krewski D, Johnson KC, Ghadirian P. Dietary patterns and risk of pancreatic cancer. Int J Cancer. 2005;114 (5):817-823.
5. Lee MH, Choi BY, Kundu JK et al. Resveratrol suppresses growth of human ovarian cancer cells in culture and in a murine xenograft model: eukaryotic elongation factor 1A2 as a potential target. Cancer Res 2009;69(18):7449-7458, Epub 2009 Sep 8.
6. Harper CE, Cook LM, Patel BB et al. Genistein and resveratrol, alone and in combination, suppress prostate cancer in SV-40 tag rats. Prostate 2009;69(15):1668-1682.
7. Chen J, Dong XS, Guo XG. Inhibitory effect of resveratrol on the growth of human colon cancer ls174t cells and its subcutaneously transplanted tumor in nude mice and the mechanism of action. Zhonghua Zhong Liu Za Zhi 2009;31(1):15–19.
8. Weng CJ, Yang YT, Ho CT, Yen GC. Mechanisms of apoptotic effects induced by resveratrol, dibenzoylmethane and their analogues on human lung carcinoma cells. J Agric Food Chem 2009;57(12):5235-5243.
9. Li Y, Bäckesjö CM, Haldosén LA, Lindgren U. Resveratrol inhibits proliferation and promotes apoptosis of osteosarcoma cells. Eur J Pharmacol 2009;609(1-3):13-18.
10. Rimando AM, Cuendet M, Desmarchelier C, Mehta RG, Pezzuto JM, Duke SO. Cancer chemopreventive and antioxidant activities of pterostilbene, a naturally occurring analogue of resveratrol. J Agric Food Chem 2002;50(12):3453-3457.
11. Ferrer P, Asensi M, Segarra R et al. Association between pterostilbene and quercetin inhibits metastatic activity of B16 melanoma. Neoplasia 2005;7(1):37-47.
12. Tolomeo M, Grimaudo S, Di Cristina A et al. Pterostilbene and 3'-hydroxypterostilbene are effective apoptosis-inducing agents in MDR and BCR-ABL-expressing leukemia cells. Int J Biochem Cell Biol 2005;37(8):1709-1726.
13. Pan MH, Chang YH, Badmaev V, Nagabhushanam K, Ho CT. Pterostilbene induces apoptosis and cell cycle arrest in human gastric carcinoma cells. J Agric Food Chem 2007;55(19):7777-7785
14. Suh N, Paul S, Hao X et al. Pterostilbene, an active constituent of blueberries, suppresses aberrant crypt foci formation in the azoxymethane-induced colon carcinogenesis model in rats. Clin Cancer Res 2007;13(1):350-355.
15. Remsberg CM, Yanez JA, Ohgami Y, Vega-Villa KR, Rimando AM, Davies NM. Pharmacometrics of pterostilbene: preclinical pharmacokinetics and metabolism, anticancer, antiinflammatory, antioxidant and analgesic activity. Phytother Res 2008;22(2):169-179
16. Ralph S, Neuzil J. Mitochondria as targets for cancer therapy. Mol Nutr Food Res 2009;53:9-28.
17. Fantin VR, Leder P. Mitochondriotoxic compounds for cancer therapy. Oncogene 2006;25(34):4787-4797.
18. Pan Z, Agarwal AK, Xu T et al. Identification of molecular pathways affected by pterostilbene, a natural dimethylether analog of resveratrol. BMC Med Genomic 2008;1:7.
19. Broekemeier KM, Dempsey ME, Pfeiffer DR. Cyclosporin A is a potent inhibitor of the inner membrane permeability transition in liver mitochondria. J-Biol-Chem 1989;264(14):7826-7830.
20. Ulrich S, Wolter F, Stein JM. Molecular mechanisms of the chemopreventive effects of resveratrol and its analogs in carcinogenesis. Mol Nutr Food Res 2005;49(5):452-461.
21. Wolter F, Akoglu B, Clausnitzer A, Stein J. Downregulation of the cyclin D1/Cdk4 Complex Occurs During Resveratrol-induced cell Cycle arrest in Colon cancer Cell Lines. J Nutr 2001;131:2197-2203.
22. Alosi JA, McDonald DE, Schneider JS et al. Pterostilbene inhibits breast cancer *in vitro* through mitochondrial depolarization and induction of caspase-dependent apoptosis. J Surg Res 2009. doi:10.1016/j.jss.2009.07.027.
23. Opipari AW Jr., Tan L, Boitano AE et al. Resveratrol-induced autophagocytosis in ovarian cancer cells. Cancer Res 2004;64 (2):696-703.

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ORIGINAL ARTICLE

Management and Outcome of Gastrointestinal Stromal Tumors of the Duodenum

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Abstract
Background Duodenal gastrointestinal stromal tumors (GISTs) are uncommon and relatively small subset of GISTs whose optimal surgical procedure has not been well defined. We conducted this study to present the surgical experience in our institution and to analyze the postoperative outcome of duodenal GISTs.
Methods A retrospective clinicopathologic analysis was performed for nine duodenal GIST patients who underwent surgery from May 2001 to April 2009. The median follow-up period was 22 months (range: 13–61 months).
Results A total of nine patients (six males/three females) with a median age of 52 years (range: 45-73 years) were treated. The most common presentation was abdominal pain (45%), and the second portion of duodenum (45%) was most common dominant site. All of the patients underwent limited resection: there were seven wedge resections with primary closures (five open/two laparoscopic) and two segmental resections with end-to-end duodenojejunostomies. The median tumor size was 3.5 cm (range: 1.9-5.5 cm), and the mitotic count was less than fivemitoses/50 high power fields (HPF) in all cases. None patients had neoadjuvant or adjuvant therapy. All of the patients were alive and disease-free.
Conclusion We obtained excellent disease-free survival following limited resection with clear margins. Limited resection should be considered a treatment option for duodenal GIST.

Keywords Gastrointestinal stromal tumor · Duodenum · Surgery

Introduction

Gastrointestinal stromal tumors (GISTs) are currently defined as specific mesenchymal neoplasms of the digestive tract containing spindle cells and showing KIT (CD117) positivity.[1,2] GISTs are uncommon malignant neoplasms. However, these represent the most common subset of mesenchymal tumors arising within the gastrointestinal tract.[3,4] The commonest site of origin is the stomach (60-70% of cases), followed by the small intestine (30%) and rarely from the rectum (5%), esophagus, colon, and appendix.[5,6] GISTs may arise in extra intestinal sites in up to 5% of cases.[5,6] Duodenal GISTs comprise a relatively small subset of GISTs with a reported frequency of 6-21% of surgically resected GISTs.[2,7]

The optimal management of GISTs is surgical resection with clear margins.[4,7] The wide margins with extensive lymphadenectomy may not be required in GISTs as GISTs are associated with negligible submucosal spread and lymphatic involvement is rare.[3,4] Unlike GISTs involving other sites of the gastrointestinal tract, the optimal surgical procedure for duodenal GISTs has not been well-characterized in the surgical literature.[7] There are currently very few reports in the English literature addressing the surgical procedures for duodenal GISTs.[4] The purpose of this study was to present the surgical experience in our institution and to analyze the postoperative outcome of duodenal GISTs.

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Patients and Methods

Between May 2001 and April 2009, 101 patients who underwent surgical resection of a GIST at the Department of Surgery, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine were retrospectively reviewed. Among the 101 patients of GIST, nine patients with duodenal GIST were enrolled in this study. The diagnosis of GIST was based on the standard histology obtained from the postoperative biopsy of the resected specimen.[1] Complete tumor removal was the management principle in each case. Limited resection with clear margins was the operation of choice whenever it was deemed technically feasible. The following characteristics were collected and analyzed on each patient: age, sex, presentation, location, operation, size, mitotic count, adjuvant therapy, and the recent follow-up details.

Results

During the study period, nine (9%) patients underwent surgery for GIST involving the duodenum (Table 1). There were six (67%) men and three (33%) women with a median age of 52 years (range: 45-73 years). Of the nine patients, 6 (67%) patients had clinical symptoms and three (33%) patients had no symptoms associated with the tumor. The tumors that had no symptom (incidental finding) were detected by routine health checkup. The most common presentation was abdominal pain (n=4, 45%), followed by incidental finding (n=3, 33%), and bleeding (n=2, 22%). Among the four patients who had complained of abdominal pain, one patient had jaundice. He had multiple stones in the common bile duct, so endoscopic retrograde cholangiopancreatography with endoscopic sphincterotomy was done before operation. The tumors were detected via endoscopy (n=6) and computed tomography (n=9). The tumors were located in the first (n=2, 22%), second (n=4, 45%), third (n=2, 22%), and fourth portion of duodenum (n=1, 11%). According the tumor location and size, nine patients underwent various procedures: there were five wedge resections with primary closures, two laparoscopic wedge resections with primary closures, and two segmental resections with end-to-end duodenojejunostomies (Table 2). Surgical margins were free of tumor in all cases. The tumor size varied from 1.9 to 5.5 cm (median 3.5 cm), and the tumors were described as well circumscribed or encapsulated. The mitotic count was less than five mitoses/50 high power fields (HPF) in all cases (Table 3). Two patients (22%) developed complications, including abdominal fluid collection and wound infection. Abdominal fluid collection was treated successfully with percutaneous drainage, which was removed after 2 weeks. Wound infection was recovered from conservative management. The median postoperative hospital stay was 9 days, with its range from 5 to 24 days. No patients had neoadjuvant or adjuvant therapy with imatinib mesylate or other systemic chemotherapy. No patients in this series were treated with adjuvant radiotherapy. The median follow-up period of nine patients with duodenal GIST that underwent surgical resection was 22 months (range: 13-61 months). All of the patients were alive and disease-free.

Discussion

GISTs are low-grade malignant mesenchymal tumors of gastrointestinal tract and are believed to originate from the pluripotential mesenchymal stem cells programmed to differentiate into the interstitial cells of Cajal.[6,8] These tumors are characterized by expression of a transmembrane receptor tyrosine kinase KIT, a product of the c-kit proto-oncogene, and identified by expression of CD117 antigen.[1]

GISTs can occur anywhere throughout the gastrointestinal tract but are most commonly found in the stomach or small intestine.[5,6] These tumors may also occur in the peritoneum and extragastrointestinal sites.[9] The small

Table 1 Clinical Features of GISTs by Tumor Location

	Stomach	Duodenum	Jejunum and ileum
Number of patients	88 (87%)	9 (9%)	4 (4%)
Age (years)	52 (31-79)	52 (45-73)	58 (39-69)
Sex (male)	46 (52%)	6 (67%)	1 (25%)
Size (cm)	2.5 (0.8-13.0)	3.5 (1.9-5.5)	4.3 (2.5-6.3)
Symptomatic	33 (38%)	6 (67%)	4 (100%)
Presentation			
Incidental finding	55 (63%)	3 (33%)	0 (0%)
Abdominal discomfort	11 (12%)	0 (0%)	0 (0%)
Abdominal pain	9 (10%)	4 (45%)	2 (50%)
Obstruction	4 (5%)	0 (0%)	1 (25%)
Bleeding	9 (10%)	2 (22%)	1 (25%)

Table 2 Characteristics of Patients with Duodenal GISTs

Case	Age (years)	Sex	Symptom	Location	Operation
1	73	Female	Abdominal pain	Second	Wedge resection
2	45	Male	Abdominal pain	Second	Wedge resection
3	52	Male	Incidental finding	Third	Wedge resection
4	65	Male	Abdominal pain, jaundice	Third	Segmental resection
5	64	Male	Incidental finding	Second	Wedge resection
6	45	Male	Bleeding	First	Laparoscopic wedge resection
7	47	Female	Abdominal pain	Second	Wedge resection
8	69	Male	Incidental finding	First	Laparoscopic wedge resection
9	49	Female	Bleeding	Fourth	Segmental resection

intestine is the second most common site of GISTs, of which approximately 20% are found in the duodenum.[8] Duodenal GISTs are uncommon tumors, representing only nine of the 101 tumors (9%) in this series. Duodenal GISTs most frequently involve the second portion of the duodenum, followed by the third portion, fourth portion, and first portion.[2] Also, in this study, the second portion of the duodenum (45%) was most commonly involved.

The clinical presentations of duodenal GISTs are highly variable according to their size and the existence of mucosal ulceration. The most common clinical presentation of duodenal GISTs has been reported to be gastrointestinal bleeding or abdominal pain.[2,4,7] In this series, the most common presentation was abdominal pain (45%), followed by incidental finding (33%) and bleeding (22%).

For GISTs of the foregut, gastrointestinal endoscopy may be diagnostic whenever the tumor is located in the stomach or in the upper duodenum. On the other hand, GISTs of the distal duodenum may remain undetected at gastrointestinal endoscopy. Alternative diagnostic means include computed tomography (CT), magnetic resonance imaging (MRI), barium study, or ultrasonography.[9] However, CT and MRI seem to be the best imaging modalities for assessment of the primary lesion and detection of metastases.[10] In this study, only six tumors in the first and second portion of the duodenum were detected via endoscopy. On CT findings, GISTs are hypervascular and may have cystic and necrotic components. Small tumors typically appear as sharply marginated smooth masses with moderate contrast enhancement. On the contrary, large tumors tend to have mucosal ulceration, central necrosis, and cavitations with heterogeneous contrast enhancement.[10,11] In contrast, the MRI features of GISTs vary. Necrosis and hemorrhage can influence the signal intensity of MR images.[9]

Surgical resection with clear margins is the desirable primary treatment of GISTs.[3] As submucosal spread and local lymph node involvement is infrequent in GISTs, wide margins with routine lymph node dissection may not be required.[3,4] Unlike GISTs involving other sites of the gastrointestinal tract, the optimal surgical procedure for duodenal GISTs has not been well-characterized.[7] Surgical removal of duodenal GISTs may be accomplished by several options, ranging from the minimal to major procedures. Limited resection should be considered a viable treatment option for duodenal GISTs when technically feasible.[4,8] Various techniques of limited resection for duodenal GISTs have been advocated depending on the site and the size of the tumors. Wedge resection with primary closure can be

Table 3 Follow-up Data of Duodenal GISTs in Relation to Tumor Size and Mitotic count

Case	Size (cm)	Mitotic count per 50 HPF	Risk	Adjuvant therapy	Status
1	2	<5	Low risk	None	NED at 61 months
2	2.7	3	Low risk	None	NED at 57 months
3	3.5	<5	Low risk	None	NED at 53 months
4	4	<5	Low risk	None	NED at 42 months
5	5.5	1	Intermediate risk	None	NED at 22 months
6	1.9	<5	Very low risk	None	NED at 22 months
7	5	1	Intermediate risk	None	NED at 21 months
8	2.5	<5	Low risk	None	NED at 17 months
9	4.5	0	Low risk	None	NED at 13 months

HPF high power field, *NED* no evidence of disease

performed for small lesions if the resulting lumen is adequate and the ampulla of Vater can be preserved.[2,4] Segmental duodenectomy with side-to-end or end-to-end duodenojejunostomy can be performed for larger tumors located at the third and fourth portion of the duodenum.[4,12] Partial duodenectomy with Roux-en-Y duodenojejunostomy can be performed for larger tumors involving the antimesenteric border of the second and third portion of the duodenum.[8] An aggressive surgical approach may be required for complete removal. Major resection via a pancreaticoduodenectomy or a pancreas-sparing duodenectomy is indicated when the tumors are located at the second portion of the duodenum.[7,13] In this study, limited resection with clear margins was routinely performed for the treatment of duodenal GIST. Wedge resection with primary closure was the most commonly performed operation in this series. In two patients, segmental duodenectomy with end-to-end duodenojejunostomys were performed because the tumors were located below the infra-ampullary portion of the duodenum and were relatively larger in size (>4 cm).

The finding of low mitotic count in duodenal GISTs in this series is consistent with the findings reported by others. Miettenen et al. reported that 72% of duodenal GISTs had mitotic count less than or equal to five mitoses/50 HPF.[2] Winfield et al. reported that 75% of duodenal GISTs had mitotic count less than five mitoses/50 HPF.[7]

The use of imatinib mesylate, a competitive inhibitor of KIT, has been shown to be effective in patients with advanced or metastatic GISTs, and is currently being evaluated in the adjuvant therapy setting following complete resection.[14,15] The use of neoadjuvant imatinib mesylate has been shown to downstage tumors.[16] The role of neoadjuvant imatinib mesylate in the management of GISTs is currently the subject of an ongoing multicenter trial.[4,17]

Duodenal GISTs are relatively uncommon mesenchymal tumors that present most commonly with abdominal pain. Disease-free survival could be achieved by performing curative surgical resection with clear margins. Limited resection should be considered a treatment option for duodenal GISTs when technically feasible.

References

1. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol 2002;33:459–465.
2. Miettinen M, Kopczynski J, Makhlouf HR, Sarlomo-Rikala M, Gyorffy H, Burke A, Sobin LH, Lasota J. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the duodenum: a clinicopathologic, immunohistochemical, and molecular genetic study of 167 cases. Am J Surg Pathol 2003;27:625–641.
3. Connolly EM, Gaffney E, Reynolds JV. Gastrointestinal stromal tumors. Br J Surg 2003;90:1178–1186.
4. Goh BK, Chow PK, Kesavan S, Yap WM, Wong WK. Outcome after surgical treatment of suspected gastrointestinal stromal tumors involving the duodenum: is limited resection appropriate? J Surg Oncol 2008;97:388–391.
5. Kwon SH, Cha HJ, Jung SW, Kim BC, Park JS, Jeong ID, Lee JH, Nah YW, Bang SJ, Shin JW, Park NH, Kim DH. A gastrointestinal tumor of the duodenum masquerading as a pancreatic head tumor. World J Gastroenterol 2007;13:3396–3399.
6. Butt J, Rowley S, Byrne PJ, Reynolds JV. Management of gastrointestinal stromal tumours: a single-centre experience. Ir J Med Sci 2007;176:157–160.
7. Winfield RD, Hochwald SN, Vogel SB, Hemming AW, Liu C, Cance WG, Grobmyer SR. Presentation and management of gastrointestinal stromal tumors of the duodenum. Am Surg 2006;72:719–723.
8. Goh BK, Chow PK, Ong HS, Wong WK. Gastrointestinal stromal tumor involving the second and third portion of the duodenum: treatment by partial duodenectomy and Roux-en-Y duodenojejunostomy. J Surg Oncol 2005;91:273–275.
9. Uchida H, Sasaki A, Iwaki K, Tominaga M, Yada K, Iwashita Y, Shibata K, Matsumoto T, Ohta M, Kitano S. An extramural gastrointestinal stromal tumor of the duodenum mimicking a pancreatic head tumor. J Hepatobiliary Pancreat Surg 2005;12:324–327.
10. Lau S, Tam KF, Kam CK, Lui CY, Siu CW, Lam HS, Mak KL. Imaging of gastrointestinal stromal tumour (GIST). Clin Radiol 2004;59:487–498.
11. Levy AD, Remotti HE, Thompson WM, Sobin LH, Miettinen M. Gastrointestinal stromal tumors: radiologic fearures with pathologic correlation. Radiographics 2003;23:283–304.
12. Sakamoto Y, Yamamoto J, Takahashi H, Kokudo N, Yamaguchi T, Muto T, Makuuchi M. Segmental resection of the third portion of the duodenum for a gastrointestinal stromal tumor: a case report. Jpn J Clin Oncol 2003;33:364–366.
13. Tisotos GG, Sarr MG. Pancreas-preserving total duodenectomy. Dig Surg 1998;15:398-403.
14. van der Zwan SM, DeMatteo RP. Gastrointestinal stromal tumor: 5 year later. Cancer 2005;104:1781–1788.
15. Demetri GD, von Mehren M, Blanke CD, van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corless C, Fletcher CD, Joensuu H. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472–480.
16. Loughrey MB, Mitchell C, Mann GB, Michael M, Waring PM. Gastrointestinal stromal tumour treated with neoadjuvant imatinib. J Clin Pathol 2005;58:779–781.
17. Eisenberg BL, Judson I. Surgery and imatinib in the management of GIST: emerging approaches to adjuvant and neoadjuvant therapy. Ann Surg Oncol 2004;11:465–475.

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ORIGINAL ARTICLE

Application of Polyethylene Glycolic Acid Felt with Fibrin Sealant to Prevent Postoperative Pancreatic Fistula in Pancreatic Surgery

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Abstract
Objective The purpose of this nonrandomized retrospective study was to report our new procedures using polyethylene glycolic acid (PGA) felt with fibrin sealant to prevent severe pancreatic fistula in patients undergoing pancreatic surgery.
Methods From 2000 to 2008, 54 and 63 patients underwent pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), respectively. Of those patients, we applied PGA felt with fibrin sealant to 18 PD patients and 26 DP patients. In PD patients, the PGA felt was wrapped around the pancreatic suture site, while in DP patients, the PGA felt was wrapped around the predictive division site. The pancreaticojejunostomy site in PD patients and the cut stump in DP patients were coated with fibrin sealant. We compared the occurrence rates for severe postoperative pancreatic fistula (POPF) that occurred after PD or DP both with and without our new procedures.
Results Before introduction of our procedures, severe POPF developed in 14 of 36 PD patients (39%) and 10 of 37 DP patients (27%). In contrast, after introduction of our procedures, the incidence of POPF was only one in both of 18 PD (6%; P=0.016) and 26 DP (4%; P=0.017) patients.
Conclusion In summary, our procedure using PGA felt with fibrin sealant may reduce the risk of severe POPF.

Keywords POPF · PGA felt · Fibrin sealant · Pancreatic surgery

Introduction

Postoperative pancreatic fistula (POPF) is the most frequent complication after pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), occurring in 3–26%[1–3] and 0–>60% of cases,[3–5] respectively. POPF often develops into further complications such as fluid collection or intra-abdominal abscesses, wound infection, and sepsis. According to the 2005 International Study Group on Pancreatic Fistula classification,[2] grade A pancreatic fistula have no clinical impact, whereas grade B and grade C pancreatic fistula require changes in clinical management or deviation from the normal clinical pathway. Thus, from a clinical perspective, it is important to reduce the risk of developing grade B or C POPF in patients undergoing pancreatectomy.

Herein, we describe our new surgical technique of applying polyethylene glycolic acid (PGA) felt with a fibrin sealant to reduce severe POPF of grade B or C, and evaluated the efficacy of these procedures in pancreaticojejunostomy and pancreatic transection patients receiving PD and DP for the prevention of grade B or C POPF.

Material and Methods

From May 2003 to April 2008, 54 and 63 patients underwent PD and DP, respectively, at the Department of

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Surgery, Kyoto Prefectural University of Medicine. Of these patients, the last 18 PD and 26 DP patients received a new surgical procedure involving application of PGA felt with fibrin sealant. POPFs were classified according to the internationally accepted definition of the International Study Group on Pancreatic Fistula.[2] We retrospectively compared the perioperative morbidity rate of grade B or C POPF in the 36 PD and 37 DP cases without our new procedure (no-procedure group), and in the 18 PD and 25 DP cases with our new procedure (procedure group); in the no-procedure group, we never used PGA felt or fibrin sealant at the anastomotic site of pancreaticojejunostomy in the 36 PD cases, or both PGA felt and fibrin sealant at the same time in the 37 DP cases. We identified the pancreatic duct using a binocular loupe or an intraoperative ultrasonography and placed a pancreatic duct stent for external drainage in all PD cases. We used a stapler for 26 of the 37 DP cases in the no-procedure group after transection and closure of the pancreatic stump. The combined use of PGA felt and fibrin sealant cost approximately $170 in Japan.

New Surgical Procedure of Pancreaticojejunostomy

The child's reconstruction was performed in all 63 PD patients. The pancreas was transected with a knife or an ultrasonic dissector, followed by identification of the main pancreatic duct. A tube was transiently inserted into the pancreatic duct. The bleeding from the cut surface of the parenchyma was then closed using single stitches of 4-0 Polydioxanon monofilament absorbable sutures (PDS) (Ethicon Endosurgery; Johnson & Johnson, Cincinnati, OH, USA), and the suture site wrapped by laying PGA felt (Gunze Co., Kyoto, Japan). The pancreatic parenchyma was sutured penetratingly using straight needles with 4-0 monofilament nonabsorbable threads through the PGA felt and the seromuscular layer of the jejunum. After anastomosis between the pancreatic main duct and the jejunal wall using four to 12 stitches with 6-0 monofilament absorbable threads, the previous 4-0 threads were tied and the pancreaticojejunostomy finished (Fig. 1). The anastomotic site was reinforced by laying a fibrinogen/thrombin-coated collagen patch (Kaketsuken, Kumamoto, Japan; dose range 0.01–0.5 ml) onto the wrapped PGA felt.

New Surgical Procedure of Pancreatic Transaction in DP

A stapling device is useful for pancreatic transection. In the staple method, we used devices that gave a staple line consisting of a triple row of closely placed staples. Before stapling, PGA felt was wrapped around the predictive staple line. The staple line was reinforced by laying a fibrinogen/thrombin-coated collagen patch onto the transected stump (Fig. 2a, b). In some cases, transection was also performed

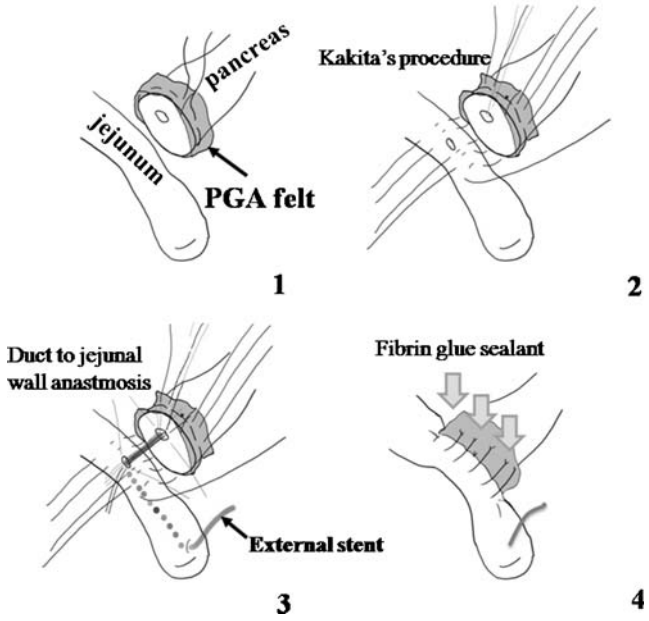

Figure 1 In PD patients, the suture site was wrapped by laying PGA felt. The pancreatic parenchyma was sutured penetratingly using straight needles with 4-0 monofilament nonabsorbable threads through the PGA felt and the seromuscular layer of the jejunum. After anastomosis between the pancreatic main duct and the jejunal wall using four to 12 stitches with 6-0 monofilament absorbable threads, the former 4-0 threads were tied and the pancreaticojejunostomy finished.

using the Echelon 60 with PGA felt (Gunze Co.) stocking type (Fig. 3a, b). The closure jaw of the staple was clamped carefully and slowly at a fixed speed, taking more than approximately 5 min. This procedure reduced the thickness of the pancreatic parenchyma at the site of planned resection and facilitated the subsequent application of the linear stapler across the pancreas. To ensure hemostasis from the pancreatic stump, the stapler was not released immediately after firing, and the jaws of the stapler were held shut for approximately 2 min. A ligation of the main pancreatic duct was unnecessary, and minor bleeding from the stump could be easily controlled by either compression or coagulation using electrocautery. This staple procedure with the above-described techniques provides a secure staple line without any tissue damage. Routine postoperative prophylactic octreotide was not used.

Postoperative Follow-up

Postoperative assessment included repeated measurement (days 1, 3, 4, and 5) of the amylase concentration in serum and drainage fluid while the drain was in place. Computed tomography was performed if the patient had any symptoms suggestive of abdominal collection (pain, fever, vomiting) or if major hyperleukocytosis was present. Oral feeding was allowed after the return of bowel function, usually before complete drain removal, except in cases of

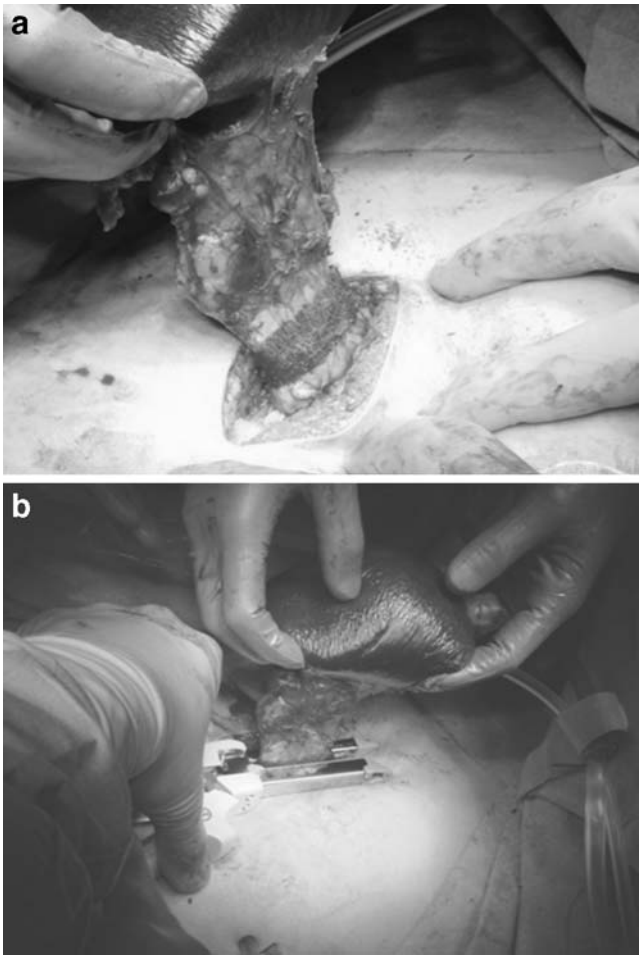

Figure 2 **a**, **b** Before stapling in DP, the PGA felt was wrapped around the predictive staple line to reduce compression tissue damage by a stapler device. The staple line was reinforced by laying a fibrinogen/thrombin-coated collagen patch onto the transected stump.

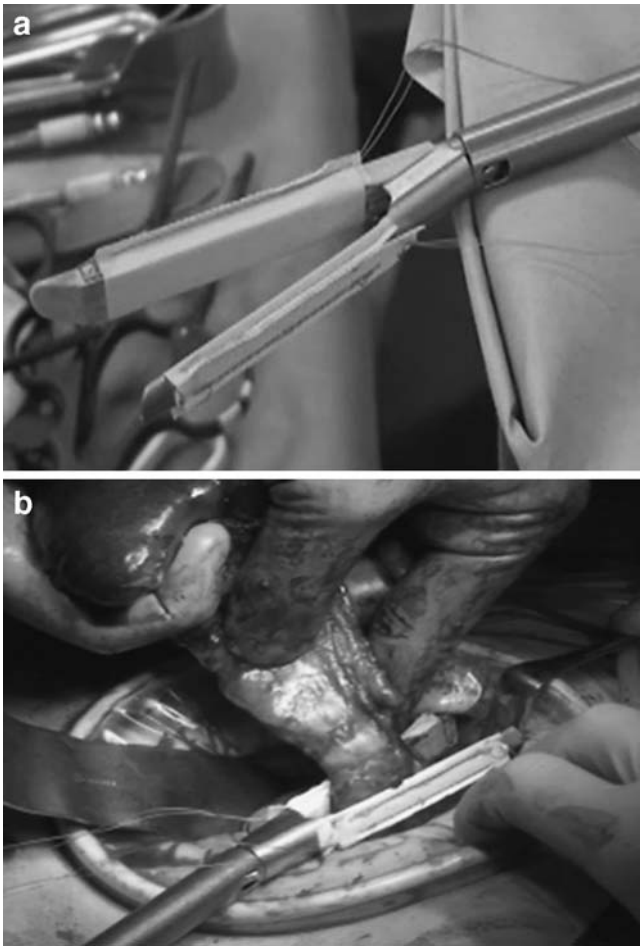

Figure 3 **a**, **b** In some cases, transection was performed using the Echelon 60 with PGA felt stocking type.

suspected or confirmed POPF. Conservative management of POPF was attempted whenever possible as initial treatment, and included total parenteral nutrition, percutaneous drainage of intra-abdominal fluid collection, antibiotics, and octreotide administration.

Statistical Methods

The perioperative morbidity rates were compared using the Mann–Whitney *U* test. Statistical significance was defined as $P<0.05$. All statistical analyses were performed using statistical software (StatView 5.0; SAS Institute, Cary, NC, USA).

Results

Tumor pathology and morbidity in all 117 cases are shown in Tables 1 and 2. The clinicopathologic features of the 36

Table 1 Indication for Pancreatectomy

	N=117
Pancreatic disease	
Ductal adenocarcinoma	51
Intraductal papillary mucinous neoplasm	23
Pseudocyst	8
Mucinous cystic neoplasm	5
Endocrine tumor	3
Solid papillary neoplasm	2
Serous cystadenoma	1
Islet cell tumor	1
Epidermoid cyst	1
Arteriovenous malformation	1
Nonpancreatic disease	
Gastric cancer	4
Gastrointestinal stromal tumor of the stomach	1
Bile duct cancer	15
Duodenal cancer	1

Table 2 Perioperative Morbidity Rates and Patterns

	PD N=54 No. of patients	DP N=63
Complications		
Absent	23 (42.6)	25 (39.7)
Present	31 (57.4)	38 (60.3)
Pancreatic fistula	31 (57.4)	32 (50.8)
Grade A	16 (29.6)	21 (33.3)
Grade B	11 (20.4)	9 (14.3)
Grade B	4 (7.4)	2 (3.2)
Intra-abdominal abscess		
SSI	6 (11.1)	3 (4.8)
Urinary infection	0	2 (3.2)
Cholecystitis	–	1 (1.6)
Chylous leakage	0	1 (1.6)
Bile leakage	1 (1.9)	0

SSI surgical site infection (excluding SSI associated with pancreatic fistula)

PD and 37 DP cases in the no-procedure group and of the 18 PD and 26 DP in the procedure group are shown in Tables 3 and 4. There were no significant differences in morbidity rates and patterns between cases in the two groups, except for grade B and C POPF.

There were four cases of postoperative mortality in the 36 no-procedure group PD cases (11.1%), but none in the 18 procedure group PD cases. Among all perioperative morbidities, POPF was the most frequent complication, occurring in 21 (58.3%) of the 36 no-procedure group PD cases and in ten (55.6%) of the 18 procedure group PD cases (Table 3). However, grade B and C POPF occurred in 14 (38.9%) of the 36 no-procedure group PD cases and in one (5.6%) of the 18 procedure group PD cases (Table 3). The occurrence rate of severe POPF in PD cases with PGA felt with fibrin sealant was significantly lower than in PD cases without PGA felt (P=0.016). Four patients with grade C in the no-procedure group PD cases also had sepsis with postoperative intra-abdominal abscess; one of those patients unsuccessfully treated by percutaneous drainage required an operative drainage.

Table 3 Clinicopathologic Factors in PD

Clinicopathologic factors in PD	Patients (N=54)	No PGA or fibrin sealant (N=36) former	With PGA and fibrin sealant (N=18) latter	P value
Patients-related factors				
Age				
≥60	43 (79.6)	28 (77.8)	15 (83.3)	0.63
<60	11 (20.4)	8 (22.2)	3 (16.7)	
Histology				
Benign	5 (9.3)	0	5 (27.8)	
Malignant	49 (90.7)	36 (100)	13 (72.2)	
Diameter of main pancreatic duct				
≥3 mm	36	23	13	0.54
<3 mm	18	13	5	
Pancreatic texture				
Soft	25 (46.3)	17 (47.2)	8 (44.4)	0.84
Firm	29 (53.7)	19 (52.8)	10 (55.6)	
Surgery-related factors				
Blood loss (g)				
≥1,000 g	33 (61.1)	22 (58.3)	11 (61.1)	0.90
<1,000 g	21 (38.9)	14 (41.7)	7 (38.9)	
Operation time				
≥420	41 (75.9)	27 (75.0)	14 (77.8)	0.82
<420	13 (24.1)	9 (25.0)	4 (22.2)	
POPF grade A, B, and C				
Present	31 (57.4)	21 (58.3)	10 (55.6)	0.85
Absent	23 (42.6)	15 (41.7)	8 (44.4)	
POPF grade B and C				
Present	15 (27.8)	14 (38.9)	1 (5.6)	0.016
Absent	39 (72.2)	22 (61.1)	17 (94.4)	

Table 4 Clinicopathologic Factors in DP

Clinicopathologic factors in PD	Patients (N=63)	No PGA or fibrin sealant (N=37) former	With PGA and fibrin sealant (N=26) latter	P value
Patients-related factors				
Age				
≥60	36 (57.1)	22 (59.5)	14 (53.8)	0.66
<60	27 (42.9)	15 (40.5)	12 (46.2)	
Histology				
Benign	30 (47.6)	15 (40.5)	15 (57.7)	0.18
Malignant	33 (52.4)	22 (59.5)	11 (42.3)	
Pancreatic texture				
Soft	35 (55.6)	19 (51.4)	16 (61.5)	0.42
Firm	28 (44.4)	18 (48.6)	10 (38.5)	
Surgery-related factors				
Blood loss (g)				
≥400 g	33 (52.4)	19 (51.4)	14 (53.8)	0.85
<400 g	30 (47.6)	18 (48.6)	12 (46.2)	
Operation time (min)				
≥210	36 (57.1)	23 (62.2)	13 (50.0)	0.34
<210	27 (42.9)	14 (37.8)	13 (50.0)	
Stump closure				
Staple	52 (82.5)	26 (70.3)	26 (100.0)	0.002
Suture	11 (17.5)	11 (29.7)	0 (0.0)	
POPF grade A, B, and C				
Present	32 (50.8)	21 (56.8)	11 (42.3)	0.26
Absent	31 (49.2)	16 (43.2)	15 (57.7)	
POPF grade B and C				
Present	11 (17.5)	10 (27.0)	1 (3.8)	0.017
Absent	52 (82.5)	27 (73.0)	25 (96.2)	

There was no postoperative mortality in DP cases. POPF occurred in 21 (56.8%) of the 37 no-procedure group DP cases and in 11 (42.3%) of the 26 procedure group DP cases (Table 4). However, grade B and C POPF occurred in ten (27.0%) of the no-procedure group DP cases and in only one (3.8%) of the procedure group DP cases. The occurrence rate of severe POPF in cases with PGA felt with fibrin sealant was significantly lower than in cases without (P=0.017). Severe POPF occurred in 11 of the 63 DP patients (Table 4); nine of the fistulas (14%) were classified as grade B. Both patients with grade C POPF also had sepsis with postoperative intra-abdominal abscess. No patients required operative drainage.

Discussion

Pancreatic fistula remains a problem after PD and DP, with several technical variations failing to reduce its incidence.[3] Most patients with this complication are treated conservatively or by interventional radiology, and if treated in a timely fashion, pancreatic fistula does not lead to mortality. Nevertheless, pancreatic fistula formation is a major source of subsequent morbidity and associated complications including abscess pseudo aneurysm, hemorrhage, and sepsis, with considerable health-care expenditure.[6,7]

We have previously examined the efficacy of various procedures to prevent severe POPF in both PD and DP patients. In pancreaticojejunostomy of PD, we first tried suturing between the seromuscular layer of the jejunum and the anterior–posterior faces of the remnant pancreas. We also started a modified Kakita's procedure[8] or duct-to-mucosa pancreaticojejunostomy. However, there were no significant differences in the occurrence rates of severe POPF using the different of anastomotic procedures. Reported risk factors of POPF in PD in patients older than 60 years of age include nondilated duct size, longer operative time, greater intraoperative red blood cell transfusions, lower surgical volume, and soft texture.[9–11] With regard to the anastomotic procedure, duct-to-mucosa

pancreaticojejunostomy and external drainage of the pancreatic duct with a stent have been recommended;[12] the efficacy of those procedures, however, remains controversial. In DP, we previously cut the stump of the remnant pancreas using a knife, then subsequently ligated the main pancreatic duct and sutured the tissue of the pancreas to close. A recently published systematic review appraised the available surgical alternatives for the management of the pancreatic stump after DP, which included duct ligation, ultrasonic dissection, the use of fibrin sealant, patches and meshes, pancreaticoenteric anastomosis, and hand-sewn and stapler closure,[4] reflecting the clinical heterogeneity in this field. The benefits of staple transection for the pancreas as a simple, quick, and secure method for closing the proximal pancreas have been well described.[13,14] However, only the randomized clinical trial of stapling vs. hand sewing showed no significant advantage of stapling (incidence of pancreatic fistula: 14% vs. 33%, respectively).[4,15] For POPF, an occurrence rate of 23% for stapled closure after DP was observed in a meta-analysis, which was slightly lower than for hand-sewn closure.[15] Furthermore, a significant reduction in the fistula rate after staple closure (using the Powered Multifire Endo GIA 60) compared with suture closure was reported (pancreatic fistula: stapler, 0% vs. suture, 35%),[14] although the opposite pattern was also demonstrated (pancreatic fistula: stapler, 25% vs. suture, 14%).[6]

Fibrin sealant is used clinically to prevent the leakage of gastrointestinal anastomoses and hemorrhages in parenchymal organs.[16–18] Suzuki et al.[19] reported that intraoperative fibrin sealant of the pancreatic stump prevented POPF in patients who underwent pancreatic surgery. A randomized clinical trial showed that POPF occurred in 15% of patients in the fibrin sealant group and in 40% of the control group.[19] Ohwada et al.[20] recommended a fibrin sealant sandwich technique for preventing POPF. This unique technique sandwiches fibrin sealant between the dorsal and ventral edges of the remnant pancreas. The incidence of POPF in that study was 9% in the sandwich technique group vs. 27% in the simple sealing group. Fibrin sealant is a biologic adhesive that can be used conveniently by spraying onto the cut surface of the pancreas.[19] However, fibrin sealant may not sufficiently block openings of small branches of the pancreatic duct that are not ligated. Therefore, in some cases, continuous exocrine pancreatic secretion from these small pancreatic ducts could lead to POPF after DP, despite the use of fibrin glue. On the other hand, Reuben et al.[21] recommended a PGA felt of a stapled pancreatic transaction line for preventing pancreatic fistulas (pancreatic fistula: PGA felt, 3.5% vs. no PGA felt, 27.5%).

We recently started applying PGA felt with fibrin sealant at the pancreaticojejunostomy and pancreatic stump for reinforcement. In PD or DP, the PGA felt worked as a cushion for a thread knot or a stapler to prevent tissue damage. If a pancreatic tissue tearing occurs, it is thought to be repaired by the fibrin sealant. The PGA felt can be easily hydrolyzed in wet conditions by fibrin glue, and the PGA felt is absorbed within 3 months.[22] In addition, because the rate of water absorption is high in the PGA felt, the fibrin glue is thought to attach firmly to the cut surface of the pancreas compared with the application of the fibrin sealant or PGA felt only. The PGA felt may focus the fibrin sealant to the cut surface of the pancreas to prevent early detachment of the fibrin sealant from the pancreas, enhancing the effects of the fibrin sealant. In the present study, the combination of the PGA felt and fibrin sealant was a significant independent factor for the prevention of severe POPF, despite the use of various procedures such as stapling or suturing with or without this combination (data not shown). The combined use of fibrin sealant and a polyethylene glycolic acid mesh patch is common for the prevention of air leakage from the lung during thoracic surgery,[23] while a PGA felt with fibrin sealant was used for hepatectomy to prevent bile leakage, although there are no reports for pancreatectomy. This is the first report of combined use of fibrin sealant and a PGA mesh patch in pancreatic surgery. In future, a prospective randomized control study is necessary to confirm the efficacy of this procedure.

In conclusion, the application of this procedure using fibrin sealant and a PGA mesh patch to the pancreaticojejunostomy and pancreatic stump could reduce severe POPF after pancreatic surgery.

References

1. Bilimoria MM, Cormier JN, Mun Y, Lee JE, Evans DB, Pisters PW. Pancreatic leak after pancreatectomy is reduced following main pancreatic duct ligation. Br J Surg 2003;90:190–196.
2. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M. International Study Group on Pancreatic Fistula Definition: postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8–13
3. Balzano G, Zerbi A, Cristallo M, Di Carlo V. The unsolved problem of fistula after left pancreatectomy: the benefit of cautious drain management. J Gastrointest Surg 2005;9:837–842.
4. Knaebel HP, Diener MK, Wente MN, Büchler MW, Seiler CM. Systematic review and meta-analysis of technique for closure of the pancreatic remnant after distal pancreatectomy. Br J Surg 2005;92:539–546.
5. Kuroki T, Tajima Y, Kanematsu T. Surgical management for the prevention of pancreatic fistula following distal pancreatectomy. J Hepatobiliary Pancreat Surg 2005;12:283–285.
6. Sheehan MK, Beck K, Creech S, Pickleman J, Aranha GV. Distal pancreatectomy: does the method of closure influence fistula formation? Am Surg 2002;68:264–268.
7. Rodriguez JR, Germes SS, Pandharipande PV, Gazelle GS, Thayer SP, Warshaw AL, Fernández-del Castillo C. Implications

and cost of pancreatic leak following distal pancreatic resection. Arch Surg 2006;141:361–366.
8. Kakita A, Yoshida M, Takahashi T. History of pancreaticojejunostomy in pancreaticoduodenectomy: development of a more reliable anastomosis technique. J Hepatobiliary Pancreat Surg 2001;8:230–237.
9. Choe YM, Lee KY, Oh CA, Lee JB, Choi SK, Hur YS, Kim SJ, Cho YU, Ahn SI, Hong KC, Shin SH, Kim KR. Risk factors affecting pancreatic fistula after pancreaticoduodenectomy. World J Gastroenterol 2008;14:6970–6974.
10. Yeo CJ, Cameron JL, Maher MM, Sauter PK, Zahurak ML, Talamini MA, Lillemoe KD, Pitt HA. A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. Ann Surg 1995;222:580–592.
11. Yang YM, Tian XD, Zhuang Y, Wang WM, Wan YL, Huang YT. Risk factors of pancreatic leakage after pancreaticoduodenectomy. World J Gastroenterol 2005;11:2456–2461.
12. Poon RT, Fan ST, Lo CM, Ng KK, Yuen WK, Yeung C, Wong J. External drainage of pancreatic duct with a stent to reduce leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy. Ann Surg 2007;246:425–435.
13. Kajiyama Y, Tsurumaru M, Udagawa H, Tsutsumi K, Kinoshita Y, Akiyama H. Quick and simple distal pancreatectomy using the GIA stapler: report of 35 cases. Br J Surg 1996;83:1711.
14. Takeuchi K, Tsuzuki Y, Ando T, Sekihara M, Hara T, Kori T, Nakajima H, Kuwano H. Distal pancreatectomy: is staple closure beneficial? ANZ J Surg 2003;73:922–925.
15. Bassi C, Butturini G, Molinari E, Mascetta G, Salvia R, Falconi M, Gumbs A, Pederzoli P. Pancreatic fistula rate after pancreatic resection: the importance of definitions. Dig Surg 2004;21:54–59.
16. Kram HB, Garces MA, Klein SR, Shoemaker WC. Common bile duct anastomosis using fibrin glue. Arch Surg 1985;120:1250–1256.
17. Kram HB, Clark SR, Ocampo HP, Yamaguchi MA, Shoemaker WC. Fibrin glue sealing of pancreatic injuries, resections and anastomoses. Am J Surg 1991;161:479–482.
18. Noun R, Elias D, Balladur P, Bismuth H, Parc R, Lasser P, Belghiti J. Fibrin glue effectiveness and tolerance after elective liver resection: a randomized trial. Hepatogastroenterology 1996;43:221–224.
19. Suzuki Y, Kuroda Y, Morita A, Fujino Y, Tanioka Y, Kawamura T, Saitoh Y. Fibrin glue sealing for the prevention of pancreatic fistulas following distal pancreatectomy. Arch Surg 1995;130:952–955.
20. Ohwada S, Ogawa T, Tanahashi Y, Nakamura S, Takeyoshi I, Ohya T, Ikeya T, Kawashima K, Kawashima Y, Morishita Y. Fibrin glue sandwich prevents pancreatic fistula following distal pancreatectomy. World J Surg 1998;22:494–498.
21. Thaker RI, Matthews BD, Linehan DC, Strasberg SM, Eagon JC, Hawkins WG. Absorbable mesh reinforcement of a stapled pancreatic transection line reduces the leak rate with distal pancreatectomy. J Gastrointest Surg 2007;11:59–65.
22. Nakamura T, Shimizu Y, Watanabe S, Hitomi S, Kitano M, Tamada J, Matsunobe S. New bioabsorbable pledgets and non-woven fabrics made from polyglycolide (PGA) for pulmonary surgery: clinical experience. Thorac Cardiovasc Surg 1990;38:81–85.
23. Kaseda S, Aoki T, Hangai N, Omoto T, Yamamoto S, Sugiura H. Treating bullous lung disease with Holmium YAG laser in conjunction with fibrin glue and DEXON mesh. Lasers Surg Med 1998;22:219–222.

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ORIGINAL ARTICLE

Surgery and Staging of Pancreatic Neuroendocrine Tumors: A 14-Year Experience

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Abstract
Background The aims of this study were to evaluate contemporary outcomes associated with the surgical management of pancreatic neuroendocrine tumors (PNETs) and to assess the prognostic value of the World Health Organization (WHO) classification and TNM staging for PNETs.
Methods The medical records of 73 consecutive patients with PNETs treated at a single institution from January 1992 through September 2006 were reviewed. Survival was analyzed with the Kaplan-Meier method (median follow-up: 43 months).
Results Median patient age was 52 years (range, 19-83 years), and 36 (49%) patients were male. Thirty-three patients had a well-differentiated neuroendocrine tumor (WDT), 26 had a well-differentiated neuroendocrine carcinoma (WDCa), and 14 had a poorly differentiated neuroendocrine carcinoma (PDCa). Fifty (68%) patients underwent potentially curative resection, and the 5-year disease-specific survival (DSS) rate for the entire cohort was 62%. WHO classification and TNM staging system provided good prognostic stratification of patients; 5-year DSS rates were 100% for WDT, 57% for WDCa, 8% for PDCa, respectively, by WHO classification ($p<0.001$), and 100% for stage 1, 90% for stage 2, 57% for stage 3, and 8% for stage 4, respectively, by TNM stage ($p<0.001$). Among the patients who underwent potentially curative resection, nodal status, distant metastasis, and tumor grade were significant prognostic factors.
Conclusion WHO classification and TNM staging are useful for prognostic stratification among patients with PNETs.

Keywords Pancreatic neuroendocrine tumor · Surgery · Staging

Introduction

Pancreatic neuroendocrine tumors (PNETs) are rare, with an estimated incidence of four to five cases per million individuals annually in the USA. These tumors account for less than 3% of all pancreatic neoplasms, although the diagnosis is increasing in frequency.[1–3] In addition, PNETs are heterogeneous collection of tumors encompassing a wide biological spectrum. As a result, reported outcomes associated with surgical therapy for PNETs are varied, and it has been challenging to identify factors affecting the long-term survival of patients with PNETs.[4] Furthermore, a widely accepted staging system to stratify patients with PNET is not yet established.

The World Health Organization (WHO) introduced a system to classify PNETs in 2000.[5] This classification defines three types of PNETs according to their clinical and histopathological features: "well-differentiated endocrine tumor (WDT)", "well-differentiated endocrine carcinoma (WDCa)", and "poorly differentiated endocrine carcinoma (PDCa)". In 2006, a new TNM staging system for PNETs was proposed by the European Neuroendocrine Tumor Society (ENETS).[6] This system is analogous to the TNM classification systems used for other solid tumors,

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enabling patient stratification using basic clinicopathological information.

The purpose of this study was to document our institutional surgical experience with PNETs. Our goals were to identify clinical factors associated with prolonged survival of patients with PNETs following surgical treatment and to assess the prognostic utility of the WHO classification and TNM staging systems.

Material and Methods

The medical records of all patients with PNETs admitted to the inpatient unit of Brigham and Women's Hospital during the period spanning January 1992 through August 2006 were analyzed. Patients were identified using the International Classification of Disease-9 codes for malignant and benign pancreatic neoplasms (codes 157.× and 211.6) and the computer-assisted hospitalization analysis for the study of efficacy management system. All patients with histologically confirmed PNETs were included in this study. This study protocol was approved by our Institutional Review Board.

Parameters obtained from the medical records included demographic data (patient age and gender), signs and symptoms present at the time of diagnosis, the operation performed and whether it was curative (complete resection with no gross residual cancer present at the completion of surgery) or palliative (gross residual cancer present at the completion of surgery), and pathological findings. Pathological parameters analyzed were tumor diameter, regional lymph node status (N), margin status, tumor grade, and presence of lymphovascular invasion (LVI).

Patients with appropriate signs, symptoms, and biochemical evidence of hormonal excess were classified as having a functional tumor. Patients without a recognizable clinical syndrome or with normal serum hormone levels were classified as having a nonfunctional tumor, regardless of results on specimen immunohistochemistry. The criterion for malignancy was the identification of nodal or distant metastasis at the time of surgery or during follow-up.

WHO classification and TNM staging systems are summarized in Tables 1 and 2.[5,6] The criteria for WHO classification includes tumor size, tumor grade (mitotic index), vascular invasion on histology, and Ki-67 index. As Ki-67 staining was not routinely performed for PNETs at our institution during the study period, we omitted Ki-67 index from our analysis. Ki-67 usually correlates with mitotic rate. It is unusual to have a high number of Ki-67-positive cells in the setting of a low mitotic rate.[7]

Disease-specific survival (DSS) was calculated from time of operation (or time of diagnosis for patients who did not undergo any surgery) through last follow-up. Recurrence-free survival (RFS) was calculated from time of pancreatic resection to time when first recurrence was detected. The survival curves for selected patient groups were derived using the method of Kaplan-Meier.[8] Survival durations for these groups were determined from the corresponding Kaplan-Meier curves and compared using the log-rank test.

Comparison of categorical variables was performed using Fisher's exact test and Pearson chi-square test as appropriate. Continuous variables are presented as mean values ± standard error unless otherwise indicated, and were compared using t tests. A p value <0.05 was considered significant.

Results

Patients

During the study period, 73 patients with PNETs were identified. The median age for this patient cohort was 52 years (range, 19-82 years). Thirty-six (49%) patients were male.

Presenting Symptoms and Signs

The frequencies with which symptoms and signs were present at the time of diagnosis are summarized in Table 3. Twenty-six (36%) patients had clinical manifes-

Table 1 WHO Classification and TNM Staging

WHO classification					
Tumor type	Size	Mitotic index (/10HPF)	LVI	Metastasis (N1 or M1)	Ki-67 index
Well differentiated endocrine tumor (WDT)					
Benign	<2 cm	<2	−	−	<2%
Uncertain	≥2 cm	2-10	+	−	>2%
Well-differentiated endocrine carcinoma (WDCa)		<10	+	+	>2%
Poorly differentiated endocrine carcinoma (PDCa)		>10	+	+	>30%

Table 2 TNM Staging

T-primary tumor	
T1	Tumor contained to the pancreas and size <2 cm
T2	Tumor contained to the pancreas and size 2-4 cm
T3	Tumor contained to the pancreas and size >4 cm or invading to duodenum/bile duct
T4	Tumor invading adjacent organs, or large vessels
N-regional lymph nodes	
N0	Metastasis absent
N1	Metastasis present
M-distant metastasis	
M0	Metastasis absent
M1	Metastasis present
Overall stage[a]	
Stage 1	T1N0M0
Stage 2	T2/3N0M0
Stage 3	T4N0M0 or T*any*N1M0
Stage 4	T*any*N*any*M1

[a] Patients with pNx were designated as N0 for overall staging

tations of hormonal excess: neuroglycopenia (n=15) for insulinoma, diarrhea (n=6) for gastrinoma and PPoma, peptic ulcer (n=5) for gastrinoma, dermatitis (n=3) for glucagonoma, palpitations (n=2) for insulinoma, and Cushing's syndrome (n=1) for ACTHoma. The distribution of tumor types according to their hormonal function is shown in Table 4. Among the 47 (64%) patients with nonfunctional tumors, more than half (64%) had abdominal pain; other symptoms and signs included weight loss (9%), jaundice (8%), nausea and vomiting (6%), and palpable abdominal mass (6%). Eight (17%) patients were found to have PNETs incidentally, during workup for unrelated conditions.

Surgical Procedures

Eighteen (23%) patients were found to have extensive liver metastasis (n=15) and/or locally advanced disease (n=3) at the time of presentation and were deemed unresectable. Sixteen of these patients underwent biopsy only, and two underwent biliary and gastric bypass procedures.

Fifty-five patients underwent primary pancreatic tumor resection: 32 (58%) patients underwent distal pancreatectomy, 12 (22%) patients underwent pancreaticoduodenectomy, 10 (18%) patients underwent enucleation, and one (2%) patient underwent central pancreatectomy. Three patients with liver metastasis underwent liver resection or radio frequency ablation (RFA) along with their pancreatic resection. One patient with adrenal metastasis underwent adrenalectomy and colectomy en-bloc in addition to pancreatic resection. There were no perioperative deaths.

Tumor Characteristics

Clinicopathological characteristics of tumors are summarized in Table 5. Thirty-one (42%) tumors were located in the head of the pancreas and 42 (58%) tumors were located in the body or tail. Forty-one (56%) tumors were classified as malignant because of the presence either of regional lymph node metastasis or distant metastasis (n=35) at time of diagnosis or exploration or detection of metastasis during follow-up (n=6). Mean tumor diameter was greater for malignant than for benign tumors (5.1±0.47 vs. 2.8± 0.58 cm, p=0.002). The median tumor diameter for our entire cohort was 3.0 cm (range 0.4-15 cm) and 22 patients (30%) had a tumor less than 2 cm in maximal diameter. Histological lymph node status was assessed in 38 patients; 11 patients (31%) had metastasis to regional lymph nodes (N1). There was no significant correlation between size of the primary tumor and N stage (mean diameter of primary tumor: 4.2±0.80 cm for N0 vs. 5.2±0.63 cm for N1, p= 0.38). Fourteen (19%) patients had tumor classified as high grade and 22 (30%) patients had tumors with documented LVI. In terms of WHO classification, 33 (45%) patients had tumors classified as WDT, and 40 (55%) patients had endocrine carcinoma (26 WECa and 14 PECa). WDT were further sub-classified into benign tumor (ten) and uncertain tumor (16). It was not possible to subclassify seven patients

Table 3 Symptoms and Signs at Presentation

Symptoms and sign	Functioning, n=26	Nonfunctioning, n=47
Abdominal or back pain	4 (16)	30 (64)
Weight loss	3 (10)	4 (9)
Jaundice	0 (0)	3 (6)
Nausea/vomit	0 (0)	3 (6)
Palpable mass	0 (0)	3 (6)
Fatigue/weakness	6 (20)	2 (4)
Ascites	0 (0)	1 (2)
Asymptomatic	0 (0)	8 (17)
Other	1 (3)	5 (11)
Hormone-related		
Neuroglycopenia	15 (50)	
Diarrhea	6 (20)	
Peptic ulcer	5 (19)	
Dermatitis	3 (10)	
Palpitations	2 (7)	
Cushing syndrome	1 (3)	

Some patients presented with more than one symptom.

Table 4 Distribution of Tumor Types

Type of tumor	Patients (%)
Functional	26 (36)
Insulinoma	16
Gastrinoma	6
Glucagonoma	3
ACTHoma	1
Nonfunctional	47 (64)

with WDT due to lack of complete histological information. In terms of TNM stage, 39 (53%) patients were assigned to stages 1 or 2 and 34 (47%) patients were assigned to stages 3 or 4 (metastatic to regional lymph nodes or distant organ).

Complete resection (R0) was achieved in 48 (86%) of 55 patients who underwent primary tumor resection; a microscopic positive margin was present in two (4%) patients. Five patients (9%) underwent primary tumor resection with distant metastatic disease left alone.

The relationship between WHO classification and TNM stage is shown on Table 6. Most patients with PDCa were stage 4 at presentation, with few of these patients undergoing complete resection, while patients with WDT were either stage 1 or 2, with all of them achieving complete resection.

Survival and Prognostic Factors

The median follow-up period was 43 months (range, 1-216 months). The 5-year DSS rate for our entire cohort was 62%. The 5-year DSS rates for patients with WDT, WDCa, and PDCa by WHO classification were 100%, 57%, and 8%, respectively ($p<0.001$, Fig. 1a). The 5-year DSS rates for patients stratified by TNM stage 1, 2, 3, and 4 were 100%, 90%, 75%, and 21%, respectively, ($p<0.001$, Fig. 1b). The 5-year DSS rates among patients who underwent R0/1 resection, those who underwent R2 resection and those who did not undergo resection were 87%, 30%, and 16%, respectively ($p<0.001$, Fig. 1c).

During follow-up, ten patients among the 48 patients who underwent R0/1 resection developed recurrence; two in the remnant pancreas, six in the liver, one in both pancreas and liver, and one in the retroperitoneal lymph nodes. Repeat resection was performed for four patients (distal pancreatectomy (two), completion pancreatectomy (one), and liver segmentectomy (one)). One patient with recurrence in the liver underwent RFA, and the remainder received chemotherapy only. The 5-year RFS rate for patients following R0/1 resection was 74%. Among patients with WDT, 5-year RFS for patients with benign tumor and those with tumor of uncertain behavior were 100% and 68%, respectively ($p=0.04$, Fig. 2).

We analyzed potential clinical prognostic factors for impact on survival following pancreatic resection. As shown in Table 7, nodal metastasis, distant metastasis, and tumor grade had significant impact on survival on univariate analysis. Tumor functional status, tumor size, and extent of resection (enucleation or formal resection) were not found to be significant prognostic predictors.

Discussion

Although the reported incidence of PNETs has increased over two- to threefold in the last 16 years,[9] PNETs are still

Table 5 Clinicopathological Features of Tumors

		N (%)
Location	Head	31 (42)
	Body/tail	42 (58)
Malignancy	Benign	32 (44)
	Malignant	41 (56)
Hormonal function	Functional	26 (36)
	Nonfunctional	47 (64)
Size (cm)	<2 cm	22 (30)
	2-4 cm	26 (36)
	>4 cm	25 (34)
Regional node	N0	26 (36)
	N1	12 (16)
	NX	35 (48)
Distant metastasis	M0	47 (64)
	M1	26 (36)
Tumor grade	Low	22 (30)
	Intermediate	13 (18)
	High	14 (19)
	Unknown	24 (33)
LVI	Yes	22 (30)
	No	19 (26)
	Unknown	32 (44)
Completeness of Resection	R0/1	50 (69)
	R2 or No resection	23 (31)
WHO classification	WDT[a]	33 (45)
	Benign	10
	Uncertain	16
	WDCa	26 (36)
	PDCa	14 (19)
TNM stage	1	21 (29)
	2	18 (25)
	3	8 (11)
	4	26 (36)

[a] Some patients had missing data to be distinguish between benign or uncertain category

Table 6 TNM Stage and Type of Surgery According to WHO Classification

	WDT (n=33)	WDCa (n=26)	PDCa (n=14)
TNM stage			
1	19 (58%)	2 (8%)	0
2	14 (42%)	4 (15%)	0
3	0	7 (27%)	1 (7%)
4	0	13 (50%)	13 (93%)
Surgery			
R0/1 resection	33 (100%)	14 (54%)	3 (21%)
R2 resection	0	3 (12%)	2 (14%)
No resection	0	9 (35%)	9 (64%)

rare and encompasses a wide spectrum of biological behavior from benign to frankly malignant. Given the lack of a widely accepted staging or classification system, compilation and comparison of surgical outcomes from individual institutions have been difficult (Table 8). In this study, we evaluated our experience of patients with PNETs using WHO classification and the new TNM staging system and demonstrated the utility of these schemes to risk-stratify patients with PNETs according to long-term prognosis.

Traditionally, the term "malignant" neuroendocrine tumor has been defined as neuroendocrine tumors with evidence of metastasis to regional lymph nodes or distant organs at presentation or during follow-up.[10–12] In our series, 56% of patients fell into this category (48% of them had metastasis either to lymph nodes or distant organs at presentation, and 8% developed metastasis during follow-up (median 28 months, range 9-56 months)) and, as expected, these patients had poorer prognosis than patients with a "benign" tumor (5-year DSS: 44% vs. 100%, $p<$ 0.001). However, this traditional classification has limited utility in predicting prognosis among individual patients undergoing surgical resection for PNET. Because some PNETs without evidence of metastasis at presentation may recur years after surgery, the term "benign" at the time of initial operation may not reflect their inherent malignant potential.

In contrast, the WHO classification incorporates histopathological criteria and provides a distinction between benign and malignant tumors that can be applied shortly after surgical resection. In our study, patients with "benign" WDT (defined by size <2 cm, low mitotic index and absence of LVI) developed no recurrences following surgical resection, while five of 14 patients with "uncertain" WDT (defined by presence of LVI or intermediate mitotic index) developed recurrence during follow-up. Similar observations were reported in a series from Memorial Sloan-Kettering.[7] Long-term follow-up to detect recurrences is therefore warranted for patients having undergone resection of "uncertain" WDTs, as it is for patients with PDCa or WDCa.

The TNM staging system for PNETs, proposed by the ENETS,[6] provides good patient stratification, is widely applicable, and may be more objective than systems that depend on subjective interpretation of immunohistochemical data. Our cohort included patients with advanced disease that precluded surgical resection or patients with

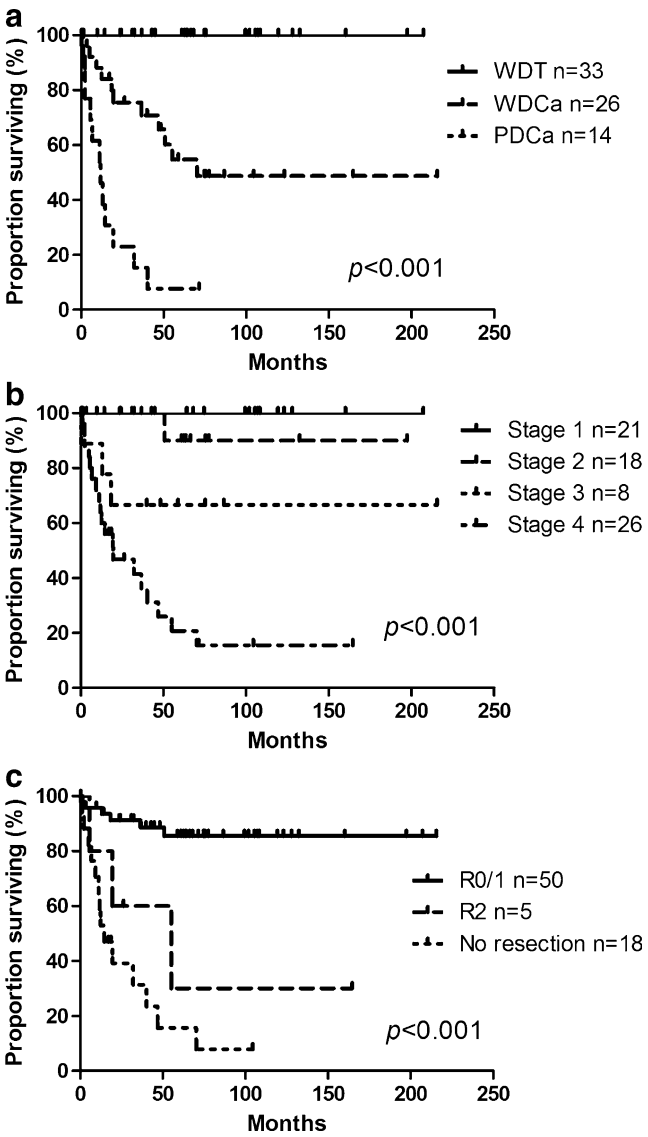

Figure 1 **a** Kaplan-Meier estimates of DSS for patients stratified by WHO classification. Five-year survival rates among patients with WDT, WDCa, and PDCa, were 100%, 57%, and 8%, respectively ($p<$ 0.001). **b** Kaplan-Meier estimates of DSS for patients stratified by TNM stage. Five-year survival rates among patients with each stage (1-4), were 100%, 90%, 88%, and 21%, respectively ($p<0.001$). **c** Kaplan-Meier estimates of DSS for patients stratified by completeness of resection (R0/1 resection, R2 resection and no resection). Five-year survival rates for these patient groups were 87%, 30%, and 16%, respectively ($p<0.001$ by log-rank test).

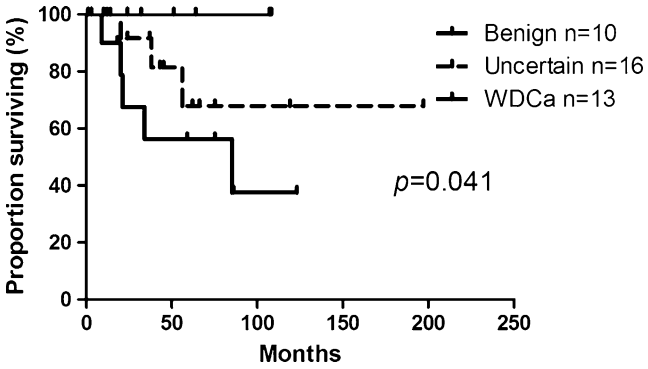

Figure 2 Kaplan-Meier estimates of RFS for patients with WDT and WDCa following surgical resection. Five-year RSS rates among patients with WDT (benign), WDT (uncertain), and WDCa were 100%, 68%, and 60%, respectively (p=0.041 by log-rank test).

small tumors that were locally excised without regional lymph node sampling. As a result, approximately half of the patients had missing information required for other classification. Nonetheless, cTNM staging was possible in all patients. This issue is particularly useful for multi-institutional trials in which accurate staging across multiple institutions is needed or evaluation of a national database including patient outcomes over multiple institutions.

Billimoria et al. tested the applicability of the TNM staging system designed for pancreatic adenocarcinoma by American Joint Committee for Cancer (AJCC) to PNETs.[13] Although AJCC TNM staging provided stage-dependent survival discrimination, nearly all of this discrimination was provided by the absence or the presence of distant metastasis. We favor the ENETS TNM staging system as it takes into consideration the more indolent course of PNETs (relative to pancreatic adenocarcinomas) and stratifies potentially respectable disease into three stages (stages 1, 2, and 3). However, we realize that our data does not allow us to determine which staging system provides most robust prognostic stratification.

We found that tumor grade, M and N stages significant as significant prognostic factors among patients having undergone resection of their PNET. Although tumor grade and distant metastasis are uniformly accepted as prognostic factors (Table 8), the prognostic significance of regional lymph node metastasis is controversial. There is conflicting evidence in the literature; Tomassetti et al. reported significantly worse outcomes for patients with regional lymph node metastasis than without such metastasis,[14] while Kazanijan et al. reported no difference in survival among these groups of patients.[10] In the study by Bilimoria et al., in which more than 3,500 patients with PNET in a national cancer database were analyzed, lymph node metastasis was a significant prognostic factor on univariate analysis, but not on multivariate analysis.[4] These disparate results can be explained at least partially by sample size considerations and the wide spectrum of biological aggressiveness of PNETs. For example, patients with small insulinomas or gastrinomas have an excellent prognosis and metastasis limited to regional lymph nodes may have minimal, if any, impact on long-term outcome.[15,16]

An important limitation of our study is incompleteness in data recorded by our pathologists for several variables (missing in 30-40% of patients for tumor grage or LVI). To detect possible bias in study findings due these missing data, we compared TNM stage distribution among patients with or without complete tumor grade and LVI data. For tumor grade, the stage distribution for patients with complete data was not different from that of patients without complete data (26% for stage 1, 28% for stage 2, 8% for stage 3, and 38% for stage 4, respectively, for patients with complete data, and 35% for stage 1, 17% for stage 2, 17% for stage 3, and 31% for stage 4, respectively, for those without complete data, p=0.45 by chi-square test).

Table 7 Univariate Analysis of Potential Prognostic Factors Predicting Survival of the Patients with PNET who Underwent R0/1 Resection (N=50)

Clinical prognostic factors	*n*	5-year DSS rate (%)	*P*
Age			
≥50 years	23	96	0.10
<50 years	27	77	
Gender			
Male	25	90	0.48
Female	25	84	
Functional tumor			
Yes	23	89	0.78
No	27	85	
Tumor size			
≥2 cm	28	82	0.26
<2 cm	22	93	
Nodal metastasis			
Positive	11	60	0.011
Negative	23	93	
Distant metastasis			
Positive	3	33	<0.001
Negative	47	92	
Grade			
Low	20	93	0.002
Intermediate	10	86	
High	3	33	
LVI			
Yes	19	79	0.103
No	19	100	
Procedure			
Formal resection	40	84	0.27
Enucleation	10	100	

Data were not available for all patients.

Table 8 Recently Reported Series of PNET Predictive Indicators Documented

Authors	Year	*N*	Nonfunctional tumor (%)	Malignancy (%)	R0/1 resection (%)	5-year OS rate (%)	Identified prognostic factors[a]
Lo et al.[19]	1996	64	53	100[b]	26	49	M status
Phan et al.[12]	1997	125	48	52	N/D	65	"Malignant" tumor, Resection margin
Solorzano et al.[20]	2001	163	100	N/D	25	43	Liver metastasis
Chu et al.[21]	2002	50	58	>78[c]	N/D	36	Liver metastasis
Hochwald et al.[22]	2002	136	64	N/D	64	N/D	Mitotic index
Kazanjian et al.[10]	2006	70	71	53	N/D	89	LVI
Bloomston et al.[23]	2006	120	46	76	77	62[d]	Tumor differentiation
Schurr et al.[18]	2007	62	74	63	73	49	WHO classification
Teh et al.[24]	2007	33	55	39	N/D	N/D	
Nguyen et al.[11]	2007	73	70	100[a]	35[e]	44	
Vagefi et al.[25]	2007	168	58	23	85	77	"Malignant" tumor
Ferrone et al.[7]	2007	183	71	N/D	100	87	T stage based on size/metastasis, tumor grade
Bilimoria et al.[4]	2008	3851[f]	N/D	84	96	59	Age, tumor grade, metastasis, hormonal function
Fischer et al.[26]	2008	118	N/D	65	87	N/D	
Current study	2009	73	64	56	68	66	Lymph node metastasis, distant metastasis, tumor grade

N/D not documented

[a] Among the patients who underwent curative resection

[b] Benign tumor was excluded

[c] Based on% of liver metastasis

[d] Outcomes following R0/1 resection

[e] R0 resection only

[f] National cancer data base

For LVI, 64% of patients with missing data were stage 4, while only 23% of those with complete data were stage 4 ($p<0.001$). When we eliminated patients with unresectable tumors from analysis, the distributions of TNM stage were similar among these two groups ($p=0.821$). (Note: patients with unresectable tumors had their diagnosis confirmed on biopsy alone; these biopsy specimens were not examined for presence or absence of LVI by our pathologists.) Based on the similar distributions of TNM stage among patients with or without complete data, missing data-related bias is unlikely to have had significant impact on the findings of our analysis of prognostic factors (which included only patients who underwent primary tumor resection).

For patients with small PNETs, the extent of surgical resection is somewhat controversial. In this study, ten patients underwent simple enucleation and achieved excellent long-term outcomes. Pitt et al. recently analyzed the series of 122 patients with neuroendocrine tumors <3 cm and showed comparable long-term outcomes with less perioperative morbidity rate in patients who underwent enucleation compared to outcomes in those who underwent formal resection.[17] Despite several reports with excellent outcomes for enucleation, the oncologic efficacy of enucleation for all patients with small PNETs remains unclear. First, the reported outcomes were of highly selected patients: for example, in this study, enucleation was only selected for insulinomas or gastrinomas <2.5 cm. Second, regional lymph node metastasis has been reported in the range from 30% to 40% of patients with PNETs[4,7,18] and the size criteria cannot exclude the chance of metastasis as Ferrone showed a 25% chance of nodal metastasis for PNET <2 cm.[7] Lastly, whether lymphadenectomy makes a difference in long-term survival is uncertain. This may depend on the biological aggressiveness of the tumor and no preoperative clinical markers capable of predicting malignant behavior are currently available. Although more data is necessary to make definitive recommendations for the surgical extent for small PNETs, our practice is to limit enucleation or limited segmental resection to small insulinomas or gastrinomas without macroscopic features of malignancy.

In summary, we report our institutional experience of PNETs based on WHO classification and TNM staging system. Both staging schemes are useful for the prognostically significant risk stratification for patients with PNETs. Standardized categorization is essential to compare one individual institutional experience to others and to develop evidence-based therapeutic strategies for this rare disease with a wide spectrum of biological behavior.

References

1. Fesinmeyer MD, Austin MA, Li CI, et al. Differences in survival by histologic type of pancreatic cancer. Cancer Epidemiol Biomarkers Prev 2005;14(7):1766–1773.
2. Gumbs AA, Moore PS, Falconi M, et al. Review of the clinical, histological, and molecular aspects of pancreatic endocrine neoplasms. J Surg Oncol 2002;81(1):45–53; discussion 54
3. House MG, Schulick RD. Endocrine tumors of the pancreas. Curr Opin Oncol 2006;18(1):23–29.
4. Bilimoria KY, Talamonti MS, Tomlinson JS, et al. Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: analysis of 3851 patients. Ann Surg 2008;247 (3):490–500.
5. Kloppel G, Perren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. Ann N Y Acad Sci 2004;1014:13–27.
6. Rindi G, Kloppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2006;449(4):395–401.
7. Ferrone CR, Tang LH, Tomlinson J, et al. Determining prognosis in patients with pancreatic endocrine neoplasms: can the WHO classification system be simplified? J Clin Oncol 2007;25 (35):5609–5615.
8. Kaplan F, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;63:475–481.
9. Fitzgerald TL, Hickner ZJ, Schmitz M, Kort EJ. Changing incidence of pancreatic neoplasms: a 16-year review of statewide tumor registry. Pancreas 2008;37(2):134–138.
10. Kazanjian KK, Reber HA, Hines OJ. Resection of pancreatic neuroendocrine tumors: results of 70 cases. Arch Surg 2006;141 (8):765–769; discussion 769–770
11. Nguyen SQ, Angel LP, Divino CM, et al. Surgery in malignant pancreatic neuroendocrine tumors. J Surg Oncol 2007;96(5):397–403.
12. Phan GQ, Yeo CJ, Cameron JL, et al. Pancreaticoduodenectomy for selected periampullary neuroendocrine tumors: fifty patients. Surgery 1997;122(6):989–996; discussion, 996–997
13. Bilimoria KY, Bentrem DJ, Merkow RP, et al. Application of the pancreatic adenocarcinoma staging system to pancreatic neuroendocrine tumors. J Am Coll Surg 2007;205(4):558–563.
14. Tomassetti P, Campana D, Piscitelli L, et al. Endocrine pancreatic tumors: factors correlated with survival. Ann Oncol 2005;16 (11):1806–1810.
15. Norton JA, Fraker DL, Alexander HR, et al. Surgery to cure the Zollinger-Ellison syndrome. N Engl J Med 1999;341(9):635–644.
16. Nikfarjam M, Warshaw AL, Axelrod L, et al. Improved contemporary surgical management of insulinomas: a 25-year experience at the Massachusetts General Hospital. Ann Surg 2008;247(1):165–172.
17. Pitt SC, Pitt HA, Baker MS, et al. Small pancreatic and periampullary neuroendocrine tumors: resect or enucleate? J Gastrointest Surg 2009;13(9):1692–1698.
18. Schurr PG, Strate T, Rese K, et al. Aggressive surgery improves long-term survival in neuroendocrine pancreatic tumors: an institutional experience. Ann Surg 2007;245(2):273–281.
19. Lo CY, van Heerden JA, Thompson GB, et al. Islet cell carcinoma of the pancreas. World J Surg 1996;20(7):878–883; discussion 884
20. Solorzano CC, Lee JE, Pisters PW, et al. Nonfunctioning islet cell carcinoma of the pancreas: survival results in a contemporary series of 163 patients. Surgery 2001;130(6):1078–1085.
21. Chu QD, Hill HC, Douglass HO, Jr., et al. Predictive factors associated with long-term survival in patients with neuroendocrine tumors of the pancreas. Ann Surg Oncol 2002;9(9):855–862.
22. Hochwald SN, Zee S, Conlon KC, et al. Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. J Clin Oncol 2002;20(11):2633–2642.
23. Bloomston M, Muscarella P, Shah MH, et al. Cytoreduction results in high perioperative mortality and decreased survival in patients undergoing pancreatectomy for neuroendocrine tumors of the pancreas. J Gastrointest Surg 2006;10(10):1361–1370.
24. Teh SH, Deveney C, Sheppard BC. Aggressive pancreatic resection for primary pancreatic neuroendocrine tumor: is it justifiable? Am J Surg 2007;193(5):610–613; discussion 613
25. Vagefi PA, Razo O, Deshpande V, et al. Evolving patterns in the detection and outcomes of pancreatic neuroendocrine neoplasms: the Massachusetts General Hospital experience from 1977 to 2005. Arch Surg 2007;142(4):347–354.
26. Fischer L, Kleeff J, Esposito I, et al. Clinical outcome and long-term survival in 118 consecutive patients with neuroendocrine tumours of the pancreas. Br J Surg 2008;95(5):627–635.

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ORIGINAL ARTICLE

Influence of Lys656asn Polymorphism of Leptin Receptor Gene on Surgical Results of Biliopancreatic Diversion

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Abstract
Background Bariatric surgery is the most effective long-term treatment for morbid obesity, reducing obesity-associated comorbidities. The purpose of the present study was to evaluate Lys656Asn polymorphism of leptin receptor gene on outcomes 1 year after biliopancreatic diversion.
Methods A sample of 41 morbidly obese patients (body mass index (BMI)>40 kg/m^2) were operated on. Biochemical and anthropometric evaluation were realized at basal visit and at each visit. The frequency of patients with diabetes mellitus, hypertension, and hyperlipidemia was recorded at each visit.
Results Thirty-two patients (78%) had genotype Lys656/Lys656, eight patients (19.5%) Lys656/Asn656 genotype, and one patient (2.4%) Asn656/Asn656 genotype. In the wild-type group, body mass index, weight, glucose, total cholesterol, LDL cholesterol, triacylglycerol, and systolic blood pressure decreased. In the mutant group, the same parameters improved. Initial weight percent loss at 1 year of follow-up was higher in mutant group than in wild-type group (38.9% vs 29.9%; $p<0.05$). Total weight loss was higher in mutant group than wild-type group (50.7 vs 37.2 kg; $p<0.05$). Basal weight and BMI were higher in mutant group than wild type.
Conclusion Weight loss was higher in mutant group (Lys656Asn and Asn656Asn) than wild-type group (Lys656Lys) after bariatric surgery. Carriers of the allelic variant (Asn) had higher basal weight.

Keywords Biliopancreatic diversion · Lys656asn · Polymorphism of leptin receptor gene · Morbid obesity · Surgery

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Introduction

The prevalence of obesity is rising.[1] Bariatric surgery is the most effective long-term treatment for morbid obesity, reducing obesity-associated comorbidities.[2]

Biliopancreatic diversion (BPD) as described by Scopinaro[3] is a mixed operation that has shown good results regarding weight loss. Nevertheless, long-term follow-up is known to be poor in some surgery studies. Perhaps the genetic background of these patients could influence follow-up and outcomes. Recently, a lack of association between Ala54Thr polymorphism of fatty acid-binding protein-2 and clinical results of biliopancreatic diversion has been described.[4]

The etiology of common obesity is complex because many genetic, environmental, and metabolic factors might act. Human obesity is characterized by high levels of leptin, and it has been suggested that obese patients may be leptin resistant. One of the explanations could be a decrease in

leptin receptor (LEPR) signaling due to a mutant leptin receptor.[5] This has been demonstrated in some severely obese humans who are homozygous for a mutation in the leptin receptor, who have very high leptin levels.[6] These mutations are extremely rare and cannot be responsible for obesity in the general population. These data suggest that less severe alterations of the normal leptin receptor gene are involved in the development of obesity.[7] Different polymorphisms in leptin receptor gene have been studied with unclear results.[8] The polymorphism on codon 656 produces a change in charge, making this change a possibility to be functional.

The purpose of the present study was to evaluate lys656asn polymorphism of leptin receptor gene outcomes 1 year after biliopancreatic diversion in morbidly obese patients.

Materials and Methods

Subjects and Surgical Procedure

Forty-one morbidly obese patients (body mass index (BMI) >40) were operated on from December 2005 to December 2007 (Table 1). We analyzed a consecutive series of patients who underwent open BPD by the Scopinaro technique.[2]

The BPD consisted of an average of 200-cm alimentary limb and 80-cm common limb. Gastric volume was measured with sterile water after stapling. Intestinal limbs were measured during surgery with a sterile tape measure.

Follow-up visits were carried out at intervals (3, 9, and 12 months). The following variables were specifically recorded: age, weight, (BMI), waist circumference, and associated morbidities.

Evaluation and Follow-up Time

Weight, BMI, fat mass, blood pressure, basal glucose, triacylglycerides, total cholesterol, LDL cholesterol, and HDL-cholesterol were measured at basal visit (before surgery) and at each visit (3, 9, and 12 months).

The frequency of patients with diabetes mellitus, hypertension, and hyperlipidemia was recorded at each visit (3, 9, and 12 months after surgery).

Hypertesion and hyperlipidemia were diagnosed in patients taking hypotensive and hypolipemic drugs, respectively. Hypertension or hyperlipidemia was diagnosed according to National Choleterol Education Program standards.[9] Diabetes mellitus was diagnosed in patients taking hypoglycemic drugs or insulin or according to the American Diabetes Association standard of diagnosis.[10]

Table 1 Preoperative Characteristics of the Patients

Morbidly obese	35
Super-obese	6
Gender (men/women)	9/32
Age (years)	42.8±12.9
BMI (kg/m^2)	46.8±6.3
Hypertension (%)	46.3%
Diabetes mellitus (%)	9.8%
Dyslipemia (%)	14.6%

Methods Used for Each Determination

Plasma glucose levels were determined by using an automated glucose oxidase method (Glucose analyser 2, Beckman Instruments, Fullerton, CA).

Serum total cholesterol, HDL-cholesterol, and triacylglyceride concentrations were determined by enzymatic colorimetric assay (Roche Diagnostics, Mannheim, Germany).

Blood pressure was measured twice after a 10-min rest with a sphygmomanometer OMRON Mx3 (Omron Matsusaka Co. Ld, Tokio Japan) and averaged.

Previous to the surgery and at 1 year after surgery, leptin was measured in frozen serum samples. Leptin was measured by ELISA (Diagnostic Systems Laboratories, Inc., TX, USA) with a sensitivity of 0.05 ng/ml and a normal range of 10–100 ng/ml.

Genotyping of LEPR Gene Polymorphism

Oligonucleotide primers and probes were designed with the Beacon Designer 4.0 (Premier Biosoft International ®, LA, CA). Polymerase chain reaction (PCR) was carried out with 250 ng of genomic DNA, 0.5 µl of each oligonucleotide primer (forward primer: 5′-GCA GTT CCT ATG AGA GGA CC-3′; reverse primer: 5′-AAA TTG GGA ATA CCT TCC AAA GT-3′), and 0.25 µl of each probe (wild probe: 5′-Fam-AGT GAC ATT TTT CTC CTT TTT CAT AGT ATC-Tamra-3′ and mutant probe: 5′-Hex-AGT GAC ATT TTT CTC GTT TTT CAT AGT AT- Tamra-3′) in a 25-µl final volume (Termociclador iCycler IQ (Bio-Rad®), Hercules, CA). DNA was denaturized at 95°C for 3 min; this was followed by 50 cycles of denaturation at 95°C for 15 s and annealing at 59.3°C for 45 s). The PCR were run in a 25-µl final volume containing 12.5 µl of IQTM Super mix (Bio-Rad®, Hercules, CA) with hot start Taq DNA polymerase.

Body Composition Measurements

Body weight was measured to an accuracy of 0.1 kg and body mass index computed as body weight/(height^2).

Statistical Analysis

The results were expressed as average ± standard deviation. The normal distribution of variables was analyzed with Kolmogorov–Smirnov test. Quantitative variables with normal distribution were analyzed with a two-tailed paired Student's *t* test. Nonparametric variables were analyzed with the Mann–Whitney and Wilcoxon tests. Qualitative variables were analyzed with the chi-square test, with Yates correction as necessary, and Fisher's test. Sample size estimation was performed based on the effects on weight loss using polymorphism frequency (30%) in obese subjects. A p value under 0.05 was considered statistically significant.

Results

Thirty-two patients (78%) had genotype *Lys656/Lys656*, eight patients (19.5%) had genotype *Lys656/Asn656* or *Asn656/Asn656* genotype (one patient (2.4%)). Patients with *Lys656/Asn656* and *Asn656/Asn656* genotypes were included in the some group (mutant-type group), and patients with *Lys656/Lys656* genotype were included in the wild-type group (dominant model).

The wild-type group consisted of seven men and 25 women (mean age was 43.6±7.3 years). The mutant-type group consisted of two men and seven women (mean age was 42.3±8.4 years). There were no statistical differences between groups. The preoperative characteristics of the patients are listed in Table 1.

Table 2 lists anthropometric parameters and blood pressure levels. In the wild-type group, body mass index, weight, and systolic blood pressure decreased. In the mutant group, the same parameters improved. Initial weight percent loss at 1 year of follow-up was higher in mutant group than in wild-type group (38.9% vs 29.9%; $p<0.05$). Total weight loss was higher in mutant-type group than wild-type group (50.7 vs 37.2 kg; $p<0.05$). Basal weight and BMI were higher in mutant-type group than wild type.

Table 3 presents biochemical parameters. In the wild-type group, glucose, total cholesterol, LDL cholesterol, and triacylglyceride concentrations decreased. In the mutant group, the same parameters improved. No differences were detected between mutant and wild genotypes in all these parameters. Leptin levels decreased in both groups. The decrease in leptin was higher in wild-type group (61.2±31 vs 23±20 ng/ml; $p<0.05$) than mutant-type group (71.5±26 vs 53±25 ng/ml; $p<0.05$).

A decrease in the frequency of cardiovascular risk factors was detected in both groups. Hypertension remained in 12.5% of wild-type patients and 11.1% of mutant-type patients. Diabetes mellitus disappeared in all patients (wild and mutant genotypes). Oral drugs or subcutaneous insulin were discontinued in all patients after surgery. Dyslipemia remained only in 9.4% of wild-type patients and 11.1% of mutant-type patients.

Discussion

The present study demonstrates that weight loss was higher in mutant group (Lys656Asn and Asn656Asn) than wild-type group (Lys656Lys) after bariatric surgery. Glycemia, plasma lipid levels, and systolic blood pressure improved during follow-up after BPD in both genotypes. Carriers of the allelic variant (Asn) had higher basal weight.

Several population-based studies have been conducted, but few studies on the functionality of this polymorphism have been reported.[11] A meta-analytic investigation of linkage and association of LEPR polymorphisms with body mass index and waist circumference concluded that, although certain genotypic effects could be population-specific, there was no statistical evidence that any allele

Table 2 Anthropometric and Blood Pressure Course

Characteristics	Basal time	3 months	9 months	12 months
Wild-type group (Lys656Lys)				
BMI(kg/m^2)	48.2±6.2	42.1±6.3*	37.3±6.1*	34.6±7.4*
Weight (kg)	124.4±19.8	105.2±16.4*	95.3±14*	87.2±17*
IEWL%	–	15.4	23.4	29.9
SBP mmHg	149±31	139.2±18*	134±15*	130.5±12*
DBP mmHg	90±28	84.1±9.5	81.2±7.9	81.2±6.5
Mutant-type group (Lys656/Asn656 and Asn656/Asn656)				
BMI(kg/m^2)	53.1±11.4	43.6±8.4*	36.5±5.1*	35.7±7.6*
Weight (kg)	131±22	104.1±30*	91.6±20*	80.3±17*
IEWL%	–	20.5	30.1	38.9
SBP (mmHg)	138±31	119±18*	120±12*	118±13*
DBP (mmHg)	91±19	79.8±11	78±5.6	75±6.9

IEWL% initial excess weight percent loss; *SBP* systolic blood pressure; *DBP* diastolic pressure
*$p<0.05$ with basal value in each group

Table 3 Biochemical Parameters

Characteristics	Basal time	3 months	9 months	12 months
Wild-type group (Lys656Lys)				
Glucose (mg/dl)	104.6±18	92.6±9*	87.7±5.1*	85±6.2*
Total ch. (mg/dl)	190.9±35	134.2±34*	127.2±30*	130±37*
LDL ch. (mg/dl)	89.8±28	63.2±34*	63.8±34*	52.6±20*
HDL ch. (mg/dl)	50±15	43.5±19	44.8±16	52.4±8
TG (mg/dl)	140.5±66	135±50	105±42*	107±40*
Mutant-type group (Lys656/Asn656 and Asn656/Asn656)				
Glucose (mg/dl)	114.6±25	98±21*	79.6±17*	90±8.7*
Total ch. (mg/dl)	195.3±37	147.6±42*	120±20*	118±24*
LDL ch. (mg/dl)	119±35	72.5±36*	60.4±31*	^{6}2.2±26*
HDL ch. (mg/dl)	50.4±7.4	45.1±15	46.2±8	51.8±18
TG (mg/dl)	123.7±61	125±22*	84±37*	100±58*

TG triacylglycerol; *ch.* cholesterol

*$p<0.05$ with basal value in each group

(Lys109Arg, Gln223Arg, Lys656Asn) is associated with BMI or weight.[12] Another study in British males showed that there was no evidence for a significant effect of the common variants on obesity or obesity-related phenotypes.[13] However, other studies have detected an association between polymorphism on codon 656 and obesity phenotypes. In postmenopausal women with intolerance of glucose (ITG), associations were found with Lys656Asn for fasting insulin. In premenopausal women with ITG, associations were found with Lys656Asn for overall glucose response to the glucose load.[14,15] An interaction has been described, too.[16] Our results have shown higher weight and BMI in Asn carrier patients.

Interventional studies with this polymorphism are limited. Lakka et al.[17] showed in Caucasian patients that exercise increased sensitivity to insulin and decreased fasting glucose in the LEPR Asn65Asn homozygotes but did not influence glucose homeostasis in Lys656Asn and Lys656Lys patients. Rossum et al.[18] did not find an association between Lys656Asn polymorphism and weight gain in a large cohort. Another study has demonstrated that, in patients on a hypocaloric diet, there was a significant decrease of weight and fat mass in wild-type group as well as mutant group, but a decline in leptin levels was only observed in the wild-type group.[19] Only one other research group[20] has studied the response to a hypocaloric diet in relationship to a different LEPR polymorphism (Thr343Ser). No effect of the assessed polymorphism in the LEPR gene on the acute decline in leptin or weight loss after energy restriction was observed.

Our results have showed a higher weight loss in mutant group than wild-type group. However, these mutant-type patients had a higher basal weight than wild-type patients. The higher weight loss could be explained by the higher basal weight. Biliopancreatic diversion is a potent surgery to lose weight in all morbidly patients, but it is indicated in super morbid patients (BMI>50) with greater weight loss.

The effects of different polymorphisms after bariatric surgery are an unclear area of investigation. Some authors have recently demonstrated that melanocortin-4 receptor gene variant determines the outcome of bariatric treatment of severe obesity.[21,22] Sesti et al.[23] have demonstrated that, after laparoscopic adjustable gastric banding, carriers of G-174G IL-6 genotype had lost more weight than G-174C or C-174C, and carriers of A866A uncoupling protein 2 genotype have lost more weight as compared with G866G. However, polymorphism Gly972Arg of insulin receptor substrate-1 gene and Pro12 Ala of the proliferator-activated receptor gamma gene did not have significant effect on weight loss.[24]

Perhaps these discrepancies could be explained by different inclusion criteria of subjects in these previous studies. First, the average BMI was different in bariatric surgery studies than hypocaloric diet studies. Second, weight loss and maintenance are different. Therefore, the question arises of whether weight loss achieved by a BPD in our study overrides the subtle polymorphism-dependent effects.

Recently, polymorphisms in a panel of obesity-related candidate genes play a minor role, if any, in modulating weight changes induced by a moderate hypo-energetic low-fat vs high-fat diet.[25] However, the vast amount of recently published data on the leptin receptor showed unexpected data, for example, association of bone mass with Gln223Arg polymorphism,[26] risk of developing breast cancer,[27] and a relationship with body mass index in persons with schizophrenia treated with olanzapine.[28]

A potential limitation of our study is the small size of our sample and the unequal size of the groups. However, considering the difficulty to study large groups in this area, it is important to learn of this small pilot studies. Another methodological limitation of our data is the unequal initial weight between the two groups; the difference in the degree of weight loss may well stem from the difference in initial

weight between the two groups or by the polymorphism. However, an interesting question is if the surgeon will think about what type of surgery must apply to a morbid patient taking to account the grade of obesity and the genotype of the patient, too.

In conclusion, the present study demonstrates that weight loss was higher in mutant group (Lys656Asn and Asn656Asn) than wild-type group (Lys656Lys) after bariatric surgery. Carriers of the allelic variant (Asn) had higher basal weight.

References

1. Aranceta J, perez Rodrigo C, Serra Majem L. Prevalencia de la obesidad en España: estudio SEEDO 97. Med clin (Barc) 1998;111:441–445.
2. de luis DA, Aller R, Izaola O, Pacheco D. Early clinical and surgical results of biliopancreatic diversion. Obes Surg 2005. 15:799–802.
3. Scopinaro N, Adami GF, Marinari GM: Biliopancreatic diversión. World J Surg 1998;22:936–946.
4. de Luis DA, González Sagrado M, Izaola O, Terroba MC, Cuellar L, Conde R, Martin T. Influence of Ala54Thr polymorphism of fatty acid-binding protein-2 on clinical results of biliopancreatic diversion. Nutrition 2008;24:300–304.
5. Schwartz MW, Woods SC, Porte D, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature 2000; 404: 661–671.
6. Clement K, Vaisse C, Lahlou N. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 1998;329:398–401.
7. Clement K. Leptin and the genetics of obesity. Acta Paediatr 1999;88:51–57.
8. Heo M, Leíble RL, Boyer BB, Cheng WK, Koulu M, Karnoven MK, et al. Pooling analysis of genetic data: The association of leptin receptor (LEPR) polymorphisms with variables related to human adiposity. Genetics 2001;159:1163–1178.
9. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2487.
10. Standards of diabetes mellitus, American Diabetes Association. Diabetes Care 2007;30:s4–s41.
11. Mars M, Van Rossum C, de Graaf C, Hoebee B, de Groot L, Kok FJ. Leptin responsiveness to energy restriction: Genetic variation in the leptin receptor gene. Obesity Research 2004;12:442–446.
12. Heo M, Leibel RL, Fontaine KR, Boyer BB, Chung WK. A meta-analytic investigation of linkage and association of common leptin receptor (LEPR) polymorphism with body mass index and waist circumference. Int J Obes 2002;26:640–646.
13. Gotoda T, Manning BS, Goldstone AP, Imrie H, Evans AL, Strosberg AD. Leptin receptor gene variation and obesity: lack of association in a white British male population. Human Mol genetics 2004:6:869–876.
14. Wauters M, Mertens I, Rankinen T, Chagnon C, Bouchard C, Van Gaal L. Leptin receptor gene polymorphisms are associated with insulin in obese women with impaired glucose tolerance. J Clin Endocrinol Metab 2001;86:3227–3232.
15. Wauters M, Considine R, Chagnon M, Mertens I, Rankinen T, Bouchard C, Van Gaal LF. Leptin levels, leptin receptor gene polymorphisms, and energy metabolism in women. Obesity Research 2002;10:394–400.
16. de Luis DA, Gonzalez Sagrado M, Aller R, Izaola O, Conde R. Influence of Lys656Asn polymorphism of the leptin receptor gene on insulin resistance in nondiabetic obese patients. J of Diab and Its Complicat 2008;22:199–204.
17. Lakka T, Rankinen T, Weisnagel SJ, Chagnon YC, Lakka HM, Ukkola O, Boule N. Leptin and leptin receptor gene polymorphisms and changes in glucose homeostasis in response to regular exercise in nondiabetic individuals. Diabetes 2004;53:1603–1610.
18. Rossum CTM, Hoebee B, van Baak M, Mars M, Saris WHM, Seidell JC. Genetic variation in the leptin receptor gene, leptin, and weight gain in young Dutch Adults. Obesity research 2003:11:377–386.
19. de Luis DA, Aller R, Izaola O, Conde R, Gonzalez M. Influence of lys656asn polymorphism of leptin receptor gene in leptin response and weight loss secondary to a lifestyle modification in obese patients. Arch of Med Research 2006: 37:854–859.
20. Mammes O, Aubert R, Betoulle D, Pean F, Herbetch B, Visvikis S, Siest G, Fumeron F. LEPR gene polymorphisms: associations with overweight, fat mass and response to diet in women. Eur J of Clin Invest 2001;31:398–404.
21. Kral JG, Branson R, PiecG. Melanocortin-4 receptor gene variants affect results of gastric banding. J Gastrointest Surg 2004;126 (Suppl 2):A774.
22. Kral JG, Lentes KU, Horber FF. Binge eating as a phenotype of melanocortin 4 receptor gene mutations, n Engl J Med 2003;349:606–609.
23. Sesti G, Perego L, Cardellini M, Andreozzi F, Ricasoli C, Vedani P et al. Impact of common polymorphisms in candidate genes for insulin resistance and obesity on weight loss of morbidly obese subjects after laparoscopic adjustable gastric banding and hypocaloric diet. The J of Clinical Endoc and Metab 2005;90:5064–5069.
24. Poitou C, LAcorte JM, Coupaye M, Bertaris S, Bedel JF, Lafon N et al. Relationship between single nucleotide polymorphisms in leptin, IL6 and adiponectin genes and their circulating product in morbidly obese subjects before and after gastric banding surgery. Obesity Surgery 2005;15:11–23.
25. Sorensen TI, Boutin P, Taylor MA, Larsen LH, Verdich C, Petersen L et al. Genetoc polymorfisms and weight loss in obesity: a randomised trial of hypo-energetic high- versus low fat diets. Plos Clin Trials 2006;1:2:e12.
26. Richert L, Chevalley T, Manen D, Bonjour JP, Rizzoli R, Ferrari S. Bone mass in prepubertal boys is associated with a Gln223Arg amino acid substitution in the leptin receptor. J Clin Endocrinol Metab. 2007;92(11):4380–6.
27. Gallicchio L, McSorley MA, Newschaffer CJ, Huang HY, Thuita LW, Hoffman SC, Helzlsouer KJ. Body mass, polymorphisms in obesity-related genes, and the risk of developing breast cancer among women with benign breast disease. Cancer Detect Prev. 2007;31(2):95–101.
28. Ellingrod VL, Bishop JR, Moline J, Lin YC, Miller del D. Leptin and leptin receptor gene polymorphisms and increases in body mass index (BMI) from olanzapine treatment in persons with schizophrenia. Psychopharmacol Bull. 2007;40(1):57–62.

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ORIGINAL ARTICLE

Evidence-Based Surgical Practice in Academic Medical Centers: Consistently Anecdotal?

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Abstract
Introduction Randomized trials, meta-analyses, and guidelines form the basis of clinical decision making. We queried a small sample of surgeons at three academic medical centers to determine whether key elements of surgical practice were concordant with available evidence.
Materials and Methods A French Society of Digestive Surgery (FSDS) questionnaire was submitted to general surgery trainees and faculty at the University of South Florida and University of Chicago and to surgical oncology fellows at the Memorial Sloan–Kettering Cancer Center. Participants were asked to respond "never," "rarely," "often," or "always" to 13 questions involving different aspects of gastrointestinal surgery. For each question, a correct evidence-based answer was available from published studies.
Results and Discussion One hundred ten surgeons (79% of eligible participants) completed the survey. Only 60% of the answers were concordant with existing data. The percentages of correct answers did not differ significantly according to institution or level of experience of participants. The low frequency of correct responses in our subjects paralleled the findings from the 2004 FSDS study. Variability in the quality of evidence and ambiguity in the survey questions may have influenced the responses, but evidence-based medicine does not appear to uniformly influence clinical decision making.

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Keywords Evidence-based practice · Surgery · Surveys

Introduction

In theory, randomized trials, meta-analyses, and guidelines should form the basis of clinical decision making and routine surgical practices. However, little is known on the impact of such data on surgical practices. Historically, surgeons have shown reluctance to accept evidence from randomized controlled trials that might alter their established practice.[1] In 2004, a survey conducted among members of the French Society of Digestive Surgery (FSDS) was published in the *Journal of Gastrointestinal Surgery*. The questionnaire included 13 questions focusing on several aspects of gastrointestinal surgery and for which level I evidence was available in the literature. The authors found that <60% of the responses were in accordance with scientific evidence.[2] Using the same questionnaire previously used by Slim et al., we queried a sample of surgeons at three separate academic medical centers to determine

whether key elements of surgical practice were concordant with available evidence. Our aim was to measure the level of implementation of available evidence in clinical practice among US surgeons.

Material and Methods

A survey was conducted among faculty and trainees (fellows and residents) from the surgical departments of the University of South Florida (Tampa, FL), the University of Chicago Pritzker School of Medicine (Chicago, IL), and among surgical oncology fellows at Memorial Sloan–Kettering Cancer Center (New York, NY). The questionnaire included 13 questions for which Slim et al. selected the correct answers on the basis of level I evidence (meta-analyses or prospective randomized trials) available at the time of their study. Table 1 shows the questions included in the questionnaire, with the relative answers as considered "correct" by Slim et al. (references are listed in the third column of Table 1). Participants were asked to choose one of four possible responses (never, rarely, often, or always) that most closely reflected their daily routines. In agreement with the methods used by Slim et al., our answers were analyzed using a binary system: responses "never" and "rarely" were considered together indicating a negative response and answers "often" and "always" indicated a positive response; the one exception was question 13 where the answers that were grouped together were "never" with "always" and "rarely" with "often."

Participants were also asked to indicate their rank as "junior resident" (postgraduate year [PGY] 1–2), "senior resident/fellow" (PGY 3–7), or "faculty". Questionnaires were distributed and collected in anonymous fashion during one of the department educational meetings.

Differences in answers between groups were analyzed with two-sided chi-squared tests and declared at the 5% significance level. Statistical analysis was performed with PASW Statistics 17.0 (SPSS, Chicago, IL).

Results

One hundred ten surgeons (79% of eligible participants) completed the survey. Using the French criteria, only 60% of the answers were "correct" (Tables 2 and 3). Six answers (1, 3, 5, 6, 8, and 12) were in agreement with scientific evidence in the majority of participants: no preoperative chest radiograph before an appendectomy in a young male patient (87%); no intra-abdominal drainage after right hemicolectomy (95%); fascial midline closure using a running monofilament suture (87%); skin closure using staples (81%); mesh herniorrhaphy in a 45-year-old man (90%); no routine cholangiography during cholecystectomy in the absence of dilated bile duct or abnormal liver function tests (83%). Two questions (2 and 13) were answered "correctly" by slightly more than half of participants: no gastric tube after left hemicolectomy (77%) and short gastric vessels ligation "on demand" during fundoplication (54%). However, there were five questions (4, 7, 9, 10, and 11) that only a minority of respondents answered "correctly": handsewn intraperitoneal colorectal anastomosis (6%), oral feeding permitted on the first postlaparotomy day (35%), no polyethylene glycol

Table 1 Thirteen Questions Presented, with Correct Answers and Confirming Evidence

	Evidence-based answer	References
1. Do you obtain a CXR before operating on a 25 y.o. male for acute appendicitis?	Never or rarely	21
2. Do you use postoperative nasogastric aspiration for left colectomy?	Never or rarely	22–24
3. Do you leave an abdominal drain during right colectomy?	Never or rarely	25
4. Do you perform a mechanical anastomosis for intraperitoneal colorectal anastomosis?	Never or rarely	4
5. Do you close the midline laparotomy using an interrupted suture of braided thread?	Never or rarely	26,27
6. Do you use staples for cutaneous suturing?	Often or always	9–11
7. Do you permit enteral feeding on the first post-laparotomy day?	Often or always	28
8. Do you repair an inguinal hernia in a 45 y.o. man using the Shouldice technique?	Never or rarely	29,30
9. Do you prepare the colon before elective surgery by means of oral polyethylene glycol?	Never or rarely	31,32
10. Do you leave the skin open after an appendectomy for gangrenous appendicitis?	Never or rarely	27
11. Do you perform a mechanical anastomosis for small intestine resection?	Never or rarely	3,5,6
12. Do you perform intra-operative cholangiography in a patient with biliary lithiasis, normal serum liver enzymes, and a small CBD?	Never or rarely	33–35
13. Do you ligate short gastric vessels during laparoscopic total fundoplication?	Rarely or often (on demand)	36–39

Table 2 Percentage of Answers in Agreement with Scientific Evidence, According to Rank of Participants

	Overall, *N*=110	Junior residents, *N*=31	Senior residents or fellows, *N*=58	Faculty, *N*=21	*p* value
1. Do you obtain a CXR before operating on a 25 y.o. male for acute appendicitis?	87%	87%	93%	71%	0.04
2. Do you use postoperative nasogastric aspiration for left colectomy?	77%	52%	88%	86%	0.01
3. Do you leave an abdominal drain during right colectomy?	95%	87%	98%	100%	0.03
4. Do you perform a mechanical anastomosis for intraperitoneal colorectal anastomosis?	6%	11%	5%	0%	0.2
5. Do you close the midline laparotomy using an interrupted suture of braided thread?	87%	83%	90%	86%	0.7
6. Do you use staples for cutaneous suturing?	81%	77%	84%	76%	0.5
7. Do you permit enteral feeding on the first post-laparotomy day?	35%	26%	40%	33%	0.4
8. Do you repair an inguinal hernia in a 45 y.o. man using the Shouldice technique?	90%	86%	91%	90%	0.7
9. Do you prepare the colon before elective surgery by means of oral polyethylene glycol?	28%	17%	31%	38%	0.2
10. Do you leave the skin open after an appendectomy for gangrenous appendicitis?	41%	33%	45%	43%	0.5
11. Do you perform a mechanical anastomosis for small intestine resection?	15%	27%	9%	14%	0.07
12. Do you perform intra-operative cholangiography in a patient with biliary lithiasis, normal serum liver enzymes, and a small CBD?	83%	70%	90%	85%	0.06
13. Do you ligate short gastric vessels during laparoscopic total fundoplication?	54%	67%	45%	60%	0.1
Overall	60%	56%	62%	60%	0.1

Table 3 Percentage of Answers in Agreement with Scientific Evidence, According to Institution of Participants

	Overall, *N*=110	USF, *N*=57	UoC, *N*=38	MSKCC, *N*=15	*p* value
1. Do you obtain a CXR before operating on a 25 y.o. male for acute appendicitis?	87%	84%	95%	80%	0.2
2. Do you use postoperative nasogastric aspiration for left colectomy?	77%	71%	76%	100%	0.06
3. Do you leave an abdominal drain during right colectomy?	95%	96%	92%	100%	0.4
4. Do you perform a mechanical anastomosis for intraperitoneal colorectal anastomosis?	6%	4%	6%	13%	0.3
5. Do you close the midline laparotomy using an interrupted suture of braided thread?	87%	96%	68%	100%	0.01
6. Do you use staples for cutaneous suturing?	81%	67%	95%	100%	0.01
7. Do you permit enteral feeding on the first post-laparotomy day?	35%	37%	24%	53%	0.1
8. Do you repair an inguinal hernia in a 45 y.o. man using the Shouldice technique?	90%	88%	89%	100%	0.3
9. Do you prepare the colon before elective surgery by means of oral polyethylene glycol?	28%	34%	21%	27%	0.4
10. Do you leave the skin open after an appendectomy for gangrenous appendicitis?	41%	39%	42%	46%	0.7
11. Do you perform a mechanical anastomosis for small intestine resection?	15%	11%	16%	27%	0.3
12. Do you perform intra-operative cholangiography in a patient with biliary lithiasis, normal serum liver enzymes, and a small CBD?	83%	89%	76%	80%	0.2
13. Do you ligate short gastric vessels during laparoscopic total fundoplication?	54%	53%	76%	0%	0.01
Overall	60%	59%	60%	64%	0.5

preparation before elective colectomy (28%), primary skin closure for gangrenous appendicitis (41%), and handsewn small bowel anastomoses (15%). Overall, the percentages of correct answers did not differ significantly according to institution (59% vs. 60% vs. 54%, $p=0.5$) or level of experience of participants (56% vs. 62% vs. 60%, $p=0.1$). However, when examining the single answers by level of training or by institution, small differences appeared. Any-level trainees were less likely to request a chest radiograph before appendectomy ($p=0.004$); junior residents were more likely to leave a nasogastric or an intraperitoneal drain after colectomy ($p=0.001$ and 0.003, respectively). A lower percentage of surgeons from University of Chicago used monofilament running sutures for abdominal closure ($p=0.01$), and a lower percentage of surgeons from University of South Florida used staples for skin closure ($p=0.01$). Comparing our study with the survey from Slim et al., it appears that, overall, French and US surgeons answered correctly the same percentage of questions (60% vs. 59%, $p=0.8$); however, the two communities tended to answer differently each question. US and French surgeons showed similar rates of correct answers in only five questions (1, 5, 7, 9, and 13; Table 4).

Discussion

We recently conducted a survey among trainees and faculty surgeons from three American academic training institutions to determine variations in the practice of "evidence-based" surgery. We adopted a questionnaire used by Slim et al. in 2004 in which practices queried were substantiated by level I evidence. Overall, only 60% of the answers were concordant with existing data. The relatively low frequency of overall correct responses in our subjects parallels the findings from the original study performed in France. Percentages of correct answers did not differ significantly according to institution (59% vs. 60% vs. 54%, $p=0.5$) or level of experience of participants (56% vs. 62% vs. 60%, $p=0.1$).

Prior to a critical analysis of these results, we should first acknowledge that, despite the fact that all questions have level I evidence-based answers, the questionnaire proposed by Slim et al. has several intrinsic flaws. Several questions concerned topics with controversial or equivocal answers. For example, while studies available at the time of the French study suggested that handsewn anastomoses were less expensive and less prone to late stenosis,[3–6] widespread clinical experience supports that both mechanical and handsewn bowel anastomoses are safe, effective, and reliable. Furthermore, two Cochrane reviews published in 2009 confirmed that overall clinical outcomes and leak rates are equivalent with either technique.[7,8] The observed "evidence-opposed" responses for question 4 (colorectal anastomosis) and question 11 (small bowel anastomosis) likely reflect the current ubiquitous use of mechanical staplers in open and laparoscopic gastrointestinal procedures and the recent surge in minimally invasive operations. If we hypothetically omitted those questions from the survey, the percentage of correct answers would rise to 69%. If we assumed, unlike the French study, "often" or "always" as the correct answers to

Table 4 Percentage of Answers in Agreement with Scientific Evidence in the Current Study Compared to the Previous French Survey

	Our study, $N=110$	Slim et al., $N=283$	p value
1. Do you obtain a CXR before operating on a 25 y.o. male for acute appendicitis?	87%	91%	0.3
2. Do you use postoperative nasogastric aspiration for left colectomy?	77%	54%	0.001
3. Do you leave an abdominal drain during right colectomy?	95%	60%	0.001
4. Do you perform a mechanical anastomosis for intraperitoneal colorectal anastomosis?	6%	42%	0.001
5. Do you close the midline laparotomy using an interrupted suture of braided thread?	87%	87%	0.9
6. Do you use staples for cutaneous suturing?	81%	49%	0.001
7. Do you permit enteral feeding on the first post-laparotomy day?	35%	30%	0.3
8. Do you repair an inguinal hernia in a 45 y.o. man using the Shouldice technique?	90%	63%	0.001
9. Do you prepare the colon before elective surgery by means of oral polyethylene glycol?	28%	25%	0.6
10. Do you leave the skin open after an appendectomy for gangrenous appendicitis?	41%	77%	0.001
11. Do you perform a mechanical anastomosis for small intestine resection?	15%	83%	0.001
12. Do you perform intra-operative cholangiography in a patient with biliary lithiasis, normal serum liver enzymes, and a small CBD?	83%	35%	0.001
13. Do you ligate short gastric vessels during laparoscopic total fundoplication?	54%	51%	0.7
Overall	60%	59%	0.8

the same questions, the percentage of correct answers would be even higher (72%).

Questions that assessed noncritical decision making (i.e., cost, cosmetic results, etc.) may have also skewed the overall percentage of correct responses. For example, available studies reveal that staple closure of the skin (question 6) offers the advantage of speed and convenience, but this should be balanced by the increased cost of the devices; cosmesis was equivalent in all studies.[9–11] We believe that, in the absence of studies showing a blatant superiority of a particular intervention, alternative practices probably should not be designated as "evidence-opposed."

Question 12 (intraoperative cholangiography) assesses a very controversial topic in the general surgery community. The decision to perform an intraoperative cholangiogram is multifactorial (i.e., uncertain or variable biliary anatomy, the risk of choledocholithiasis, or medicolegal ramifications) and can involve subjective factors. Published evidence has not shown a definitive advantage for the routine use of cholangiogram during elective cholecystectomy.[12]

However, the fact remains that only 60% of the answers were in agreement with scientific evidence. Even if we take in consideration the potential questionnaire flaws and exclude the topics on bowel anastomoses and intraoperative cholangiography, the percentage of correct answers only increases to 67%. This relatively low rate of "correct" responses is actually consistent with other studies which have previously shown a low level of acceptance of scientific evidence among surgeons. For instance, despite solid data regarding the use of drains, antibiotic prophylaxis, and subcutaneous heparin to prevent thromboembolic complications in colorectal surgery, Wasey and coworkers have clearly demonstrated overuse of drains, underuse of heparin, and misuse of antibiotics (timing, duration) on a colorectal service.[13] A recent survey of perioperative practices in five European countries showed wide variation in practice, with the majority of practice at odds with current best evidence.[14]

Our survey showed minimal variations between the institutions and among trainees and their instructors. The influence of the apprenticeship model of surgical training likely creates modeled behavior. The use of this survey in three academic medical centers represents an extreme form of undercoverage bias. The results might have been different if conducted in private practice hospitals or hybrid medical centers where premiums on cosmesis, efficiency, or resource allocation may differ.

We observed a percentage of overall correct answers similar to the 2004 FSDS study. Although we used the same questionnaire utilized by Slim et al., a comparison with their study is limited by the fact that we have queried different populations in a different country and at different times; but even with these limits, our data suggests that despite the 5 years that have lapsed since the French study, implementation of certain evidences among the surgical community remains low.

Adherence to evidence-based practices, as measured by the number of "correct" responses, is reported here, but this is not the only relevant issue. It may be more important to understand if relatively low adherence is due to a knowledge gap or if it is due to entrenched practice patterns.

Ideally, medical and surgical decision making should be guided by sound, reliable, and current evidence. The medical community has been placing a high value on synthesizing evidence into systematic reviews, developing computerized clinical evidence-based decision algorithms, and improving electronic access to this information.[15] Despite these efforts, dissemination and implementation of evidence-based guidelines into clinical practice remains slow and inconsistent.[16–18] Overcoming bias, habitual practice, and surgical dogma may contribute to this delay; surgeons in particular often make choices according to their personal experience and with regard to available resources. Ultimately, adherence to evidence-based practices will be measured and such metrics may influence quality rates and decisions about payment or reimbursement. It is not unconceivable that, in the near future, following approval of the healthcare reform in the USA, national regulatory agencies might generate a list of nonevidence-based approaches, in order to deny reimbursements to certain treatments.

In medicine and surgery, clinical judgment represents an amalgam of knowledge, bias, and experience. Scientific evidence will continue to influence decision making. Recent vagaries in clinical trials (e.g., perioperative beta-blockade and tight serum glucose control)[19,20] support skepticism and restraint. It is paramount that we remain vigilant and continue to critically analyze all "evidence-based" data before altering our clinical practice.

Conclusions

The low frequency of correct responses in our subjects paralleled the findings from the 2004 FSDS study as well as other publications on the implementation of scientific evidence into clinical practice. Evidence-based results do not appear to uniformly influence clinical decision making.

References

1. Brennan MF. Is nil per os still appropriate for patients undergoing upper gastrointestinal surgery? Nat Clin Pract Gastroenterol Hepatol 2008;5:660–661.
2. Slim K, Panis Y, Chipponi J. Half of the current Practice of gastrointestinal surgery is against the evidence: a survey of the

French Society of Digestive Surgery. J Gastrointest Surg 2004;8:1079–1082.
3. Izbicki JR, Gawad KA, Quirrenbach S, Hosch SB, Breid V, Knoefel WT, Küpper HU, Broelsch E. Is the stapled suture in visceral surgery still justified? A prospective controlled, randomized study of cost effectiveness of manual and stapler suture. Chirurg 1998;69:725–734
4. MacRae HM, McLeod RS. Handsewn vs. stapled anastomoses in colon and rectal surgery. Dis Colon Rectum 1998;41:180–189.
5. Reiling RB, Reiling WA, Bernie WA, Huffer AB, Perkins NC, Elliott DW. Prospective controlled study of gastrointestinal stapled anastomoses. Am J Surg 1980;139:147–152.
6. West of Scotland and Highland Anastomosis Study Group. Suturing or stapling in gastrointestinal surgery: a prospective randomized study. Br J Surg 1991;78:337–341.
7. Matos D, Atallah A, Castro A, Silva Lustosa S. Stapled versus handsewn methods for colorectal anastomosis surgery. Cochrane Database Syst Rev 2009;(3):CD003144.
8. Choy P, Bissett I, Docherty J, Parry B, Merrie A. Stapled versus handsewn methods for ileocolic anastomoses. Cochrane Database Syst Rev 2007;(3):CD004320.
9. Gatt D, Quick CRG, Owen-Smith MS. Staples for wound closure: a controlled trial. Ann R Coll Surg Engl 1982;67:318–320.
10. Lubowski D, Hunt D. Abdominal wound closure comparing the proximate stapler with sutures. Aust NZ J Surg 1985;55:405–406.
11. Ranaboldo CJ, Rowe-Jones DC. Closure of laparotomy wounds: skin staples versus sutures. Br J Surg 1992;79:1172–1173.
12. Massarweh N, Flum D. Role of intraoperative cholangiography in avoiding bile duct injury. J Am Coll Surg 2007;204:656–662.
13. Wasey N, Baughan J, de Gara CJ. Prophylaxis in elective colorectal surgery. The costs of ignoring the evidence. Can J Surg 2003;46:279–284
14. Lassen K, Hannemann P, Ljungqvist O, Fearon KF, Dejong CH, vonMeyenfeldt MF, Hausel J, Nygren J, Andersen J, Revhaug A. Patterns in current perioperative practice: survey of colorectal surgeons in five northern European countries. BMJ 2005;330:1420–1421.
15. Rothemberger DA. Evidence-based practice requires evidence. Br J Surg 2004;91:1387–1388.
16. Guyatt GH, Meade MO, Jaeschke RZ, Cook DJ, Haynes RB. Practicioners of evidence based care: not all clinicians need to appraise evidence from scratch but all need some skills. BMJ 2000;320:954–955.
17. McColl A, Smith H, White P, Field J. General practitioners' perception of the route of evidence based medicine: a questionnaire survey. BMJ 1998;316:361–365.
18. Meakins JL. Evidence-based surgery. Surg Clin North Am 2006;86:1–16.
19. Chopra V, Plaisance B, Cavusoglu E, Flanders S, Eagle K. Perioperative beta-blockers for major noncardiac surgery: primum non nuocere. Am J Med 2009;122:222–229.
20. Lipshutz A, Gropper M. Perioperative glycemic control. Anesthesiology 2009;110:408–421.
21. Bouillot JJ, Fingerhut A, Paquet JC, Hay JM, Coggia M. Are routine preoperative chest radiographs useful in general surgery? Eur J Surg 1996;162:597–604.
22. Cheatham ML, Chapman WC, Key SP, Sawyers JL. A meta-analysis of selective versus routine nasogastric decompression after elective laparotomy. Ann Surg 1995;221:469–478.
23. Petrelli NJ, Stulc JP, Rodriguez-Bigas M, Blumenson L. Nasogastric decompression following elective colorectal surgery: a prospective randomized study. Am Surg 1993;59:632–635.
24. Sakadamis A, Ballas K, Kabaroudis A. Role of nasogastric intubation in major abdominal operations: a prospective randomized study. Med Sci Res 1999;27:789–791.
25. Urbach DR, Kennedy ED, Cohen MM. Colon and rectal anastomoses do not require routine drainage: a systematic review and meta-analysis. Ann Surg 1999;229:174–180.
26. Hodgson NCF, Malthaner RA, Østbye T. The search for an ideal method of abdominal fascia closure: a meta-analysis. Ann Surg 2000;231:436–442.
27. Rucinski J, Fabian T, Panagopoulos G, Schein M, Wise L. Gangrenous and perforated appendicitis: a meta-analytic study of 2532 patients indicates that the incision should be closed primarily. Surgery 2000;127:136–141.
28. Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding versus “nil by mouth” after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. BMJ 2001;323:773–776.
29. Cheek CM, Black NA, Devlin HB, Kingsnorth AN, Taylor RS, Watkin DF. Groin hernia surgery: a systematic review. Ann R Coll Surg Engl 1998;80:S1–S80.
30. EU Hernia Trialists Collaboration. Mesh compared with non-mesh methods of open groin hernia repair: systematic review of randomized controlled trials. Br J Surg 2000;87:854–859.
31. Miettinem RPJ, Laitinem ST, Mäkelä IT, Pääkkönen ME. Bowel preparation with oral polyethylene glycol electrolyte solution vs. no preparation in elective open colorectal surgery. Dis Colon Rectum 2000;43:669–677.
32. Platell C, Hall J. What is the role of mechanical bowel preparation in patients undergoing colorectal surgery. Dis Colon Rectum 1998;41:875–883.
33. Clair DG, Carr-Locke DL, Becker JM, Brooks DC. Routine cholangiography is not warranted during laparoscopic cholecystectomy. Arch Surg 1993;128:551–555.
34. Nies C, Bauknecht F, Groth C et al. Intraoperative cholangiography as a routine method? A prospective, controlled, randomized study. Chirurg 1997;68:892–897.
35. Soper NJ, Dunnegan DL. Routine versus selective intra-operative cholangiography during laparoscopic cholecystectomy. World J Surg 1992;16:1133–1140.
36. Blomqvist A, Dalenbäck J, Hagedorn C, Lönroth H, Hyltander A, Lundell L. Impact of complete gastric fundus mobilization on outcome after laparoscopic total fundoplication. J Gastrointest Surg 2000;4:493–500.
37. Chrysos E, Tzortzinis A, Tsiaoussis J, Athanasakis H, Vassilakis JS, Xynos E. Prospective randomized trial comparing Nissen to Nissen–Rossetti technique for laparoscopic fundoplication. Am J Surg 2001;182:215–221.
38. O'Boyle CJ, Watson DI, Jamieson GG, Myers JC, Game PA, Devitt PG. Division of short gastric vessels at laparoscopic nissen funduplication: a prospective double-blind randomized trial with 5-year follow-up. Ann Surg 2002;235:165–170.
39. Watson DI, Pike GK, Baigrie RJ, Mathew G, Devitt PG, Britten-Jones R, Jamieson GG. Prospective double-blind randomized trial of laparoscopic Nissen fundoplication with division and without division of short gastric vessels. Ann Surg 1997;226:642–652.

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CASE REPORT

Remnant Torsion Causing Budd-Chiari Syndrome After Right Hepatectomy

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Abstract
Introduction Torsion or rotation of the remnant left liver after right hepatectomy is a potential cause of venous outflow obstruction. This can occur by external compression on the inferior vena cava or kinking of the left hepatic vein.
Discussion We report a case of a young female who underwent right hepatectomy for stage IV colorectal metastases and suffered remnant left liver torsion causing acute Budd-Chiari syndrome. She was managed by placement of a metal stent across the area of stenosis which resolved her ascites and hyperbilirubinemia.

Keywords Torsion · Budd-Chiari · Liver failure · Hepatectomy · Stent

Case Report

A 46-year-old female underwent right hepatectomy for stage IV colorectal metastases following 12 weeks of neoadjuvant fluorouracil (Pharmacia and Upjohn, Kalamazoo, MI, USA), oxaliplatin (Sanofi-Aventis, Bridgewater, NJ, USA), and bevacizumab (Genentech, South San Francisco, CA, USA). After mobilization of the right lobe and falciform ligament, the operation was performed in a standard fashion with both inflow (right hepatic artery and portal vein) and outflow (right hepatic vein) ligation prior to transection. Parenchymal transection was performed with the CUSA ultrasonic surgical aspiration system (Valleylab, Boulder, CO, USA), and crossing tributaries were clamped and suture ligated. Routine low central venous pressure anesthesia was provided, and no inflow (Pringle) occlusion was used with an estimated blood loss of 150 ml. Pathology revealed five nodules of metastatic colonic adenocarcinoma without evidence of chemotherapy-associated liver injury. At our institution, we do not routinely reapproximate the remnant liver to the abdominal wall using the divided falciform ligament.

On the day following surgery, her serum total bilirubin was 4.8 mg/dl (0.6 mg/dl preoperatively) and had progressively increased, peaking at 10.7 mg/dl on hospital day 13, although she remained asymptomatic other than mild postoperative ascites. She underwent extensive workup, including abdominal ultrasound with Doppler, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiography with sphincterotomy, and abdominal computed tomography scan, all of which failed to reveal an etiology for her postoperative hyperbilirubinemia except for a nearly occlusive thrombus of a posterior branch of the left hepatic vein and moderate ascites. She was started on therapeutic anticoagulation with low-molecular-weight heparin.

A decision was made on hospital day 15 to pursue hepatic venography including an inferior venacavogram which revealed a significant narrowing (Fig. 1, white arrow) within the retrohepatic inferior vena cava (IVC). The level of stenosis appeared cephalad to the left hepatic vein given the position of the diaphragm (Fig. 1, black arrow) and right atrium (Fig. 1, box). We believed that torsion of the remnant left liver around the IVC caused clinically significant outflow obstruction. There was a

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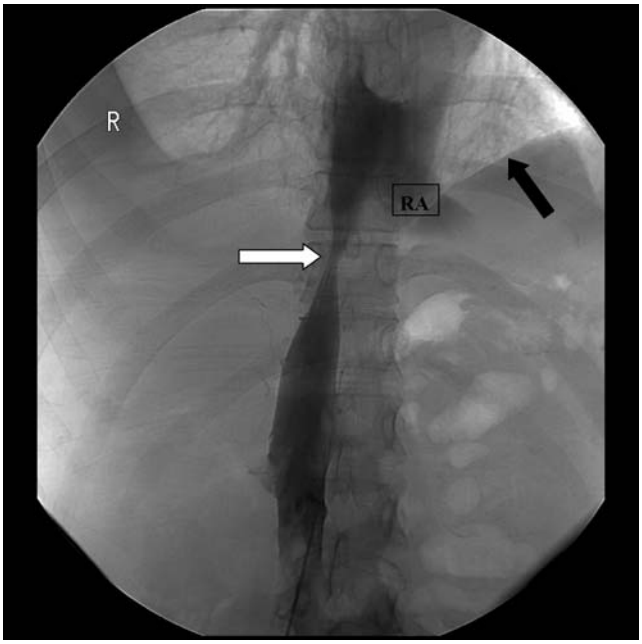

Figure 1 The *white arrow* on this inferior venacavogram demonstrates the area of narrowing within the retrohepatic vena cava. The *black arrow* delineates the left diaphragm. The boxed "*RA*" represents the right atrium.

significant 10 mmHg gradient across this lesion. A 20-mm self-expanding Gianturco stent (Cook Medical, Bloomington, IN, USA) was placed across the stenosis (Fig. 2, white bracket) which decreased the pressure gradient to 1 mmHg.

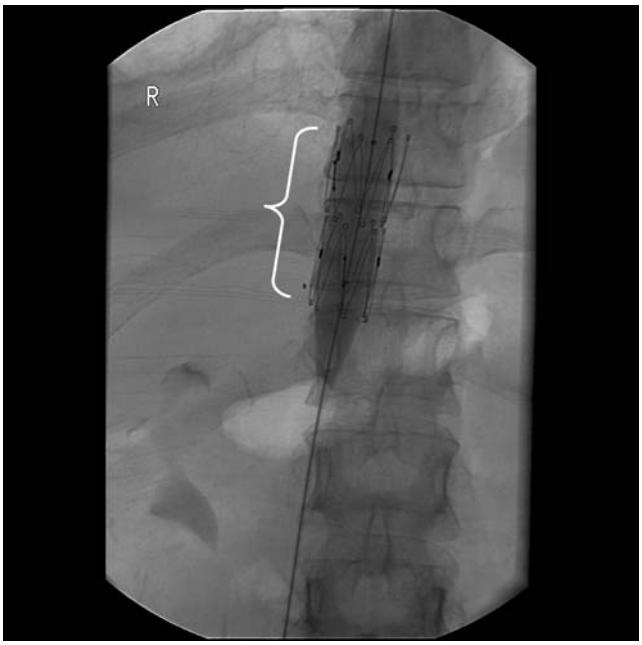

Figure 2 The *white bracket* in this contrast-enhanced fluoroscopic image demonstrates the 20-mm self-expanding Gianturco stent has been deployed across the area of stenosis within the retrohepatic inferior vena cava.

After this procedure, the patient's total bilirubin gradually decreased, and she was discharged on hospital day 18 with a level of 6.5 mg/dl. At follow-up appointments at 2 and 8 weeks, she had total bilirubin levels of 3.0 and 1.6 mg/dl, respectively.

Discussion

Torsion or rotation of the remnant left liver into the right subphrenic space is a potential cause of venous outflow obstruction (Fig. 3). This can occur by external compression on the IVC or kinking of the left hepatic vein. The phenomenon has only been reported in case reports.[1–4] One group examined the left hepatic venous outflow by Doppler ultrasound immediately after right hepatectomy and found significant decreases in flow velocity with the remnant liver in the spontaneous position.[5] Their solution is hepatopexy of the remnant liver by fixing the divided falciform ligament to the abdominal wall, thereby returning the liver to its anatomical position.

Critics of routine pexy of the remnant liver argue that portal flow to the liver should improve because of the more vertical and thus aligned left portal vein. While this may be theoretically true, it does not account for the left hepatic vein which can kink and contribute to hepatic outflow obstruction.

The long-term data demonstrate that IVC stent placement for the treatment of Budd-Chiari syndrome is effective and reliable. This treatment modality is specifically useful when there is a short segment of obstruction either at the IVC or ostium of a main hepatic vein. Over a 7-year follow-up period, one group had a 96.7% patency rate.[6]

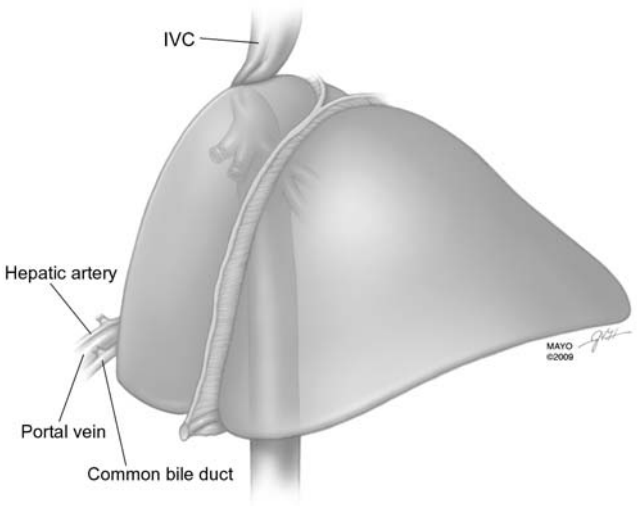

Figure 3 This is a depiction of the proposed mechanism of injury: torsion of the remnant left liver about the IVC causing outflow obstruction and Budd-Chiari syndrome.

Various reports of metallic stent placement for treatment of other causes of venous outflow obstruction abound the literature including patients with intractable ascites due to polycystic liver disease,[7] patients with malignant liver tumors,[8] and post-right lateral sector living-donor liver transplantation.[9] Patients should be maintained on anticoagulation for at least 6 months following placement of the stent.

Kishi et al. analyzed the physiologic effects of stent placement for caval obstruction secondary to malignancy.[8] As expected, the immediate effect of IVC stent was recovery of caval flow. Secondary effects included increased atrial filling potentially leading to pulmonary edema and tachyarrhythmias, prominent diuresis secondary to increased renal blood flow and decrease in edema and ascites caused by migration of extravascular fluid into the intravascular space. Our patient did not experience the cardiac effects, but she did diurese 3.5 L of urine on post-procedure day 1, and her ascites did decrease following stent placement.

In summary, we report the case of a 46-year-old female who experienced hyperbilirubinemia following right hepatectomy for colorectal metastases. Extensive workup revealed a stenosis in the retrohepatic inferior vena cava likely secondary to torsion of the remnant liver. She was managed successfully with placement of a metallic stent across the area of stenosis with resultant normalization of her hyperbilirubinemia. We suggest that hepatopexy using the divided falciform ligament should be considered routine practice following right hepatectomy to prevent this rare but potentially deadly complication of remnant liver torsion and outflow obstruction.

Conflicts of Interest None

References

1. Benesch M, Urban C, Deutschmann H, Hausegger KA, Hollwarth M. Management of Budd-Chiari syndrome by hepatic vein stenting after extended right hepatectomy. J Pediatr Surg 2002;37(11):1640–1642.
2. Paineau J, Bourgoin S, Letessier E, Hamy A, Visset J. Acute Budd-Chiari syndrome following hepatectomy. Apropos of two cases. Journal de Chirurgie (Paris) 1993;130(11):453–456.
3. Pitre J, Panis Y, Belghiti J. Left hepatic vein kinking after right hepatectomy: a rare cause of acute Budd-Chiari syndrome. Br J Surg 1992;79(8):798–799.
4. Sequeira FW, Weber TR, Smith WL, Careskey JM, Cairo MS. Budd-Chiari syndrome caused by hepatic torsion. AJR Am J Roentgenol 1981;137(2):393–394.
5. Ogata S, Kianmanesh R, Belghiti J. Doppler assessment after right hepatectomy confirms the need to fix the remnant left liver in the anatomical position. Br J Surg 2005;92(5):592–595.
6. Zhang CQ, Fu LN, Xu L, Zhang GQ, Jia T, Liu JY, Qin CY, Zhu JR. Long-term effect of stent placement in 115 patients with Budd-Chiari syndrome. World J Gastroenterol 2003;9(11):2587–2591.
7. Grams J, Teh SH, Torres VE, Andrews JC, Nagorney DM. Inferior vena cava stenting: a safe and effective treatment for intractable ascites in patients with polycystic liver disease. J Gastrointest Surg 2007;11(8):985–990.
8. Kishi K, Sonomura T, Fujimoto H, Kimura M, Yamada K, Sato M, Juri M. Physiologic effect of stent therapy for inferior vena cava obstruction due to malignant liver tumor. Cardiovascular Interventional Radiology 2006;29(1):75–83.
9. Tanimoto Y, Tashiro H, Itamoto T, Toyota N, Kohashi T, Amano H, Ohdan H, Ishiyama K, Oshita A, Asahara T. Hepatic venous outflow obstruction after right lateral sector living-donor liver transplantation, treated by insertion of an expandable metallic stent. J Hepatobiliary Pancreatic Surg 2008;15(2): 228–231.

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HOW I DO IT

Reconstruction of the Common Hepatic Artery at the Time of Total Pancreatectomy Using a Splenohepatic Bypass

Matthias H. Seelig · Orlin Belyaev · Waldemar Uhl

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Abstract Arterial involvement by a periampullary adenocarcinoma is often a contraindication for resection, since an R0 resection cannot be achieved. This is usually observed in cases with involvement of the superior mesenteric artery. Involvement of the common hepatic artery, however, requires a bypass procedure if the gastroduodenal artery was divided during the resection. In such cases, the splenic artery can be used as an inflow-source provided that there is no stenosis of the celiac trunk and the splenic blood flow is preserved via the short gastric arteries. We describe a technique used in four cases for the reconstruction of the common hepatic artery following a segmental resection of this vessel en bloc with a periampullary tumor during pancreatectomy. The inflow is maintained by a splenohepatic bypass using the splenic artery.

Keywords Common hepatic artery · Pancreatectomy · Splenohepatic bypass

Introduction

The standard procedure for resection of periampullary tumors is a pancreaticoduodenectomy according to the classic technique of Whipple or in the pylorus-preserving modification of Traverso–Longmire. In cases of locally advanced or multicentric tumors, or when the remaining pancreas is not suitable for a pancreaticojejunostomy, a total pancreatectomy with splenectomy may be performed.[1] Such a procedure carries the risk of significant morbidity, but mortality has recently fallen to less than 5% for pancreaticoduodenectomy at high-volume centers of excellence for pancreatic surgery.[2] As experience has increased, even multivisceral resections or resections involving venous and/or arterial reconstructions for locally advanced tumors can nowadays be performed without significantly increasing the perioperative risk. However, wedge resections or complete resections with end-to-end anastomosis of the superior mesenteric or the portal vein are still much more common than arterial reconstructions for local tumor involvement.[3] In general, involvement of the celiac trunk or the superior mesenteric artery is regarded as a sign of unresectability. A thorough evaluation of the visceral arteries using a computed tomography (CT) or magnetic resonance angiography is mandatory before any pancreatic resection since recent data confirmed that undetected stenoses are more often present than anticipated and may lead to significant postoperative ischemic complications.[4,5] However, it should be clear that not all stenoses become problematic. This is particularly true if the patient has a replaced right hepatic artery that often is well outside of the resection zone.

Stitzenberg et al. reported on 12 patients with resection of the celiac trunk (n=10) or the hepatic artery (n=2) during resection of pancreatic adenocarcinoma following neoadjuvant radiochemotherapy. Reconstruction was performed using venous interposition grafts. There was no postoperative death, and median survival following resection was 17 months (1–36 months) with a 3-year survival of 17%.[6]

Besides venous or prosthetic interposition grafts, the proper hepatic artery may be reconstructed by using the gastroduodenal artery.[7] However, this technique can only

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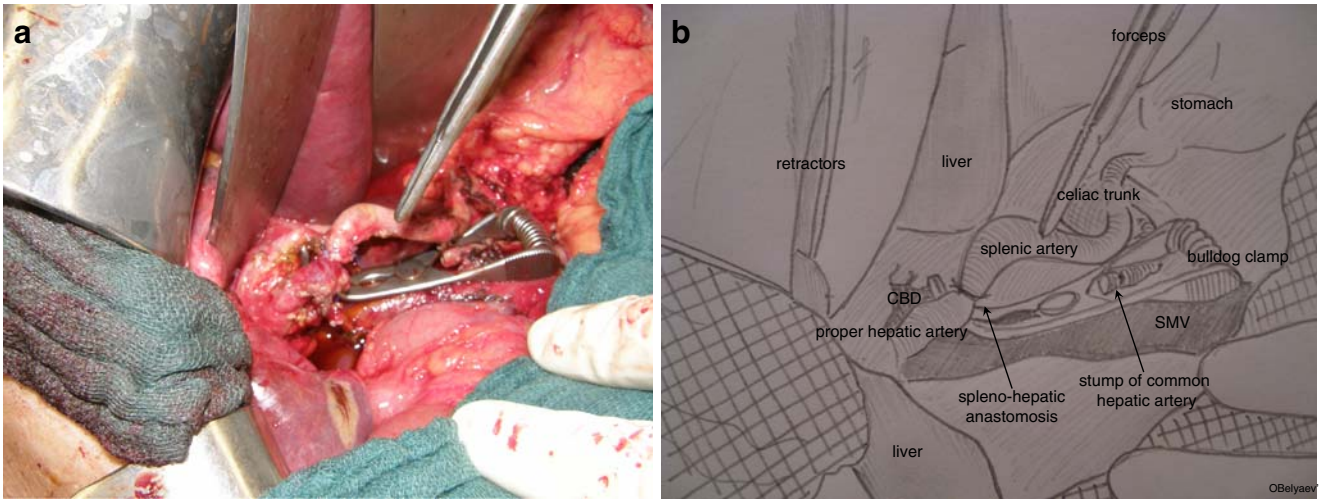

Fig. 1 **a** Intraoperative image of the final spleno-hepatic bypass. A bulldog clamp is placed on the proximal common bile duct. The forceps point to the splenic artery. **b** Explanation of the intraoperative image. *SMV* superior mesenteric vein, *CBD* common bile duct.

be chosen when the common hepatic artery is intact. When the common hepatic artery has to be sacrificed for oncologic reasons, the splenic artery is a potential option for reconstruction. It is occasionally possible to excise the common hepatic artery but leave the gastroduodenal artery intact, thus maintaining the arterial flow in the proper hepatic artery via the gastroduodenal artery.

When a vascular reconstruction is required, prosthetic material should be avoided in general due to potential risk of infection. Venous interposition grafts require additional harvesting from somewhere in the abdomen or from the extremities, and two anastomoses have to be performed. The use of the splenic artery described herein can easily be performed and requires only one anastomosis.

Technique

In order to proceed with this procedure, tumor involvement of the common hepatic artery must be verified. An isolated stenosis of the splenic artery must also be excluded in the preoperative imaging. The tumor should otherwise be resectable. In the course of a standard pancreatoduodenectomy, the gastroduodenal artery is isolated, clamped, and then divided between 4-0 nonresorbable polypropylene ligatures. For this procedure, the gastroduodenal artery need not be divided, as it is being resected en bloc with the common hepatic artery. The patient is heparinized, and after obtaining proximal and distal vascular control, the common hepatic artery is divided proximally near the celiac trunk.

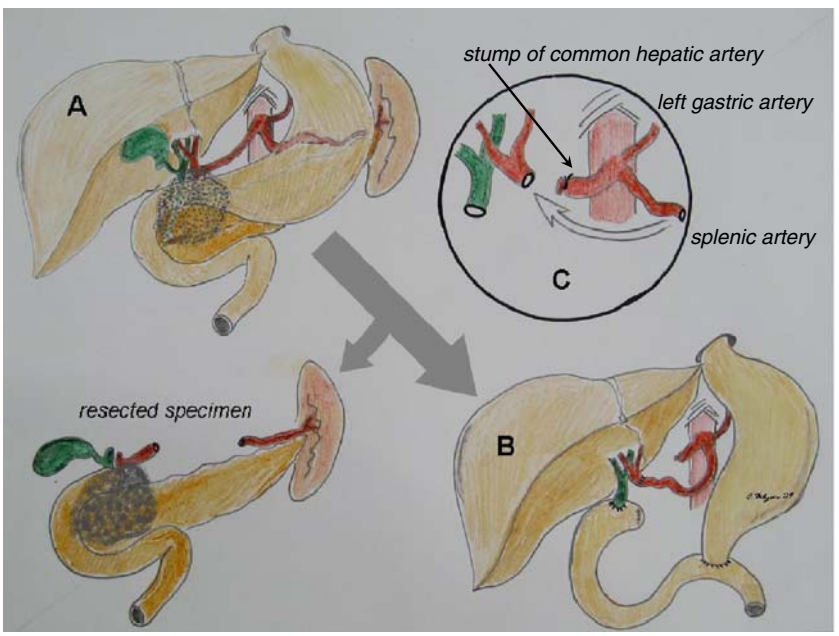

Fig. 2 Technique of the spleno-hepatic bypass after resection of the common hepatic artery. **a** A large T4N1M0 cancer infiltrating the common hepatic artery. **b** Final view of the completed reconstruction. **c** Close view of the arterial transfer from the celiac trunk.

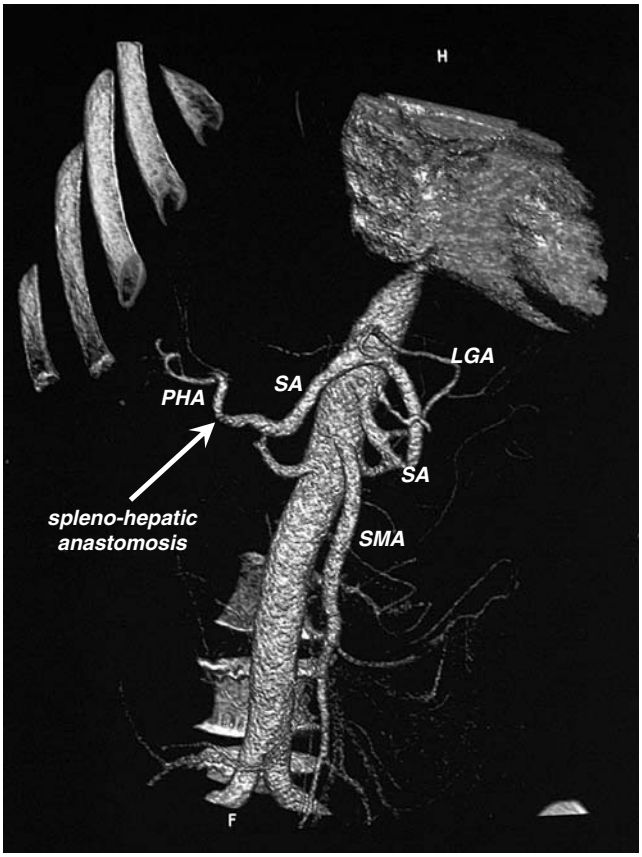

Fig. 3 A CT angiography 6 months postoperatively. The bypass is open; however, there is a moderate stenosis at the proximal splenic artery. *LGA* left gastric artery, *PHA* proper hepatic artery, *SA* splenic artery, *SMA* superior mesenteric artery. The *arrow* points to the intact spleno-hepatic anastomosis.

The distal transection site lies just proximal to the bifurcation of the proper hepatic artery. The pancreatic head resection is completed as usual, after division of the common bile duct and the duodenum in the post-pyloric region. Care should be taken to divide only the proximal part of the gastrocolic ligament in order to preserve a sufficient blood flow to the spleen via the short gastric vessels if a spleen preserving pancreatectomy is intended. When a distal pancreatic resection is required as in cases of positive resection margins, multicentric tumors, or very soft pancreatic tissue, the pancreatic tail should meticulously be dissected from the splenic artery. The splenic vein may be divided near the venous confluence using 2-0 polypropylene ligatures. The splenic artery is then completely mobilized over a segment of about 5–6 cm. The length should allow a tension-free anastomosis to the proximal hepatic artery. The splenic artery is divided, its distal end being closed with a 2-0 nonresorbable suture. The proximal part is bent over from the left to the porta hepatis on the right. A spatulated end-to-end anastomosis between the splenic artery and the proper hepatic artery is performed using interrupted 7-0 polypropylene sutures (Figs. 1 and 2). After completion of the anastomosis, a pulsatile flow is confirmed by palpation in the hepatic artery. Figure 3 shows a CT angiography of the bypass during a follow-up examination.

Comment

Reconstructions of the hepatic artery are usually performed using a saphenous vein graft, which can be easily anastomosed to any artery that allows a sufficient inflow. A drawback is the fact that two anastomoses have to be performed. A prosthetic graft carries also the risk of potential contamination. The splenic artery usually offers plenty of length required to reach the porta hepatis. Furthermore, only a single anastomosis has to be performed, and there is no mismatch of the vessel diameter. Care should be taken to prevent a kinking of the artery, which may result in an early thrombosis. As long as the short gastric arteries are preserved in a spleen preserving pancreatectomy, a splenic infarction is not to be expected. However, the spleen will usually be removed en bloc with the specimen for oncologic reasons. The reported technique of reconstruction of the hepatic artery widens the armamentarium of the pancreatic surgeon in selected cases where an R0 resection can only be achieved by resecting the common hepatic artery together with the pancreas.

References

1. Müller MW, Friess H, Kleeff J, Dahmen R, Wagner M, Hinz U, Breisch-Girbig D, Ceyhan GO, Büchler MW. Is there still a role for total pancreatectomy? Ann Surg 2007;246:966–975.
2. Reddy S, Wolfgang CL, Cameron JL, Eckhauser F, Choti MA, Schulick RD, Edil BH, Pawlik TM. Total pancreatectomy for pancreatic adenocarinoma. Evaluation of morbidity and long-term survival. Ann Surg 2009;250:282–287.
3. Yekebas EF, Bogoevski D, Cataldegirmen G, Kunze C, Marx A, Vashist YK, Schurr PG, Liebl L, Thieltges S, Gawad KA, Schneider C, Izbicki JR. En bloc vascular resection for locally advanced pancreatic malignancies infiltrating major blood vessels: perioperative outcome and long-term survival in 136 patients. Ann Surg 2008;247:300–309.
4. Farma JM, Hoffman JP. Nonneoplastic celiac axis occlusion in patients undergoing pancreaticoduodenectomy. Am J Surg 2007;193:341–344.
5. Gaujoux S, Sauvanet A, Vullierme M-P, Cortes A, Dokmak S, Sibert A, Vilgrain V, Belghiti J. Ischemic complications after pancreaticoduodenectomy. Incidence, prevention, and management. Ann Surg 2009;249:111–117.
6. Stitzenberg KB, Watson JC, Roberts A, Kagan SA, Cohen SJ, Konski AA, Hoffman JP. Survival after pancreatectomy with major arterial resection and reconstruction. Ann Surg Oncol 2008;15:1399–1406.
7. Sarmiento JM, Panneton JM, Nagorney DM. Reconstruction of the hepatic artery using the gastroduodenal artery. Am J Surg 2002;185:386–387.

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REVIEW ARTICLE

Congenital Anomalies of the Gastrointestinal Tract Diagnosed in Adulthood—Diagnosis and Management

George Vaos · Evangelos P. Misiakos

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Abstract
Introduction Congenital anomalies of the gastrointestinal tract are a significant cause of morbidity in children and less frequently in adults. In rare cases, they may run undetected during childhood and may present during adolescence. These abnormalities include developmental obstructive defects of the duodenum and the small intestine, anomalies of rotation and fixation, intestinal duplications, and anomalies of the colon and rectum.
Discussion When detected in adulthood, they may require different evaluation and surgical correction. Some of these anomalies should be managed surgically as soon as they cause symptoms. Others may cause persistent problems in adulthood requiring medical management for years. Herein, we present a comprehensive review of all the different ways of diagnosis and management of these anomalies reported in the literature.

Keywords Congenital anomalies · Gastrointestinal tract · Adult

Introduction

Congenital anomalies of the gastrointestinal (GI) tract commonly present in the neonatal period or early infancy. Some of them can have life-threatening consequences if diagnosis is delayed. Therefore, the prognosis is largely dependent upon early diagnosis and appropriate management and surgical treatment. However, in rare cases, they can present de novo during adolescence. These lesions may form an important part of pathology in patients along time out of the cradle. When diagnosed in adulthood, they may require a different perspective than in children regarding management and surgical correction. In this study, we present descriptions of the most common anomalies which may be encountered in the adult. We propose management options according to the current medical literature.

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Congenital Anomalies

Adult Idiopathic Hypertrophic Pyloric Stenosis

Congenital hypertrophic pyloric stenosis is a benign disease caused by hypertrophy of the circular muscle fibers of the pylorus. It is manifested usually during the first 2 months of life. Its incidence is approximately 0.25–0.5% of all births. A mild form of congenital pyloric stenosis may occasionally present later in adult life.[1] The exact occurrence of this form cannot be estimated accurately, since the majority of these patients are asymptomatic for years. Zavala et al.[2] reported on a family with both congenital and adult type of hypertrophic pyloric stenosis. This hypothesis is further supported by the fact that approximately 80% of patients with the adult form of the disease are men, which is in accordance with the male predominance of congenital pyloric stenosis.[3] In addition, this form of primary pyloric stenosis should be differentiated from the secondary form,

which is caused by other diseases of the gastrointestinal tract, such as peptic ulcer disease, hypertrophic gastritis, or malignancy.[4]

In the adult idiopathic hypertrophic pyloric stenosis (AIHPS), the pylorus is bulbous or fusiform, with its thickest portion at the pyloroduodenal junction[5] (Fig. 1). Microscopically, there is a substantial hypertrophy of the circular and occasionally of the longitudinal muscle in a focal or diffuse fashion.[6,7]

Clinical diagnosis depends primarily on the specific symptomatology, which consists of symptoms of delayed gastric emptying, without the presence of pain. Other diseases which may cause delayed gastric emptying such as diabetes mellitus, scleroderma, gastroparesis, or secondary pyloric stenosis should be ruled out.[8]

AIHPS can coexist with other rare congenital anomalies, such as congenital hypothyroidism, congenital diaphragmatic hernia, congenital short bowel, jejunal atresia, and recessive polycystic kidney disease.[2,9]

The radiologic and endoscopic studies are often nonspecific. In upper GI series, the diagnosis should be suspected in case there is elongation of the pyloric canal accompanied often by a marked dilatation of the stomach.[7,9] In AIHPS, the narrowed pyloric canal may be seen as an extremely thin line of barium (string sign).[10] A marked thickening of the pyloric muscle may produce a convex indentation at the base of the duodenal bulb, causing a mushroom-like deformity (Kirklin's sign).[11] In addition, the presence of a barium-filled cleft between the hypertrophied muscle and the fibers of the pylorus itself can project into either one or both sides of the pylorus proximal to the base of the bulb (Twining's sign).[12] However, none of the above signs are pathognomonic, whereas the presence of two or more of them strengthens the radiologic diagnosis.[7] Endoscopy is also useful for diagnosis: a fixed narrowed pylorus with a smooth border is the classic finding and is described as a "donut" or as the cervix sign.[5,13] Another feature is the failure of the pylorus to close completely.[14] Moreover, intubation of the duodenum with the endoscope can be unfeasible.

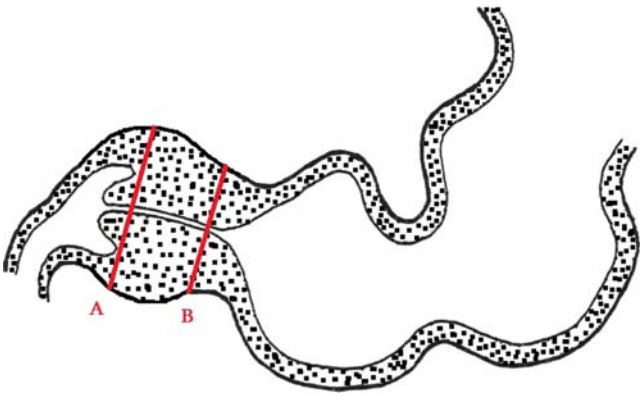

Figure 1 In AIHPS, the pylorus is bulbous or fusiform, with its thickest portion at the pyloroduodenal junction (*A*=pyloroduodenal junction, *B*=pylorogastric junction).

As for therapy, the first aim is to rule out carcinoma histologically, with a full thickness biopsy.[15] Endoscopic dilatation of the pylorus has been suggested for patients with a high surgical risk but carries a high recurrence rate.[6,14] The Ramstedt pyloromyotomy, which is often used in children, is troublesome in adults because it may cause mucosal ulceration or pyloric scarring with only partial relief.[4,14]

Pyloroplasty is an acceptable option (Fig. 1); however, there is a trend for recurrent obstruction. Brahos et al.[16] first performed the double pyloroplasty technique, a posterior myotomy combined with the classical Weinberg modification of the Heineke-Miculicz pyloroplasty. This technique enables the surgeon to obtain biopsies, and it helps to avoid a gastric resection, especially in high-risk patients.

However, a distal gastric resection with Billroth I and II anastomosis is the most recommended procedure,[5,15] especially for patients with a thick pylorus, which renders a pyloroplasty technically difficult (Table 1).

The introduction of laparoscopic pyloromyotomy by Alain et al. in 1991[17] has opened new horizons in the treatment of hypertrophic pyloric stenosis. The laparoscopic approach carried the general advantages of laparoscopic surgery, but it had a considerable complication rate when it was first applied in children.[18] There are scattered reports of adult cases with AIHPS, which were treated laparoscopically with satisfactory results.[14,19]

Congenital Duodenal Anomalies

Congenital duodenal anomalies are defects in the embryologic development of the foregut. While the primitive foregut undergoes lengthening and rotation in the early embryonic life, the hepatobiliary and pancreatic anlagen begin as buds at the middle of the duodenum and gradually grow and rotate. During this period, duodenal atresias, intraluminal webs, annular pancreata, and various malrotations may develop. The annulus may completely or partially encircle the duodenum and may loosely be attached to the duodenal serosa or occasionally may be interdigitated with the muscularis mucosa of the duodenum. As for the webs, there are complete duodenal atresias or imperforate webs, intraluminal imperforate webs, and perforated webs with eccentric or central apertures. Most of the webs occur in areas of fusion or visceral outgrowth, hence their propensity to occur in the ampullary region.[20] The incidence of these anomalies in the pediatric population is estimated to be one in 20,000 to 40,000 births, with incomplete obstructive lesions accounting for only 2% of them.[20,21] Duodenal stenosis from annular pancreas is also

Table 1 Treatment Modalities of the Main Congenital Anomalies of the GI Tract in Adults

Congenital anomaly	Surgical treatment	GR	LE
Hypertrophic pyloric stenosis	Distal gastric resection, pyloroplasty	C	4
Duodenal webs	Duodenotomy, web excision	C	4
Annular pancreas	Duodenojejunostomy	C	4
Intestinal malrotation			
Intestinal obstruction	Ladd procedure	A	1c
Chronic obstruction	Ladd procedure	C	4
Asymptomatic	second look	C	4
Gastrointestinal duplication	Cyst excision, intestinal resection	C	4
Jejunoileal atresia and stenosis	Intestinal resection (infanthood)	A	1c
Meckel's diverticulum			
Complicated	Ileal resection, diverticulectomy	A	1c
Incidental finding	Observation	B	3a

GR grade of recommendation, *LE* level of evidence

very rare in adults. In fact, Ravitch[22] found only three cases of this anomaly in 20,000 autopsies in John Hopkins Hospital.

The delayed presentation of these anomalies in the adolescent or adult period can hardly be explained. Total duodenal obstruction is not compatible with long-term survival. However, there are numerous reports describing annular pancreata and duodenal webs in the second, third, and later decades of life. These isolated cases may survive with liquid diet for years.[21] In such cases, the presence of a dilated stomach with a proximal duodenal bulb suggests a gradual loss of peristaltic action to overcome a narrowing of the descending portion of the duodenum.

Clinical symptomatology consists of postprandial epigastric fullness, nausea, vomiting, and weight loss. Duodenal web patients may suffer from peptic ulcer disease, but this is not the case in patients with annular pancreata.[21] In the latter group of patients, the development of acute pancreatitis in the annulus causes acute duodenal obstruction, with subsequent resolution of the pancreatic inflammation allowing relief of the obstruction.[23] In some patients with annular pancreata, true duodenal stenosis may gradually develop, due to repeated attacks of pancreatitis in the annular tissue or from reactive fibrosis in the duodenal wall.[24]

Diagnosis of both lesions is efficiently done with upper GI contrast studies. A transverse diaphragm in the descending duodenum with an eccentric or central aperture may be seen in patients with webs. The annular pancreas can be diagnosed with computed tomography (CT) and magnetic resonance imaging, whereas in upper GI series a smooth or tapered narrowing of the second part of the duodenum with dilatation of the proximal bulb can be seen.[24] In addition, endoscopic retrograde cholangiopancreatography can delineate the ductal system of the annulus and its junction with the ventral pancreatic and biliary ducts.[20]

In the treatment of duodenal webs, bypass procedures were used in the past but have been largely abandoned. The most widely used procedure now is longitudinal duodenotomy followed by excision of the web, mucosal reapproximation, and transverse closure of the duodenum. During the excision of the web, intubation of the bile duct and the ampulla with a probe should be done, as to avoid damage in the biliopancreatic sphincteric mechanism.[20] As for the annular pancreas, resection of the annulus was done frequently in the past and was often followed by pancreatic fistula formation. In addition, division of the annulus did not necessarily relieve the obstruction, since the narrowed duodenum might be permanently stenotic due to the intermingling of the annular tissue with the duodenal wall.[24] Nowadays, the annular constriction of the duodenum could be bypassed by duodenoduodenostomy or duodenojejunostomy to the first duodenal portion.[20] A retrocolic duodenojejunostomy, favored by Warren and associates,[24] is the procedure of choice in adults, as it offers decompression of the proximal duodenum and a satisfactory bypass.

The laparoscopic approach has been introduced in the treatment of congenital duodenal anomalies in adults. There has been a report of two cases of annular pancreas treated successfully with laparoscopic gastrojejunostomy.[25]

Intestinal Malrotation

The term "intestinal malrotation" refers to a spectrum of anomalies involving the position and peritoneal attachments of the small and the large bowel. A wide diversity of anatomic anomalies, ranging from a not-quite-normal intestinal position to complete nonrotation or to reverse rotation, results in a wide variety of clinical manifestations. Progress in the understanding of the pathogenesis of intestinal malrotation was done only after normal embryology of the gastrointestinal tract was described, first by

Meckel in 1817 and then more extensively by Mall in 1987.[26,27]

However, the embryological analysis of the disease was not completely understood until 1923, when Dott[28] described the anatomic variations of malrotation and correlated them with points of aberrant or failed embryologic development. The incidence of malrotation in the general population is not known. It is estimated to range from one in 6,000 to one in 200 of live births.[29,30] Most cases (90%) present during the first year of life. However, a small percentage of individuals with malrotation enter adulthood with it undetected.[29,31]

The most significant anomalies of rotation and fixation are nonrotation, malrotation, and reverse fixation. In nonrotation, the most frequently encountered anomaly, the midgut returns to the peritoneal cavity after rotating only 180° instead of the normal 270°. The postarterial limb returns to the abdominal cavity first instead of last. Therefore, the small intestine lies on the right side of the abdomen and the colon on the left. The ileum crosses the midline from right to left to enter the cecum. Adult patients with nonrotation are usually asymptomatic, but often volvulus may accompany this anomaly.[32] In malrotation, the prearterial segment, which returns to the abdomen first, is usually in a normal position, and the degree of malrotation is indicated by the position of the cecum. Thus, the cecum may be on the left side, higher than normal on the right side, or in an intermediate position (Fig. 2). Reverse rotation occurs when the postarterial segment of the midgut returns to the abdomen first. The cecum begins its migration and passes to the right behind the superior mesenteric artery. Finally, the transverse colon lies behind the duodenum and is separated from it by the superior mesenteric artery.[31,32]

Clinical presentation varies according to the degree and type of malrotation. In itself, abnormal positioning of the intestine does not cause symptoms. These arise from the abnormal position and fixation of the bowel, which allow the bowel to twist. The obstruction may be complete or partial and results from midgut volvulus or, less frequently, Ladd bands or internal hernia. Therefore, the clinical manifestations of rotation anomalies may be identical to those of proximal small-bowel obstruction (complete or partial), with or/without symptoms secondary to vascular occlusion.[32]

Moreover, there are patients with chronic abdominal complaints, including pain and intermittent obstruction or with atypical symptoms similar to those of common abdominal conditions.[31] Patients presenting with bilious vomiting, acute abdominal pain, fever, tachycardia, and peritoneal tenderness on physical examination should be suspected of having an abdominal disaster. Confirmatory laboratory tests include an elevated white blood cell count and acidosis with an elevated base deficit and lactate level. In addition, abdominal pain usually cannot be relieved with nasogastric decompression. These patients require immediate exploratory laparotomy, which usually reveals midgut volvulus and vascular compromise with resultant intestinal ischemia. Patients with chronic abdominal complaints usually present with recurrent episodes of crampy abdominal pain, nausea, and bilious vomiting. These episodes may have been present or may have a more recent onset. Delay in diagnosis is common in the majority of these patients.[31,33] Anatomic finding at surgery in these patients include mixed rotation or nonrotation with intermittent or partial midgut volvulus, partial intestinal obstruction due to Ladd bands (Fig. 3), or internal hernias. A third group of patients may be asymptomatic or have atypical complaints and suddenly come to our attention with an acute abdominal condition unrelated to malrotation but with bizarre abdominal findings due to their unusual gastrointestinal anatomy. For example, we may have cecal perforation in a patient with nonrotation with pain localized to the left abdominal quadrant or appendicitis in a patient with a subhepatic cecum with pain localized in the right upper quadrant.[31] Preoperative diagnosis may be difficult in these patients and usually is done intraoperatively.

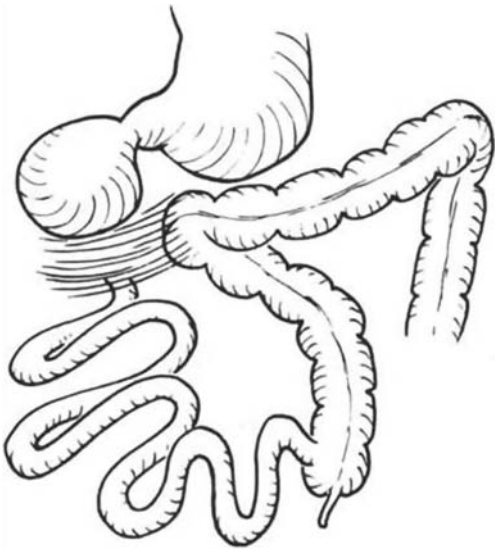

Figure 2 In malrotation, the cecum most frequently lies on the left side of the abdomen; the anomaly is frequently associated with the presence of Ladd bands, which may compress the duodenum.

The diagnosis of these anomalies in adults usually requires a variety of diagnostic modalities, such as plain abdominal radiographs, upper GI series, and CT scan.

Plain abdominal radiography may show signs of abnormally located bowel, i.e., small-bowel markings mainly on the right and large-bowel markings mainly on the left. Such X-rays may prompt further evaluation. Upper GI series is the standard of reference in the diagnosis of malrotation. It

can indicate the level and nature of obstruction. They may show a duodenal–jejunal junction which fails to cross midline and is located below the level of the duodenal bulb or malposition of the right colon and the cecum. When a volvulus is present, the small bowel usually has a "corkscrew" appearance because it twists around the superior mesenteric artery.[32] CT scan may reveal right-sided small intestine and a left-sided cecum, with/without an inverse relationship of the superior mesenteric artery and superior mesenteric vein, a highly indicative sign of malrotation. Midgut volvulus is seen as a dilated fluid-filled stomach, thick-walled loops of ischemic right-sided small intestine, and often free intraperitoneal fluid.[34] Three-dimensional helical CT may reveal twisting of the superior mesenteric vein about the superior mesenteric artery. In general, identification of an abnormality requires meticulous diagnostic evaluation with additional diagnostic modalities.

Treatment should be addressed to each individual patient according to the degree and severity of malrotation and the timing of diagnosis. Patients with intestinal obstruction should undergo an explorative laparotomy. At surgery, the volvulus should be reduced and any nonviable bowel should be resected. Treatment of the underlying malrotation includes lysis of all adhesions and abnormal bands, straightening of the duodenum so it descends directly into the right lower quadrant, appendectomy, and widening of the small-bowel mesentery (Ladd procedure)[35,36] (Table 1). Cecopexy is not recommended since there is no proof it has anything to offer in terms of perioperative or postoperative morbidity.[31,33,37] Patients with chronic abdominal complaints should undergo a thorough radiologic evaluation before proceeding to surgical intervention. At surgery, when the obstruction is found secondary to Ladd bands, all abnormal intestinal attachments should be lysed. When an internal hernia is found, the hernia should be reduced; the sac should be resected; and the hernia defect should be closed. When there is reverse rotation, any adhesions between the mesentery of the small and the large intestine should be lysed, and the intestine should be rotated clockwise 360°, so as to create a condition of nonrotation. A Ladd procedure should be added in all above cases[31] (Table 1).

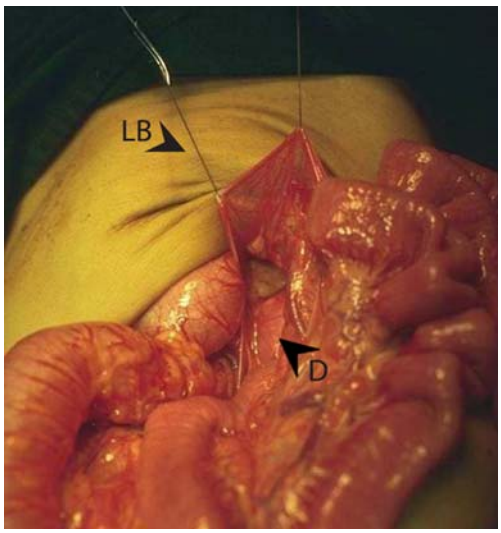

Figure 3 Complete dissection of the Ladd bands (*LB*), before division, on both the lateral and medial aspect of the duodenum (*D*).

There is an increasing use of laparoscopy for the treatment of malrotation in children as well as in adults.[38] The Mayo Clinic series,[39] the largest one reported for adults, confirmed that laparoscopic Ladd procedure is safe, feasible, and effective. In addition, it offers the patients the benefits of laparoscopy, such as early recovery and short hospital stay. Laparoscopy also is helpful when the diagnosis of malrotation is not certain. Mazziotti et al.[40] have developed a method to determine whether laparoscopic Ladd procedure is indicated: if the length between the duodenojejunal junction and the ileocecal valve is less than half the transverse diameter of the peritoneal cavity, the procedure is indicated to prevent volvulus. However, when laparoscopy is used, conversion to open procedure is common because of the difficulties encountered. Nevertheless, some authors[41] support that laparoscopy is not suitable for acute conditions, such as midgut volvulus, due to the excessive intestinal distension.

Malrotation that is discovered at the time of exploratory laparotomy/laparoscopy for an emergency condition, such as appendicitis or hollow viscus perforation, should be left to treat on an elective basis. If malrotation subsequently gives rise to symptoms or if the patient decides its correction, then malrotation can be treated on a later date.

There is a substantial controversy regarding the surgical correction of malrotation in case it is discovered incidentally on radiologic examination, while the patient is asymptomatic. Since many patients remain asymptomatic for their entire life, certain authors support that operation is not justified unless the patients develops symptoms directly related to malrotation.[42,43] However, others advocate that surgical intervention is required anyway, due to the significant risk of midgut volvulus, even years after a symptom-free period.[44,45]

Several studies have indicated that certain anatomic characteristics, such as an abnormal position of the duodenal–jejunal junction or isolated malrotation of the cecum, may have some predictive value regarding the possibility of volvulus.[46] However, there are no official criteria by which the risk of volvulus can be predicted. In general, the decision for surgery in patients with asymptomatic malrotation should be made by the surgeon and the patient, after having discussed extensively the risks and benefits of the operative and nonoperative approaches.

Gastrointestinal Duplication

Gastrointestinal duplications are congenital malformations that can be encountered anywhere throughout the gastrointestinal tract, from the mouth to the anus. They occur mostly in pediatric patients but may occasionally run asymptomatic for years and present later in the adult life. They can be spherical cysts (Fig. 4) or tubular structures. They are attached to the wall of an adjacent part of the gastrointestinal tract and possess at least one exterior layer of smooth muscle and are lined with various types of gastrointestinal mucosa.[47] The lumen of the duplication cysts usually lies between the leaves of the mesentery but may be entirely separated, with a mesentery of its own, formed by splitting of the original. There have been many theories regarding its pathogenesis. The most dominant one supports that duplication cysts appear at an early stage of embryological development due to incomplete separation of the primitive gut from the notochord. This theory is supported by the fact that these formations often coexist with osseous anomalies of the axial skeleton.[48,49]

Gastric duplications are noncommunicating cysts usually located along the greater curvature of the stomach. Gastric cysts are very rare as they account for 2% to 7% of all gastrointestinal duplications.[50] They most often present with pain and vomiting.[51,52] They are usually diagnosed as a result of a complication, such as gastrointestinal bleeding.[51] Bleeding within the gastrointestinal tract may result from intussusception, peptic ulceration of the cyst lining, or necrosis of the cystic mucosa due to continuous pressure from the expanding cyst.[53,54] Gastric duplications communicating with the pancreatic duct may be a cause of recurrent pancreatitis or peptic ulceration.[55,56] Computed tomography and magnetic resonance imaging are common methods for evaluating tumors along the upper GI tract and may raise the suspicion for gastric duplication.[57] ^{99}Tc scintigraphy is also a valuable diagnostic tool because of its high specificity to identify gastric mucosa.[58] Very few reports so far have presented the use of laparoscopic surgery in the treatment of gastric duplications.[59] In the laparoscopic approach, the goal is to excise completely the gastric duplication without violation of the gastric lumen, whenever possible.

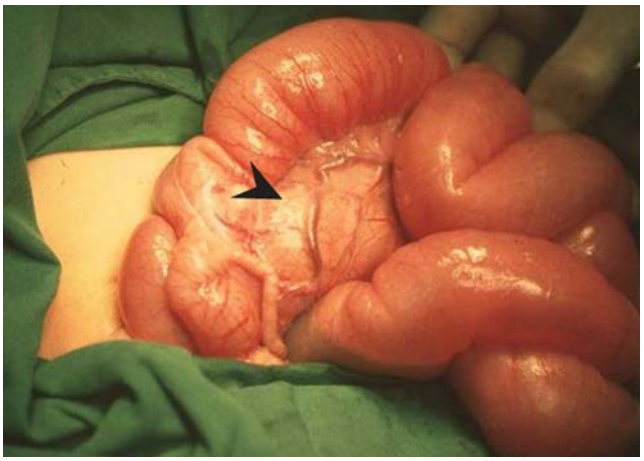

Figure 4 A spherical type of duplication cyst in the small bowel of an adolescent boy.

The small intestine is a more common site for these formations. Ileum is the most common site for gastrointestinal duplication, accounting for over 60% of cases.[60] Duplication in the small intestine can be asymptomatic for years but can present abruptly with lower gastrointestinal bleeding. These cases should undergo the routine diagnostic evaluation for gastrointestinal bleeding, but usually the source of bleeding is identified at laparotomy.[61] At surgery, the lesions should be resected along with a portion of the adjacent intestine. The mucosa of the duplication should be completely removed because, when mucosa remains, acid peptic ulceration from ectopic gastric mucosa may lead to bleeding and often requires reoperation.[53]

Colonic duplications are rare, accounting for 4–18% of all gastrointestinal duplications, with the cecum being the most common location. Colonic duplications are also asymptomatic for prolonged periods but may result in significant morbidity and mortality in case of complications, such as acute bowel obstruction or severe gastrointestinal hemorrhage.[61] Colonic cysts can be asymptomatic for years but usually present with pain and/or obstructive symptoms.[62] Occasionally, they may present with a complication, such as obstruction, bleeding, or constipation. Abrupt hemorrhage with hemodynamic instability may occur in case of a cyst lined with ulcerated mucosa which erodes into adjacent organs and/or vessels.[53,63] Cystic duplications can cause obstruction of the colon as a result of direct compression, intussusception, or volvulus whereas tubular duplications of the rectum may have direct communication with the perineum.[61,63] There are several reports of intestinal carcinomas found within duplication cysts.[62,64] Preoperative diagnosis is often difficult, and the radiographic findings may be nonspecific. Ultrasonography and computed tomography may be useful in obtaining a diagnosis.[53,63]

Treatment is reserved for symptomatic cases and usually includes excision of the cyst with the neighboring part of the intestine because of the intimate attachment of the common wall or because isolated resection of the cyst would compromise blood flow to the adjacent segment of the colon.[61,63,65] Cyst excision is mandatory for the possibility of malignant degeneration. Postoperative complications are nonspecific and include postoperative bleeding, infection, and bowel obstruction. However, in case of large duplication segments, injury to the normal intestine with resultant short bowel syndrome is also a possibility.[53]

Despite these problems, the overall outcome after surgery for intestinal duplications is generally favorable.

The laparoscopic approach has also been introduced in the treatment of duplications of the small and the large bowel in children[60] as well as in adults[66–68] with promising results.

Jejunoileal Atresia and Stenosis

Atresia and stenosis are common birth effects affecting the small intestine. The duodenum is the most common site, followed by the jejunum and the ileum; however, it can also affect multiple sites in the small intestine.[69] The approximate incidence in the Western societies has been reported to be approximately three to four per 10,000 births in the general population.[69–71] The mechanism responsible for its pathogenesis is not well clarified. Although in the 1950s the dominant theory was that intestinal atresia was the result of vascular accidents during the fetal life,[72] today most researchers support the hypothesis of the pivotal role of genetic and embryogenetic factors which lead to the development of this anomaly.[73]

This defect may take several forms, such as the apple-peel atresia, multiple intestinal atresia with short-gut syndrome, proximal jejunal atresia with megaduodenum, and colon atresia.[73,74] All above formations are usually discovered during the neonatal or infantile life and require immediate correction. However, long-term complications in these patients may present later during childhood or adolescence and may require reintervention.[75]

Meckel's Diverticulum

Meckel's diverticulum is a congenital blind pouch in the small bowel, which results from an incomplete obliteration of the vitelline duct during the fifth week of gestation. This entity took its name after Johann Friedrich Meckel the younger who first studied the diverticulum's anatomy and embryology.[76] For Meckel's diverticulum, the common rule found in every review book for general surgery is the "rule of twos," i.e., it is found in 2% of the population, twice as common in males, most frequently found in those less than 2 years of age, and usually 2 ft from the ileocecal valve.[77] For that reason, surgical residents begin searching for this anomaly with their first surgical exploration. However, a true diverticulum is rarely discovered in the adult (Fig. 5), and complications related to this anomaly rarely occur with increasing age.[78]

The development of this anomaly occurs with the failure of obliteration of the proximal vitelline duct during the seventh to eighth week of gestation. This diverticulum is categorized as a true diverticulum because it contains the normal layers of the small bowel. It may contain ectopic mucosa, such as gastric mucosa which is responsible for the adjacent ulceration of the ileum.[77] Pancreatic mucosa is the second most common ectopic mucosa found in this diverticulum. Occasionally, the diverticulum may be the site of a malignant tumor. Weinstein et al.[78] published the most thorough description of malignancy in Meckel's diverticulum: in a series of 80 malignant cases, there were 35 sarcomas, 29 carcinoids, and 16 adenocarcinomas.

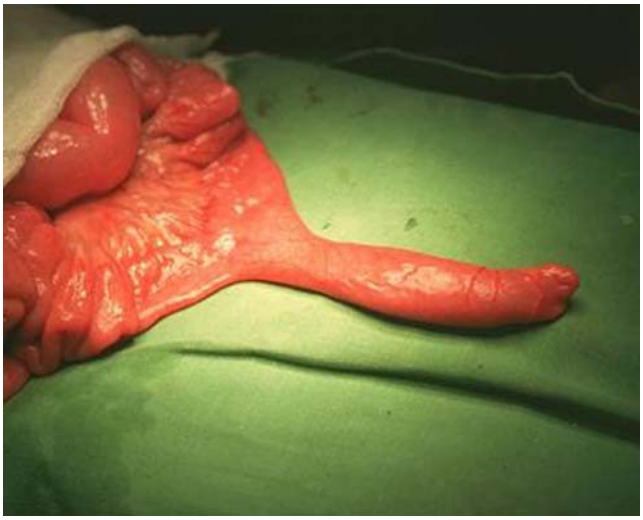

Figure 5 A Meckel's diverticulum discovered incidentally in a 16-year-old boy during an exploratory laparotomy for acute pain in the right iliac fossa.

Meckel's diverticulum usually does not give symptoms. A small percentage of patients may give symptoms, with the obstructive symptoms being the most prevalent in the adult, and they are most commonly due to intussusception, volvulus, inflammatory adhesions, diverticular strictures, enteroliths, or incarcerated hernia.[78–81] Inflammation (diverticulitis) and/or perforation are found in up to 20–30% of symptomatic patients and are often indistinguishable from acute appendicitis.[80] Bleeding is the most common complication in children and is reported in over 50% of cases.[82,83] In adults, bleeding is the presenting complaint in only 11.8% of cases.[79] Bleeding is usually minor, resulting in chronic anemia. Occasionally, it may cause massive lower gastrointestinal bleeding in adults, as several case reports describe in the literature.[77,84] However, it occurs less often than obstruction. Yamaguchi et al.[79], in a series comprising almost 50% adults, showed hemorrhage as being less common than obstruction at a rate of approximately 5:1 (54%:12%). Preoperative evaluation of Meckel's diverticulum is difficult, and routine radiological studies, such as plain abdominal radiograph, arteriography, upper GI series, and computed tomography, are often nondiagnostic and theretofore of limited diagnostic value.[85] In suspected symptomatic Meckel's diverticulum, preoperative evaluation includes ^{99m}Tc (technetium-99m pertechnetate)

scanning, which relies on the presence of ectopic gastric mucosa.[86] In this study, ^{99m}Tc is injected intravenously, and over time it accumulates in the gastric mucosa. Because complications such as bleeding are caused by the ectopic gastric tissue, diagnosis may be helped in symptomatic cases. In children, the scan has a sensitivity of 85% and specificity of 95%, but in adults, the sensitivity drops to 62.5% and the specificity to 9%. The accuracy of the scan can be improved with the use of pentagastrin or cimetidine.[85,87] When the scan is nondiagnostic or in patients with nonbleeding presentation, ultrasonography is perhaps the most useful noninvasive method of achieving diagnosis.[88]

The choice of treatment of Meckel's diverticulum depends on whether it was discovered incidentally or it caused symptoms. Ileal resection including the diverticulum is the treatment of choice for asymptomatic diverticulum because the extent of heterotopic tissue cannot be determined safely by palpation, and ulcerations may recur in case the ectopic tissue persists. Ileal resection permits the removal of any inflamed or heterotopic tissue.[89]

The most controversial issue in the management of Meckel's diverticulum is the decision of surgical resection in asymptomatic cases discovered incidentally. Postoperative morbidity and mortality depend on the indication for removal. While the mortality after surgical excision is almost zero, morbidity in asymptomatic patients is 8.6%, which is close to the 8.3% morbidity found in symptomatic patients (8.5% overall).[77] Those who support incidental excision believe the relatively high mortality and morbidity rates with symptomatic disease justify the associated morbidity of elective excision. The opponents of incidental excision quote the low (4.2%) lifetime risk of symptoms development.[90] In addition, a recent systematic review has shown that there is no compelling evidence to support prophylactic resection.[91] In fact, resection of incidentally detected Meckel's diverticulum has a significantly higher early morbidity rate than leaving the diverticulum in situ (5.3% vs 1.3%, $P<0.0001$; Table 1).[92]

Nowadays, the advent of laparoscopy may have changed this scenario. Laparoscopy permits a complete abdominal exploration, increasing the number of incidentally found diverticula. The laparoscopic approach is extremely useful as it permits the removal of an incidentally found diverticulum with a gastrointestinal stapling device.[93] Nevertheless, laparoscopy has been used to treat patients with Meckel's diverticulum complicated by intestinal obstruction or bleeding caused by heterotopic gastric mucosa.[94,95]

Conclusions

Diagnosis of a congenital anomaly of the GI tract in an adult is not a rare event. Some of these anomalies may remain undetected for years and are diagnosed on the basis of incidental findings at routine examination in the adult life. Indeed, congenital anomalies can form an important part of the daily practice of the general surgeon on patients in the adult life. A thorough knowledge of basic embryology is necessary to understand these lesions. Management considerations in the adult patients are often different compared to the pediatric group. Some of these patients may have persistent problems in adulthood requiring medical attention for years. In addition, there is a large variety of available therapeutic options to offer to adult patients with congenital anomalies of the GI tract. For most of the reviewed diseases, evidence-based management directions are difficult, due to a lack of randomized trials and long-term follow-up.

References

1. Ikenaga T, Honmyo U, Takano S, et al. Primary hypertrophic pyloric stenosis in the adult. J Gastroenterol Hepatol 1992;7:524–526.
2. Zavala C, Bolio A, Montalvo R. Hypertrophic pyloric stenosis: adult and congenital types occurring in the same family. J Med Genet 1969;6:126–128.
3. van Roggen JFG, van Krieken JH. Adult hypertrophic pyloric stenosis: case report and review. J Clin Pathol 1998;51:479–480.
4. Quigley RL, Pruitt SK, Pappas TN, Akwari O. Primary hypertrophic pyloric stenosis in the adult. Arch Surg 1990;125:1219–1221.
5. Go TS, Morse WH. Hypertrophic pyloric stenosis in adults. Am J Gastroenterol 1973;60:400–405.
6. Dye TE, Vidals VG, Lockhart CE, Snider WR. Adult hypertrophic pyloric stenosis. Am Surg 1979;45:478–484.
7. Hellan M, Lee T, Lerner T. Diagnosis and therapy of primary hypertrophic pyloric stenosis in adults: case report and review of the literature. J Gastrointest Surg 2006;10:265–269.
8. Navab F, Flores L. Multinodular adult hypertrophic pyloric stenosis. J Clin Gastroenterol 1989;11:667–670.
9. Papaziogas B, Lazaridis C, Souparis A, et al. Idiopathic hypertrophic pyloric stenosis combined with left paraduodenal hernia. Med Princ Pract 2007; 16:151–154.
10. Kleitsch WP. Pyloric hypertrophy in the adult. Nebr State Med J 1953;38:87–89.
11. Kirklin BR, Harris MT. Hypertrophy of the pyloric muscle of adults: a distinctive roentgenologic sign. Am J Roentgenol 1933;29:437–442.
12. Twining EW. Chronic hypertrophic stenosis of the pylorus in adults. Br J Radiol 1933;6:644–655.
13. Schuster MM, Smith VM. The pyloric "cervix sign" in adult hypertrophic pyloric stenosis. Gastrointest Endosc 1970;16:210–211.
14. Danikas D, Geis WP, Ginalis EM, Gorcey SA, Stratoulias C. Laparoscopic pyloroplasty in idiopathic hypertrophic pyloric stenosis in an adult. JSLS 2000; 4:173–175.
15. Simson JN, Thomas AJ, Stoker TA. Adult hypertrophic pyloric stenosis and gastric carcinoma. Br J Surg 1986;73:379–380.
16. Brahos GJ, Mack E. Adult hypertrophic pyloric stenosis managed by double pyloroplasty. JAMA 1980;243:1928–1929.
17. Alain JL, Grousseau D, Terrier G. Extramucosal pyloromyotomy by laparoscopy. Surg Endosc 1991;5:174–175.

18. van der Bilt JDW, Kramer WLM, van der Zee DC, Bax NMA. Laparoscopic pyloromyotomy for hypertrophic pyloric stenosis. Impact of experience on the results in 182 cases. Surg Endosc 2004;18:907–909.
19. Selzer D, Croffie J, Breckler F, Rescorla F. Hypertrophic pyloric stenosis in an adolescent. J Laparoendosc Adv Surg Tech 2009;19:451–452.
20. Ladd AP, Madura JA. Congenital duodenal anomalies in the adult. Arch Surg 2001;136:576–584.
21. Ross JA. Congenital abnormalities in adult surgery. J R Coll Surg Edinb 1980;25:8–16.
22. Ravitch MM. The pancreas in infants and children. Surg Clin North Am 1975;55:377–385.
23. Sperazza JC, Flanagan RA Jr, Katlic MR. Annular pancreas and intermittent duodenal obstruction in an alcoholic adult. Clev Clin J Med 1992;59:208–210.
24. Lloyd-Jones W, Mountain JC, Warren KW. Annular pancreas in the adult. Ann Surg 1972;176:163–170.
25. De Ugarte DA, Dutson EP, Hiyama DT. Annular pancreas in the adult: management with laparoscopic gastrojejunostomy. Am Surg 2006;72:71–73.
26. Touloukian RJ, Smith EI. Disorders of rotation and fixation. In O'Neill JA, Rowe MI, Grosfeld JL, et al, eds. Pediatric surgery. 5th ed. St. Louis: Mosby, 1998, pp 1199–1214.
27. Skandalakis JE, Gray SW, Ricketts R, Richardson DD. The small intestines. In Skandalakis JE, Gray SW, eds. Embryology for surgeons: the embryological basis for the treatment of congenital anomalies. 2nd ed. Baltimore: Williams & Wilkins, 1994, pp 184–236.
28. Dott NM. Anomalies of intestinal rotation: their embryology and surgical aspects with report of five cases. Br J Surg 1923;11:251–286.
29. Clark LA, Oldham KT. Malrotation. In Ashcraft KW, Murphy JP, Sharp RJ, et al, eds. Pediatric surgery. 3rd ed. Philadelphia: Saunders, 2000, pp 425–442.
30. Donnellan WL, Kimura K. Malrotation, internal hernias, congenital bands. In Donnelan WL, Burrington JD, Kimura K, eds. Abdominal surgery of infancy and childhood. New York: Harwood Academic Publishers, 1996, 43:1–27.
31. Kapfer SA, Rappold JF. Intestinal malrotation—not just the pediatric surgeon's problem. J Am Coll Surg 2004;199:628–635.
32. Berrocal T, Lamas M, Gutierez J, et al. Congenital anomalies of the small intestine, colon and rectum. Radiographics 1999;19:1219–1236.
33. Firor HV, Steiger E. Morbidity of rotational abnormalities of the gut beyond infancy. Clev Clin Q 1983;50:303–309.
34. Bodard E, Monheim P, Machiels F, et al. CT of midgut malrotation presenting in an adult. J Comput Assist Tomogr 1994;18:501–504.
35. Ladd WE. Congenital obstruction of the duodenum in children. N Engl J Med 1932;206:277–283.
36. Ladd WE, Gross RE. Abdominal surgery of infancy and childhood. Philadelphia: Saunders, 1941, pp 53–70.
37. von Flue M, Herzog U, Ackermann C, et al. Acute and chronic presentation of intestinal nonrotation in adults. Dis Colon Rectum 1994;37:192–198.
38. Seymour NE, Andersen DK. Laparoscopic treatment of intestinal malrotation in adults. JSLS 2005;9:298–301.
39. Matzke GM, Dozois EJ, Larson DW, Moir CR. Surgical management of intestinal malrotation in adults: comparative results for open and laparoscopic Ladd procedures. Surg Endosc 2005;19:1416–1419.
40. Mazziotti MV, Strassberg SM, Langer JC. Intestinal rotation abnormalities without volvulus: the role of laparoscopy. J Am Coll Surg 1997;185:172–176.
41. Fu T, Tong WD, He YJ, et al. Surgical management of intestinal malrotation in adults. World J Surg 2007;31:1797–1803.
42. Gohl ML, Demeester TR. Midgut nonrotation in adults: an aggressive approach. Am J Surg 1975;129:319–323.
43. McVay MR, Kokoska ER, Jackson RJ, Smith SD. The changing spectrum of intestinal malrotation: diagnosis and management. Am J Surg 2007;194:712–719.
44. Maxson RT, Franklin PA, Wagner CW. Malrotation in the older child: surgical management, treatment, and outcome. Am Surg 1995;61:135–138.
45. Praise P, Flageole H, Shaw KS, et al. Should malrotation in children be treated differently according to age? J Pediatr Surg 2000;35:756–758.
46. Schey WL, Donaldson JS, Sty JR. Malrotation of bowel: variable patterns with different surgical considerations. J Pediatr Surg 1993;28:96–101.
47. Macpherson RI. Gastrointestinal duplications: clinical, pathologic, etiologic, and radiologic considerations. Radiographics 1993;13:1063–1080.
48. Bentley JFR, Smith JR. Developmental posterior enteric remnant and spinal malformations. Arch Dis Child 1960;35:76–86.
49. Johnstone MJ, Clegg JF. Gastrointestinal haemorrhage from small bowel duplication. Postgrad Med J 1977;53:700–702.
50. Coit DG, Mies C. Adenocarcinoma arising within a gastric duplication cyst. J Surg Oncol 1992;50:274–277.
51. Youngblood P, Blumenthal BI. Enteric duplication cyst. South Med J 1983;76:670–672.
52. Klimopoulos S, Gialvalis D, Marougas M, et al. Unusual case of massive hemorrhage of a gastric hemorrhage of a gastric duplication cyst in a very advanced age. Langenbecks Arch Surg 2008;394:745–747.
53. Holcomb GW 3rd, Gheissari A, O'Neill JA, et al. Surgical management of alimentary tract duplications. Ann Surg 1989;209:167–174.
54. Faerber EN, Balsara R, Vinocur CD, de Chadarevian JP. Gastric duplication with hemoptysis: CT findings. Am J Roentgenol 1993;161:1245–1246.
55. Longmire WP, Rose AS. Haemoductal pancreatitis. Surg Gynecol Obstet 1973;136:246–250.
56. Rao KLN, Pimpalwar A, Vaiphei K, Chowdhary S. Intrapancreatic gastric duplication cyst presenting as lower gastrointestinal bleeding. J Pediatr Surg 2003;38:243–244.
57. Zeebregts CJ, Slot B, Brinkhuis M, Gerritsen JJ. Gastric duplication cyst. Arch Surg 2004;139:687–688.
58. Dittrich JR, Spottswood SE, Jolles PR. Gastric duplication cyst: scintigraphy and correlative imaging. Clin Nucl Med 1997;22:93–96.
59. Machado MAC, Santos VR, Martino RB. Laparoscopic resection of gastric diverticulum. Surg Laparosc Endosc Perc Tech 2003;13:268–270.
60. Puliglanda PS, Nguyen LT, St-Vil D, et al. Gastrointestinal duplications. J Pediatr Surg 2003;38:740–744.
61. Fotiadis C, Genetzakis M, Papandreou I, et al. Colonic duplication in adults: Reports of two cases presenting with rectal bleeding. World J Gastroenterol 2005;11:5072–5074.
62. Choong CK, Frizelle FA. Giant colonic diverticulum: report of four cases and review of the literature. Dis Colon Rectum 1998;41:1178–1185.
63. Frittelli P, Costa G, Zanella L, et al. Intestinal duplication in the adult. A case report of a colonic duplication and a review of the literature. Chir Ital 2002;54:721–728.
64. Horie H, Iwasaki I, Takahashi H. Carcinoid in a gastrointestinal duplication. J Pediar Surg 1986;21:902–904.
65. Robert J, Ambrosetti P, Widgren S, Rohner A. Perforated tubular duplication of the sigmoid colon in adults. Gastronerol Clin Biol 1990;14:776–779.

66. Jimenez M, Cadiere GB, Dapri G, et al. Duodenal duplication cyst in an adult: first simultaneous laparoscopic and endoscopic surgery. J Laparoendosc Adv Surg Tech A 2009;19:207–710.
67. Salameh JR, Votanopoulos KI, Hilal RE, et al. Rectal duplication cyst in an adult: the laparoscopic approach. J Laparoendosc Adv Surg Tech A 2002;12:453–456.
68. Kabay S, Yucel M, Yaylak F, et al. Combined duplication of the colon and vermiform appendix in an adult patient. World J Gastroenterol 2008;28:641–643.
69. Cragan JD, Martin ML, Moore CA, Khoury MJ. Descriptive epidemiology of small intestinal atresia, Atlanta, Georgia. Teratology 1993;48:441–450.
70. Ethen MK, Canfield MA. Impact of including elective pregnancy terminations before 20 weeks gestation on birth defect rates. Teratology 2002;66:S32–S35.
71. Harris J, Kallen B, Robert E. Descriptive epidemiology of alimentary tract atresia. Teratology 1995;52:15–29.
72. Louw JH, Barnard CN. Congenital intestinal atresia: observations on its origin. Lancet 1955;2:1065–1067.
73. Shorter NA, Georges A, Perenyi A, Garrow E. A proposed classification system for familial intestinal atresia and its relevance to the understanding of the etiology of jejunoileal atresia. J Pediatr Surg 2006;41:1822–1825.
74. Touloukian RJ. Diagnosis and treatment of jejunoileal atresia. World J Surg 1993;17:310–317.
75. Escobar MA, Ladd AP, Grosfeld JL, et al. Duodenal atresia and stenosis: long-term follow-up over 30 years. J Pediatr Surg 2004;39:867–871.
76. Edmonson JM. Johann Friedrich Meckel the younger: Meckel's diverticulum. Gastrointest Endosc 2001;54:19A–20A.
77. Stone PA, Hofeldt MJ, Cambell JE, et al. Meckel diverticulum: ten-year experience in adults. South Med J 2004;97:1038–1041.
78. Weinstein EC, Cain JC, Remine W. Meckel diverticulum: 55 years of clinical and surgical experience. JAMA 1962;182:251–253.
79. Yamaguchi M, Takeuchi S, Awazu S. Meckel diverticulum: investigation of 600 patients in Japanese literature. Am J Surg 1978;136:247–249.
80. Park JJ, Wolff BG, Tollefson MK, et al. Meckel diverticulum. The Mayo Clinic experience in 1476 patients (1950–2002). Ann Surg 2005;241:529–533.
81. Dumper J, Mackenzie S, Mitchell P, et al. Complications of Meckel's diverticula in adults. Can J Surg 2006;49:353–357.
82. Rutherford RB, Akers DR. Meckel diverticulum: a review of 148 pediatric patients with specific reference to the pattern of bleeding and to mesodiverticular vascular bands. Surgery 1966;59:618–626.
83. Mackey WC, Dineen P. A fifty-year experience with Meckel diverticulum. Surg Gynecol Obstetr 1983;156:56–64.
84. Lichtstein DM, Herskowitz B. Massive gastrointestinal bleeding from Meckel's diverticulum in a 91-year-old man. South Med J 1998;91:753–754.
85. Martin JP, Connor PD, Charles K. Meckel's diverticulum. Am Fam Physician 2000;44:1037–1042.
86. Lin S, Suhocki PV, Ludwig KA, et al. GI bleeding in adult patients with Meckel diverticulum: the role of technetium 99m pertechnetate scan. South Med J 2002;95:1338–1341.
87. Sfakianakis GN, Conway JJ. Detection of ectopic gastric mucosa in Meckel's diverticulum and in other aberrations by scintigraphy: I. Pathophysiology and 10-year clinical experience. J Nucl Med 1981;22:647–654.
88. Daneman A, Lobo E, Alton DJ, Shuckett B. The value of sonography, CT and air enema for detection of complicated Meckel diverticulum in children with non-specific clinical presentation. Pediatr Radiol 1998;28:928–932.
89. Williams RS. Management of Meckel's diverticulum. Br J Surg 1981;68:477–480.
90. Soltero MJ, Bill AH. The natural history of Meckel diverticulum and its relation to incidental removal. Am J Surg 1976;132:168–173.
91. Zani A, Eaton S, Rees CM, Pierro A. Incidentally detected Meckel diverticulum: to resect or not to resect? Ann Surg 2008;247:276–281.
92. Cullen JJ, Kelly KA, Moir CR, et al. Surgical management of Meckel's diverticulum: an epidemiologic, population-based study. Ann Surg 1994;220:564–568, discussion 568–569.
93. Bona D, Schipani LS, Nencioni M, Rubino B, Bonavina L. Laparoscopic resection for incidentally detected Meckel diverticulum. World J Gastroenterol 2008;14:4961–4963.
94. Ishigami S, Baba K, Kato K, et al. Small bowel obstruction secondary to Meckel diverticulum detected and treated laparoscopically-case report. Surg Laparosc Endosc Percutan Tech 2006;16:344–346.
95. Rivas H, Cacchione RN, Allen JW. Laparoscopic management of Meckel's diverticulum in adults. Surg Endosc 2003;17:620–622.

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GI IMAGE

A Case of Fulminant Portal Pyemia Complicating Hemicolectomy for Polyps: Literature Review and Case Report

Ayad Harb · Olivia Smith · Helen Lloyd · Ziad Harb · John G. Payne

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Abstract
Introduction Portal pyaemia is a rare phenomenon that can complicate a variety of pathologies and surgical procedures. It has a predilection for elderly and immunocompromised patients.
Discussion We present a review of the related literature and report an exceptional case of fulminant portal pyaemia, with an atypical presentation in a patient with few typical risk factors, complicating an elective surgical procedure for benign disease.
Conclusion Portal pyaemia is a condition which can lead to acute overwhelming sepsis and carries a high mortality. It should be considered a differential in abdominal sepsis when no overt abdominal source is found.

Keywords Portal pyemia · Portal vein thrombosis · Portal vein septic thrombophlebitis · Pneumatosis intestinalis

Introduction

Portal pyemia is the combination of infection and thrombosis within the portal vein. It is a condition which carries a grave prognosis and, prior to the liberal use of antibiotics, was invariably fatal. It has been reported in all age groups and as a secondary phenomenon of numerous pathologies; it continues to carry significant diagnostic and therapeutic challenges. We present a review of the literature and a report of an unusual presentation of fulminant portal pyemia in a 70-year-old man.

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Case Report

A 70-year-old man underwent a right hemicolectomy and ileocolic anastomosis for diverticulosis and colonic polyps. There was no evidence of tumor invasion or lymphadenopathy and no intraoperative complications.

Initial postoperative recovery was uneventful. By day 6, the patient had developed diarrhea, worsening renal impairment, and confusion. There was no complaint of abdominal pain or fever. He was admitted to the intensive treatment unit (ITU) that day with multiorgan failure.

Computed tomography (CT) scan was performed which showed air throughout the portal venous system (Figs. 1 and 2). There was also gas in the superior mesenteric vein and pneumatosis intestinalis affecting the greater part of the distal small bowel (Fig. 3). The ileocolic anastomosis was intact. There was no free fluid or air in the abdomen or pelvis. The appearance was consistent with infarction of the small bowel with gas in the bowel wall and the portal venous system.

The patient underwent an emergency laparotomy on day 6. This demonstrated extensive intramural gas throughout small bowel and, despite internal herniation of the small bowel through the mesentery, there was no evidence of ischemia or infarction. The bowel was decompressed and the mesenteric defect repaired.

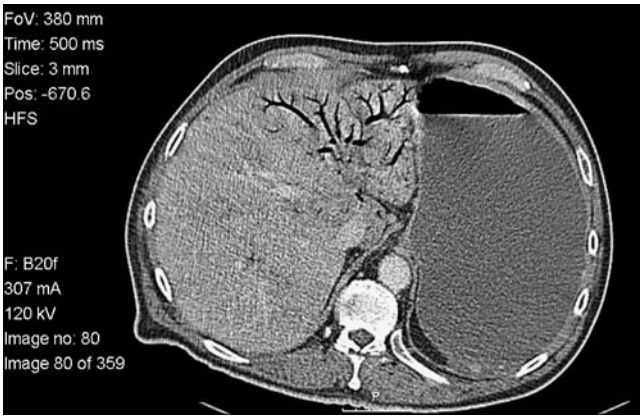

Figure 1 CT scan showing air throughout the portal venous system.

The patient continued to deteriorate on ITU and died 2 days later following a cardiac arrest. A postmortem declared the cause of death as acute respiratory distress syndrome, but could not identify an underlying pathology. Blood and fecal cultures taken preoperatively and postoperatively yielded no positive results. Histology from the initial operation confirmed low-grade tubular adenomas, hyperplastic polyps, and lymph nodes which showed no malignancy.

Discussion

Portal pyemia is the combination of infection and thrombosis within the portal vein. It occurs when pyogenic bacteria gain access to the liver by direct extension from contiguous organs or by embolization of septic foci from parts of the gastrointestinal tract drained by the portal vein. Hepatic clearance of bacteria via the portal system is a normal phenomenon in healthy individuals; however, biliary obstruction, poor perfusion, or microembolization can lead to bacterial proliferation, tissue invasion, and abscess formation within the portal vein. Our study adds to the small bank of reported cases of portal pyemia in medical literature.

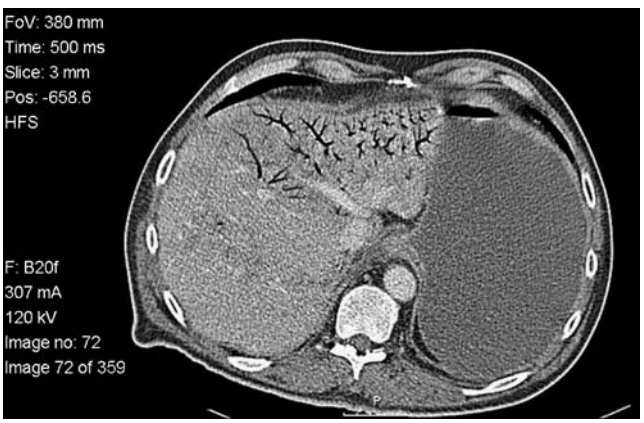

Figure 2 CT scan showing air throughout the portal venous system.

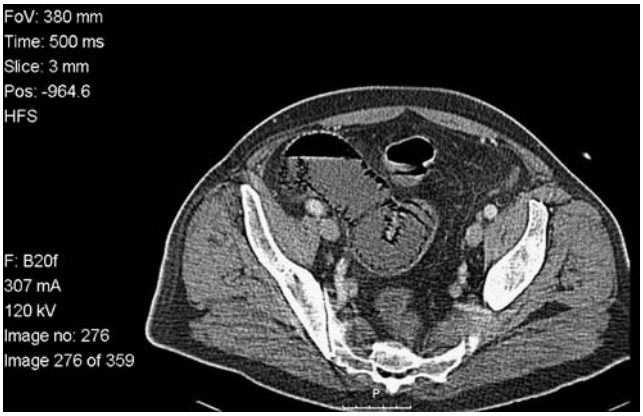

Figure 3 CT scan showing gas in the superior mesenteric vein and pneumatosis intestinalis affecting the greater part of the distal small bowel.

According to a report by Plemmons et al. in 1973, diverticulitis accounts for 68% of cases.[1] Appendicitis, inflammatory bowel disease, intestinal obstruction, and liver abscesses have also been described as antecedents in portal pyemia, as have infected pancreatic necrosis and sepsis affecting the biliary tree.[1–3] It has also been reported in noninfective illnesses such as rectal carcinoma, by Ritchie et al. in 1971.[4]

Portal pyemia is classically of insidious onset and expected to present with typical symptoms and signs of pain, icterus, and fever.[3] This was not the case with our patient whose primary presentation was acute in onset with subtle and secondary signs of sepsis such as confusion and renal failure. This was a case of fulminant portal pyemia and rapid deterioration, despite immediate antibiotic therapy and surgical intervention. In young and previously healthy patients, subtle signs may herald the onset of severe disease.

The incidence and epidemiology of portal pyemia has not been accurately documented; however, past reports have demonstrated a predilection for elderly, immunocompromised, and diabetic patients. The incidence is likely to be higher in countries where premium health care is not readily available. However, as this case demonstrates, the diagnosis should not be overlooked in patients without significant past medical history or risk factors. The majority of cases previously reported have been either as a direct consequence of intra-abdominal sepsis or secondary to existing intestinal disease, such as inflammatory bowel disease. There have been no previous reports of fatal portal pyemia complicating an elective surgical procedure for benign disease in the absence of chronic illness.

CT scan is the imaging study of choice for detecting portal pyemia and is useful in ruling out other differential diagnoses.[3] The usefulness of ultrasound scanning for detecting portal pyemia is unproven. A report by von

Bertele in 1993 found that ultrasound was not a reliable or viable alternative.[2] In fulminant abdominal sepsis, it may be possible to diagnose on plain abdominal X-ray by the presence of branching radiolucency in the liver.

The earliest reported case of portal pyemia in 1949 was secondary to staphylococcal infection; however, the organisms isolated most often are *Escherichia coli*, *Klebsiella pneumonia*, and *Bacteroides* anaerobes. Polymicrobial cultures involving different streptococcal species are characteristic.[5] In this case, there was no evidence of underlying intestinal sepsis to account for the extensive intramural gas and portal pyemia that was seen intraoperatively. Gas within the biliary tree as demonstrated on CT would indicate the presence of gas-forming organisms; however, no pus was seen intraoperatively and cultures failed to demonstrate the presence of such organisms. Blood and swab cultures commonly do not yield positive results due to the prior use of potent antibiotics.

Treatment should be started if portal pyemia is suspected clinically. The patient should be managed in a high dependency unit with antibiotics, fluid resuscitation, and thromboembolism anticoagulant prophylaxis.[1] This should be followed by drainage or resection of any primary septic source. Prolonged antibiotic courses are required especially when treating infection within a thrombus. This was highlighted by Al-Jahdali et al. in 1994 who treated patients with aggressive antibiotic therapy for 2 weeks and thereafter the primary septic source was resected.[3]

Surgical intervention is usually by way of percutaneous drainage, although laparotomy and washout is indicated in cases where percutaneous drainage is not possible or has failed, when antibiotic therapy has failed, or with the coexistence of intra-abdominal disease that requires operative management.[3,5]

Complications of portal pyemia include hepatic abscess formation, which may rupture into adjacent organs or body cavities, with consequent pleuropulmonary and intra-abdominal sequelae. These include pleural empyema, bronchohepatic fistula, and subphrenic abscess. Other potential complications are venous infarction of the bowel, which is the main rationale for anticoagulation, and portal hypertension (Budd–Chiari syndrome) when a large abscess compresses the inferior vena cava and the hepatic veins. Rupture into the pericardium or brain abscess from hematogenous spread are rare complications.[5]

In summary, portal pyemia is a rare phenomenon associated with multiple clinical conditions and a high mortality rate. It should be considered a differential in abdominal sepsis when no overt abdominal source is found. Patients should be commenced on antibiotics early and surgical intervention is often indicated. It is a condition which can lead to acute overwhelming sepsis and carries a high mortality. We have highlighted an exceptional case of fulminant portal pyemia with an atypical presentation in a patient with few typical risk factors, complicating an elective surgical procedure for benign disease.

References

1. Plemmons RM, Dooley DP, Longfield R. Septic thrombophlebitis of the portal vein (pylephlebitis): diagnosis and management in the modern era. Clin Infect Dis 1995;21:1114–1120.
2. Von Bertele MJ. Late presentation of portal vein thrombosis as a complication of appendicitis. J R Army Med Corps 1993;139 (3):135–136.
3. Al-Jahdali H, Pon C, Thompson WG, Matzinger FR. Non fatal portal pyaemia complicating Crohn's disease of the terminal ileum. Gut 1994;35(4):560–561.
4. Ritchie JD et al. Portal pyaemia secondary to carcinoma of the rectum. Aust N Z J Surg 1975;45(3):284–285.
5. Wireko M, Berry P, Brennan J, Aga R. Unrecognised pylephlebitis causing life-threatening septic shock: a case report. World J Gastroenterol 2005;11(4):614–615.

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GI IMAGE

Frey Procedure for Pancreaticopleural Fistula

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Case Report

A 59-year-old woman with alcoholic chronic pancreatitis and multiple readmissions for exacerbation developed acute shortness of breath. Chest X-ray showed massive right-sided pleural effusion, and a thoracocentisis revealed amylase content of 12,000 U/L. Magnetic resonance cholangiopancreatography (MRCP) suggested presence of the pancreatic pseudocyst in the porta hepatitis with possible pancreaticopleural fistula (PPF). Pleural effusion recurred soon after thoracocentesis despite treatment with total parenteral nutrition (TPN) and somatostatin. An endoscopic retrograde cholangiopancreatography (ERCP) was not possible secondary to duodenal stenosis caused by the inflammatory pancreatic head mass. The patient underwent an exploratory laparatomy during which a direct pancreatic ductogram demonstrated the PPF tract (Figs. 1 and 2). Fistula was outlined by the methylene blue injection into the main pancreatic duct. A Frey procedure (pancreatic head local resection and pancreatojejunostomy), to provide decompression of the pancreatic duct, as well a gastro-jejunostomy and feeding jejunostomy were performed. Postoperative course was complicated by bleeding from pancreatic branches of the splenic artery, requiring embolization per interventional radiology. There was no recurrence of PPF on subsequent 3 years follow-up.

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Discussion

PPF is the rare complication of pancreatitis, with the incidence of 0.4–4.5%.[1–3] Only 63 cases have been reported so far in the English literature. Majority of patients are alcoholics with chronic pancreatitis in which PPF develops as the sequela of the incompletely formed/ruptured pancreatic pseudocyst or direct pancreatic duct leak. Most common presenting symptom is shortness of breath due to the pleural effusion. Thoracocentesis reveals elevated amylase content. PPF could be demonstrated by ERCP, MRCP, or CT with sensitivity 78%, 80%, and 47%, respectively.[2] Medical therapy with TPN and somatostatin is effective in only 30–60% of the cases. ERCP with pancreatic stent placement results in resolution of PPF in majority of the cases.[4] In our patient, ERCP was not possible because of the duodenal stenosis. Surgery is used

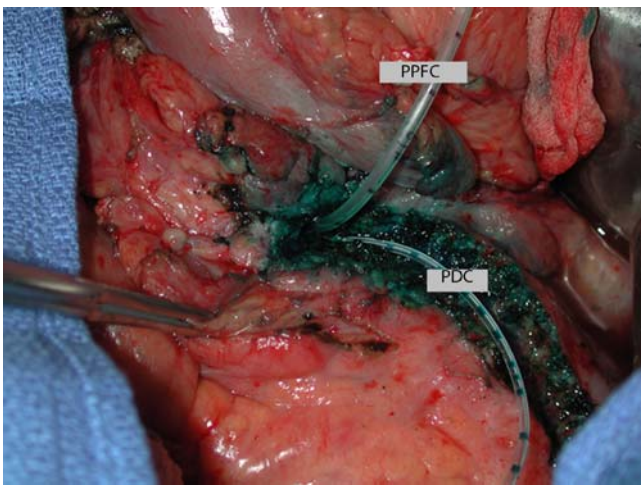

Figure 1 Intraoperative photo showing cored pancreatic head and longitudinal opening of the pancreatic duct. PPFC indicates catheter in pancreaticopleural fistula, PDC-catheter in main pancreatic duct.

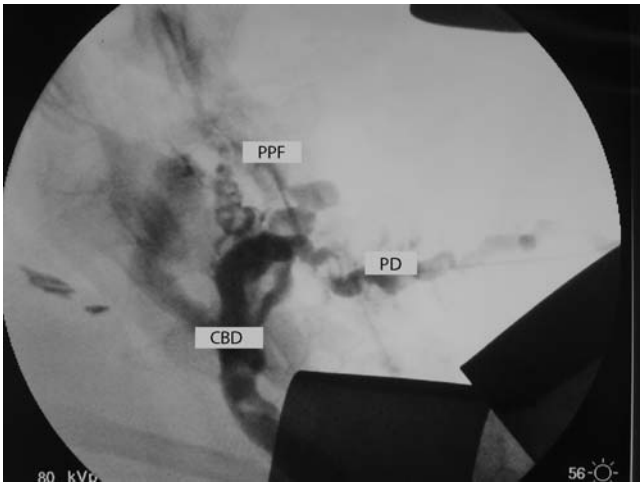

Figure 2 Intraoperative ductogram showing PPF. *PPF* pancreaticopleural fistula, *PD* pancreatic duct, *CBD* common bile duct.

if stent placement and/or medical therapy fails and usually includes distal pancreatectomy or pancreatojejunostomy. When surgery is used to treat PPF, success rate is vastly superior to the medical treatment (94% vs. 31%), and more than 80% of the patients recover without any sequela.[1] In cases of pancreatic head inflammatory mass, compressing adjacent structures, Frey procedure provides effective decompression of both pancreatic duct and duodenal/bile duct stenosis. To our knowledge, only one case of Frey procedure to treat PPF was reported to date in English literature.[5]

References

1. King JC, Reber HA, Shiraga S, Hines OJ. Pancreatic–pleural fistula is best managed by early operative intervention. Surgery 2009; doi:10.1016/j.surg.2009.03.024.
2. Ali T, Srinivasan N, Le V, Chimpiri AR, Tierney WM. Pancreaticopleural fistula. Pancreas 2009;38(1):e26–e31.
3. Oh YS, Edmundowicz SA, Jonnalagadda SS, Azar RR. Pancreaticopleural fistula: report of two cases and review of the literature. Dig Dis Sci 2006;51(1):1–6.
4. Khan AZ, Ching R, Morris-Stiff G, England R, Sherridan MB, Smith AM. Pleuropancreatic fistulae: specialist center management. J Gastrointest Surg 2009;13(2):354–358.
5. Izbicki JR, Bloechle C, Knoefel WT, Wilker DK, Dornschneider G, Seifert H, Passlick B, Rogiers X, Busch C, Broelsch CE. Complications of adjacent organs in chronic pancreatitis managed by duodenum-preserving resection of the head of the pancreas. Br J Surg 1994;81(9):1351–1355.

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LETTER TO THE EDITOR

Letter to the Editor. Re: Conservative Management of Acute Appendicitis

Luca Ansaloni · Fausto Catena · Federico Coccolini · Filippo Gazzotti · Antonio Daniele Pinna

Received: 25 July 2009 / Accepted: 11 January 2010 / Published online: 2 February 2010

To the Editor:

We read with great interest the article by Malik and Bari recently published on your journal[1] regarding the conservative management of acute appendicitis (AA). We congratulate the authors that performed this randomized controlled trial (RCT) comparing antibiotic treatment to appendectomy in unselected patients with noncomplicated AA, most probably even in a difficult setting with limited resources.

The authors' conclusions—that antibiotic treatment in the patients with AA is quite effective, and these patients may not need surgery, experiencing less pain and requiring less analgesia, but have high recurrent rate[1]—has the potential for significant clinical implications. However, we have developed serious concerns with regard to the study, which questions the validity of these conclusions.

First, the inclusion of patients has not been properly accounted for. It is not stated how many eligible patients in the study period were those from which the 80 enrolled were extracted. In particular, it is not declared how many patients with AA refused to participate in the study, how many decided by themselves after the enrolment to change the study group (from antibiotic treatment to appendectomy and from appendectomy to antibiotic treatment), and finally, how many were not included in the study for the surgeon's decision. All these figures in a RCT should be known and taken in account when extrapolating results and drawing conclusions for the general population.

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Further, the authors stated that "the appropriate sample size was determined by considering a power of 80% and an alpha error of 5%."[1] Sample size calculation requires four components: the type I error (or α; 0.05 in the study), the power ($1-\beta$), and the event rate in both groups.[2] Unfortunately, the authors did not declare the event and its rates in the two groups from which they calculated the sample size of 80 patients (40 for each group).

Moreover, it is not affirmed if an "intention to treat" analysis has been used in comparing the outcomes in the two groups. In particular, it should be interesting to know where the authors wrote: "There was a significant decrease in analgesic consumption in patients managed with antibiotics ($p<0.001$) and significantly less pain was observed after 12 h of conservative treatment ($p<0.001$). Significantly lower pain scores were also noted by the surgeon. The WBC count declined significantly faster in patients treated with antibiotics, and mean temperature was significantly lower on days 1 and 2 ($p<0.05$) with not more than 0.5°C difference. However, the pattern of CRP levels in both groups was the same,"[1] if the two patients operated on within 24 h in the antibiotic group were also included in the analysis of the outcomes of the antibiotic group. By the way, we note that it should be more correct and effective in the results sections to express the numerical data of both groups, more than only the statistical significance of their inference.

Besides, we question the authors' conclusion in the abstract where they stated "that antibiotic treatment in the patients with AA is quite effective, and these patients may not need surgery."[1] If efficacy for antibiotic treatment is defined as definite improvement without the need for surgery within a median follow-up of at least 1 year, considering that, in the antibiotic group, two patients were operated on within 24 h because of peritonitis due to

perforated AA and four patients operated on within 1 year as a result of recurrent AA, it can be calculated as 85% (34 out of 40, 95% confidence interval 70–93%, Wald method). This means that these patients may need surgery with high probability up to 30% of cases.

Based on the results, although we agree with the authors that a "conservative approach for AA seems to be of special benefit to peripheral health centers especially in developing countries with poor health services and other areas still lacking operating facilities,"[1] we would not recommend antibiotic treatment as an alternative to surgery in the general population. Although this study may indicate that conservative antibiotic treatment could be cost-effective, avoiding unnecessary surgery and associated morbidity and mortality, its data cannot change the statement that surgery remains the golden standard for AA, despite its continuing clinical challenges.

Further, it should be considered that, in the literature, there are two other RCTs on the same subject, both performed in Sweden, including respectively 252 adult male and 369 unselected patients,[3,4] but they are both burdened by obvious methodological errors.[5,6]

So all considered in the final, well-designed RCTs in larger populations are still needed to establish the superiority of antibiotic treatment over surgery in AA.

References

1. Malik AA, Bari SU. Conservative management of acute appendicitis. J Gastrointest Surg 2009;13:966–970.
2. Schulz KF, Grimes DA. Sample size calculations in randomised trials: mandatory and mystical. Lancet 2005;365:1348–1353.
3. Styrud J, Eriksson S, Nilsson I, Ahlberg G, Haapaniemi S, Neovius G, et al. Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial. World J Surg 2006;30:1033–1037.
4. Hansson J, Körner U, Khorram-Manesh A, Solberg A, Lundholm K. Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. Br J Surg 2009;96:473–481.
5. Søreide K, Kørner H, Søreide JA. Type II error in a randomized controlled trial of appendectomy vs. antibiotic treatment of acute appendicitis. World J Surg 2007;31:871–872.
6. Sanabria A, Sanchez C. Letter 2: Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients (Br J Surg 2009;96:473–481). Br J Surg 2009;96:952–953.

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LETTER TO THE EDITOR

Clarification

Ajaz A. Malik · Shams ul Bari

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To the editor

We have gone through the letter sent to the editor by our esteemed readers regarding the conservative management of acute appendicitis (AA). We are highly thankful for their valuable suggestions which are well-taken. We also appreciate their concerns and their keen interest in the study. Here, we would like to mention that none of our patients refused to accept the study and none of our patients requested for any change in the line of treatment. Only two patients were excluded from the study because of increasing abdominal pain and generalized peritonitis and subsequent data was discounted.

We agree with the view that despite the fact that conservative treatment could be cost-effective, avoiding the unnecessary surgery and associated morbidity and mortality, surgery is still the gold standard for AA. Further, as we have already mentioned in the manuscript, well-designed randomized controlled trials in a large population are still needed to establish the superiority of antibiotic treatment over surgery in AA.

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