J Gastrointest Surg (2009) 13:1021–1022
DOI 10.1007/s11605-009-0868-9

SSAT CONTROVERSY IN GI SURGERY DEBATE

Transplantation Versus Resection for Hepatocellular Carcinoma in the Mild Cirrhotic: Framing the Debate

Michael A. Choti

Received: 23 February 2009 / Accepted: 6 March 2009 / Published online: 31 March 2009

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, with more than one million cases diagnosed worldwide each year. Complex management options confront those treating patients with this disease, shedding light on the importance of a multidisciplinary team for optimal care. Liver resection and liver transplantation are the principle potentially curative treatments for HCC. For those without cirrhosis, surgical resection with partial hepatectomy is the treatment of choice. However, no more than 30% of patients with HCC present with resectable disease, and cirrhosis is present in up to 90%.[1] The presence of extrahepatic disease, lack of sufficient hepatic functional reserve, multifocal disease within the liver, tumors in locations not amenable to resection, and main portal vein involvement, as well as comorbid disease, are all contraindications to resection. For early HCC associated with more advanced cirrhosis, liver transplantation is clearly considered the best treatment option. The most commonly accepted conditions for transplantation for HCC are the Milan criteria: solitary tumor with diameter ≤5 cm or 2–3 tumor nodules with the largest diameter ≤3 cm, and absence of macroscopic vascular invasion or extrahepatic metastasis.[2]

This paper was originally presented as part of an SSAT Controversies in GI Surgery debate entitled, "Hepatocellular Carcinoma in the Mild Cirrhotic: Transplant or Resect?", at the SSAT 49th Annual Meeting, May 2008, in San Diego, CA, USA.

M. A. Choti (✉)
Department of Surgery, Johns Hopkins Hospital,
600 North Wolfe Street, Blalock 665,
Baltimore, MD 22187, USA
e-mail: mchoti@jhmi.edu

M. A. Choti
Division of Surgical Oncology, Department of Surgery,
School of Medicine, The Johns Hopkins University,
Baltimore, MD, USA

The controversy lies in the optimal surgical management of the patient with early HCC associated with mild well-compensated cirrhosis. In the accompanying two articles, the authors have been asked to debate the question of whether liver resection or transplantation should be the optimal initial treatment for such patients. The goal is to provide information to the reader regarding the evidence by which recommendations may be made, as well as to help understand the complexities which come into play when considering these two disparate treatment options.

Comparisons of long-term survival after liver resection and transplantation should be considered the most important outcome measure. Indeed, many studies have addressed long-term survival differences for early HCC in patients with preserved liver function.[3–5] Yet, biases in patient selection and lead-time bias due to the waiting times and dropout before liver transplantation confound the ability to make valid comparisons. With regard to the risk of recurrence, many might argue that liver transplantation provides the best cure with removal of the cirrhotic liver and, thus, reduced risk of intrahepatic recurrent or multifocal disease. However, this benefit may be offset by problems specifically related to transplantation: graft rejection, immunosuppression, recurrent viral hepatitis, and perhaps increased risk for extrahepatic recurrence in some patients.

While some might strongly feel that any therapeutic decision should be based only on what is optimal for that patient, this debate might also be also framed in an ethical context. Specifically with the current severe shortage of donor organs, the use of liver transplantation as an initial treatment for all patients with early HCC and mild cirrhosis may not be an optimal use of organs for the community as a whole, decreasing the probability of obtaining an organ for other patients with advanced cirrhosis and no alternative therapeutic options. Likewise, the use of live donor

transplantation, with the associated risk in the healthy donor, may be considered unethical by some when a comparable alternative of resection exists.

Rather than an all-or-none view of these treatment options, the utilization of a strategy of hepatic resection as the initial treatment with transplantation as a salvage treatment in case of tumor recurrence or liver failure has gained acceptance in some centers.[6] In patients who develop intrahepatic recurrence or new disease following partial hepatectomy, salvage transplantation may still be possible, provided the recurrent tumors are within the Milan criteria. Such a strategy reduces the use of donor organ utilization because some patients may remain disease-free long term while others would be able to delay transplantation. However, this strategy is based on the supposition that most recurrences will still be transplantable and that salvage transplantation can achieve long-term survival comparable to primary transplantation in that patient. Moreover, some have reported increased perioperative mortality in salvage transplantation.[7]

The complexities and disparities in these two treatment options provide for a lively debate topic. Given the absence of prospective studies comparing these different therapeutic approaches, current treatment recommendations are often based on individual factors beyond oncologic criteria, including center expertise, patient comorbid disease, donor availability, and patient preference. As eloquently implied in these accompanying articles, what is ultimately needed but unlikely double is a randomized comparison of hepatic resection versus liver transplantation.

References

1. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology 2002;35:519–524. doi:10.1053/jhep.2002.32089.
2. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–699. doi:10.1056/NEJM199603143341104.
3. Bigourdan JM, Jaeck D, Meyer N, et al. Small hepatocellular carcinoma in Child A cirrhotic patients: hepatic resection versus transplantation. Liver Transpl 2003;9:513–520. doi:10.1053/jlts.2003.50070.
4. Cha CH, Ruo L, Fong Y, et al. Resection of hepatocellular carcinoma in patients otherwise eligible for transplantation. Ann Surg 2003;238:315–321.
5. Bellavance EC, Lumpkins KM, Mentha G, et al. Surgical management of early-stage hepatocellular carcinoma: resection or transplantation? J Gastrointest Surg 2008;12(10):1699–1708. doi:10.1007/s11605–008–0652–2.
6. Belghiti J, Cortes A, Abdalla EK, et al. Resection prior to liver transplantation for hepatocellular carcinoma. Ann Surg 2003;238:885–892. doi:10.1097/01.sla.0000098621.74851.65.
7. Adam R, Azoulay D, Castaing D, et al. Liver resection as a bridge to transplantation for hepatocellular carcinoma on cirrhosis: a reasonable strategy? Ann Surg 2003;238:508–518. doi:10.1097/01.sla.0000098112.04758.4e.

J Gastrointest Surg (2009) 13:1023–1025
DOI 10.1007/s11605-008-0784-4

2008 SSAT OTHER

Hepatocellular Carcinoma: Resection or Transplantation

Robin D. Kim · Alan W. Hemming

Received: 22 October 2008 / Accepted: 24 November 2008 / Published online: 17 December 2008

Abstract Management of hepatocellular carcinoma in the early cirrhotic remains controversial. The exact role of liver transplantation versus resection remains to be determined. The following short review attempts to present the evidence for the respective roles of liver transplantation versus liver resection in early stage HCC.

Keywords Hepatocellular carcinoma · Resection · Transplantation

The introduction of Hepatitis C (HCV) into the North American population in the late 1970s and early 1980s has caused a dramatic increase in hepatocellular carcinoma (HCC) in the West. HCV infection leads to the development of HCC approximately 10 years after the establishment of cirrhosis with a progressively higher risk of development of HCC the longer the duration of HCV and cirrhosis. HCC is amenable to surgical cure in only 15% of patients at the time of presentation and has become a significant health care issue. HCC is potentially cured by liver resection (LR) or liver transplantation (LT). The superiority of one modality over the other remains controversial. In specific circumstances, it is clear that liver transplantation may be the only option such as when an early stage tumor occurs in a patient that clearly does not have sufficient hepatic reserve to tolerate resection, while in other cases such as an early stage tumor in a noncirrhotic patient, resection is inarguably the appropriate course. There remains a controversy, however, over the management of patients with early stage tumors and well-compensated cirrhosis that would tolerate resection or transplantation. By interpreting the currently available evidence, we hope to establish consensus regarding the management of HCC amenable to both LR and LT.

To date, there have been two key factors that inhibit a meaningful comparison of LR to LT for HCC. The level of evidence is not robust, since there are no randomized controlled trials that directly compare the two modalities. Most series are retrospective and frequently compare a series of either LR or LT patients to historical controls of the alternate modality. There is a small number of case control studies that attempt to match patients retrospectively on tumor and liver function characteristics that may represent the best available evidence.[1] Secondly, in these studies, there is an initial selection bias which differentiates LR and LT candidates that impacts HCC recurrence, overall and disease-related survival. These differences are illustrated in a recent case-control study comparing LR and LT for HCC within Milan Criteria, in which LT recipients had higher Child-Pugh scores (worse liver disease) but smaller tumors.[2]

A meaningful comparison of LR versus LT should analyze only those patients with Child-Pugh scores of A, absence of portal hypertension, and small HCCs amenable to either modality. Specific tumor characteristics would include a single lesion up to 5 cm in size with no gross vascular invasion identified preoperatively. Comparing

This paper was originally presented as part of an SSAT Controversies in GI Surgery debate entitled, "Hepatocellular Carcinoma in the Mild Cirrhotic: Transplant or Resect?", at the SSAT 49th Annual Meeting, May 2008, in San Diego, CA, USA. The other article presented in the debate was Pawlik TM, Resection for Early Hepatocellular Carcinoma.

R. D. Kim · A. W. Hemming (✉)
Division of Transplantation and Hepatobiliary Surgery,
Department of Surgery,
University of Florida School of Medicine,
1600 S.W. Archer Rd., Room 6142, P.O. Box 100286,
Gainesville, FL 32610-0286, USA
e-mail: hemming@surgery.ufl.edu

resection to transplantation across the Milan criteria (i.e., including cases with up to three lesions none of which is greater than 3 cm) is likely inappropriate since liver resection for multifocal disease is known to have a less favorable outcome. To determine the benefits of each modality, results should be assessed versus the natural history of the disease which, in this case, includes progression of liver dysfunction as well as tumor progression and spread. There is little natural history data regarding patients with these characteristics since the vast majority undergoes some form of therapy. The best available study followed 48 patients with small HCCs and compensated cirrhosis who were excluded from all treatment for medical, tumoral, or demographic reasons, in whom 1, 2, and 3 year survival rates were 80%, 65%, and 50%, respectively.[3] This suggests that untreated small HCCs in patients with preserved liver function may not be as rapidly fatal as once thought and would suggest that a minimum goal of therapy must be to surpass no therapy at all.

LR for HCC is attractive because it is widely available and curative in 45% of patients to whom it can be applied. LR has limitations due to the competing need for parenchymal preservation due to underlying liver disease that must be balanced with the need for optimal resection margins. Additionally, LR does not address the potential for liver disease progression and tumor recurrence in the remnant liver. HCC recurs or develops de novo in 50% to 80% of patients at 5 years after resection with the majority recurring within 2 years.[1,4] The causes of death following HCC resection include progressive liver disease, the formation of new tumors in the remnant liver, and HCC recurrence from incomplete resection. Patients with recurrence, not surprisingly, have significantly shorter survival compared to those who do not. These recurrence rates are reflected in overall 5 year disease-free survivals of 39% to 48% in recently reported LR series.[2,4]

Despite its retrospective design and modest size, Mazzaferro's confirmation in 1996 that survival following LT for small HCCs was comparable to that of non-HCC indications endures today. Specifically, patients transplanted with a single lesion that is 5 cm or less, or up to three lesions all no greater than 3 cm in diameter, have an overall and disease-free survival at 4 years of 92% and 85%, respectively.[5] Theoretically, LT is an ideal therapy, since no tumorigenic liver remnant is left behind, and the underlying liver dysfunction is restored. HCC recurrence rates of 4% to 10% have been demonstrated in patients transplanted with tumors within Milan Criteria, and most recur within 2 years of LT.[5] The causes of death following LT for HCC include complications of transplantation and recurrence or rarely de novo HCC. Recurrent HCC following LT decreases survival, with 5 years survival rates for patients with and without recurrence of 95% to 60% in more recent series of tumors strictly within Milan Criteria.[4] Recent series report 5 year disease-free survival for LT of 84% to 64%.[2]

The short review thus far illustrates that using the best available evidence, patients with small HCCs that are eligible for either LR or LT have a better survival with LT than resection and that tumor recurrence rates are significantly higher for LR. Therefore, in an ideal world with unlimited organs, LT would offer improved oncologic outcomes over LR. However, because of the growing liver graft shortage in the West and throughout the world, the superior outcomes of LT may be significantly mitigated by patient removal, while on the waiting list for transplantation, largely from tumor progression.

In order to compare the actual survival rates of LT to that of LR, an intention-to-treat analysis incorporating drop-out on the waiting list would be more accurate than analysis of postsurgical results alone. A number of series have determined that the survival benefits of LT for HCC are realized when patients wait less than 6 months from time of listing until transplant.[1] UNOS assigns additional MELD points to patients with stage T2 tumors within Milan Criteria to reduce waiting-list drop-out due to tumor progression. Although these points are regionally determined, patients are typically given 21 MELD points that are adjusted upward each 3 months if patients remain on the list. UNOS reported that as of early 2006, 17,500 patients awaited livers and 14,000 of them waited longer than 6 months. (www.UNOS.org). However, for patients listed with small T2 HCCs that received MELD exceptions specifically, the 2007 SRTR showed a wide regional variation in the range of median times to transplant from 25 to 156 days. Approximately 55% of patients listed with early stage tumors were transplanted within 3 months of listing with approximately 80% of patients transplanted within 6 months. This would suggest that, in the majority of regions, LT is a better option than LR. This may not be the case in regions where waiting time for transplant exceeds 6 months.

In conclusion, there is really no doubt that LT offers better survival than LR in patients with early stage tumors, compensated cirrhosis, and hepatitis C if access to transplantation is not hindered. However, delay in access to LT may mitigate the benefits of LT and make LR an equivalent or preferable option in regions where time to transplant exceeds 6 months. This should not be construed to mean the modalities are equivalent if both are equally accessible.

References

1. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907–1917. doi:10.1016/S0140-6736(03)14964-1.
2. Poon RT, Fan ST, Lo CM, et al. Difference in tumor invasiveness in cirrhotic patients with hepatocellular carcinoma fulfilling the Milan

criteria treated by resection and transplantation: impact on long-term survival. Ann Surg 2007;245:51–58. doi:10.1097/01.sla.0000225255.01668.65.

3. Llovet JM, Bustamante J, Castells A, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology 1999;29:62–67. doi:10.1002/hep.510290145.
4. Cha CH, Ruo L, Fong Y, et al. Resection of hepatocellular carcinoma in patients otherwise eligible for transplantation. Ann Surg 2003;238:315–321.
5. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–699. doi:10.1056/NEJM199603143341104.

J Gastrointest Surg (2009) 13:1026–1028
DOI 10.1007/s11605-008-0779-1

2008 SSAT OTHER

Debate: Resection for Early Hepatocellular Carcinoma

Timothy M. Pawlik

Received: 22 October 2008 / Accepted: 24 November 2008 / Published online: 23 December 2008

Abstract The management of patients with cirrhosis and early hepatocellular carcinoma (HCC) meeting the Milan criteria is controversial. Although liver transplantation for early HCC has been shown to have excellent long term survival rates and low recurrence rates, its application is limited by organ availability. Hepatic resection is an alternative therapy for early HCC. Hepatic resection can be performed safely in patients with early HCC and well-compensated cirrhosis. In addition, the reported 5-year survival rates are in the range of 50%. Resection may also allow a better understanding of tumor biology through pathologic examination of the specimen while also providing a potentially curative therapeutic option. The management of patients with early HCC is complex. Resection should not be viewed as opposing transplantation. Rather, hepatic resection should be seen as complementary to transplantation. The best therapeutic strategies for patients with early HCC and well-compensated cirrhosis should be dependent on the individual clinical situation, not adherence to dogmatic universal adoption of either resection or transplantation.

Keywords Heptocellular carcinoma · Early stage · Resection · Transplantation · Outcome

Rather than advocating liver transplantation for all patients with early hepatocellular carcinoma (HCC) in the setting of well-compensated cirrhosis, the prudent select utilization of surgical resection for early HCC is warranted. The foundation of any coherent argument in favor of liver resection must rest on proof that it is safe, efficacious, and offers potential benefits over transplantation.

Surgery in patients with underlying cirrhosis can be associated with substantial morbidity and mortality. Although perioperative mortality can be as high as 30% to 50% in patients who are Child–Turcotte–Pugh B or C, Child–Turcotte–Pugh A patients have an associated surgical mortality of 5% to 10%. More recently, however, the combination of better patient selection, as well as better preoperative optimization, has further decreased the mortality associated with hepatic resection in patients with cirrhosis. The model for end-stage liver disease (MELD) has recently been shown to be a very accurate and less cumbersome way to accurately predict postoperative liver failure and mortality. Patients with MELD score <9 had a reported mortality rate of zero in two recent large institutional series of patients undergoing resection of HCC.[1,2] In addition, for patients with cirrhosis being considered for surgical resection, computed tomography volumetry can be helpful. Accurate identification of patients with an inadequate future liver remnant and subsequent utilization of portal vein embolization may allow for safer resection in a subset of patients. Taken together, these advancements in patient selection and preoperative optimization have resulted in contemporary perioperative rates of 0% to 5% for patients with well-compensated cirrhosis who undergo resection of early HCC.

This paper was originally presented as part of an SSAT Controversies in GI Surgery debate entitled, "Hepatocellular Carcinoma in the Mild Cirrhotic: Transplant or Resect?", at the SSAT 49th Annual Meeting, May 2008, in San Diego, California. The other article presented in the debate was Kim RD and Hemming AW, "Hepatocellular Carcinoma: Resection or Transplantation."

T. M. Pawlik (✉)
Departments of Surgery, Johns Hopkins School of Medicine,
600 North Wolfe Street, Halsted 614,
Baltimore, MD 22187-6681, USA
e-mail: tpawlik1@jhmi.edu

In addition to being safe, surgical resection can be an efficacious therapy for early HCC. In most series, surgical resection of early HCC has a reported 5-year survival of 45% to 50% compared with 65% to 70% for transplantation. However, direct comparison of resection versus transplantation survival data can be difficult to interpret. The better results with transplantation may reflect—in part—the more stringent selection of patients for transplantation. In fact, Cha et al.[3] reported that partial hepatectomy in patients with early HCC who were otherwise eligible for transplantation had a comparable 5-year survival to that reported for liver transplantation. Other data have similarly confirmed that certain patients with early HCC can have durable long-term survival following surgical resection. For example, Izumi et al.[4] reported a 5-year survival of more than 75% in patients with a solitary HCC tumor without vascular invasion following hepatic resection. In aggregate, these data serve to emphasize that certain subsets of patients can enjoy excellent long-term prognosis following hepatic resection.

Unlike transplantation, which treats both the underlying cirrhosis and the malignancy, hepatic resection only extirpates the tumor. As such, hepatic resection has been associated with higher rates of intrahepatic recurrence. However, in those patients who remain free of recurrence, the 5-year survival following resection of HCC can exceed 80%.[3] Resection may be more appropriate, therefore, for patients at lower risk of intrahepatic recurrence, with transplantation being the preferred initial treatment modality for patients at highest risk of early tumor recurrence. While the cumulative intrahepatic recurrence rate may be as high as 60% in patients with hepatitis C infection, recurrence is significantly lower in both hepatitis B and non-hepatitis cirrhotic patients. A rationale approach may therefore be to favor utilization of hepatic resection versus transplantation in non-hepatitis C patients due to a different natural history of their underlying disease.

The use of hepatic resection as first line therapy for early HCC can be further justified if salvage transplantation remains an option among those patients who do recur. Reporting on over 450 patients who underwent resection of early HCC, Poon et al.[5] noted that 80% of patients who recurred had a transplantable recurrence using the same criteria as for primary transplantation. In addition, Belghiti et al.[6] reported that salvage transplantation was as safe and efficacious as primary liver transplantation. Specifically, in the series from Belghiti,[6] global morbidity and perioperative mortality were comparable between primary and salvage transplantation. In addition, primary versus salvage transplantation was associated with similar long-term survival rates. A strategy that selectively utilizes resection as first-line therapy followed by salvage transplantation has several obvious advantages. First, the patient avoids a more complex operative procedure and the need for immunosuppression. In addition, such a strategy spares the use of liver grafts, avoids potential problems with prolonged waiting times, and provides the patient with rapid access to an effective therapy.

If liver transplantation were adopted as the universal strategy for all patients with early HCC, demand on organ availability and waiting times for grafts would inevitably worsen. This point is critical to consider as some of the reported improved survival following liver transplantation versus hepatic resection is predicated on short waiting times and low dropout rates. Shah et al.[7] reported that, while survival after liver transplantation was better than resection when measured from the time of surgery, survival from time of listing or hepatic resection was not different between the two groups. This group also noted that patients who waited longer than 4 months for liver transplantation had over a twofold higher risk of death. In a separate study, Sarasin et al.[8] utilized decision-making analyses to show that if the time delay before receiving a transplant exceeded 8 months, hepatic resection became the preferred strategy. In addition, the authors noted that as the time delay before receiving a transplant increased and the gain in life expectancy provided by liver transplantation decreased, the subsequent marginal cost-effectiveness of transplantation decreased. The problem of prolonged waiting times and dropout can be considerable. Yao et al. noted that the cumulative probabilities for dropout at 6, 12, and 24 months were 7.3%, 25.3%, and 44%, respectively. As such, the universal adoption of transplantation would seemingly worsen the dropout problem and may further attenuate any relative potential benefit of transplantation.

Bridge therapy has been advocated as a means to address prolonged waiting times. Bridge therapy may include, among other things, non-surgical locoregional therapies such as transarterial chemoembolization and radiofrequency ablation. However, in some patients, resection may not only represent an alternative bridge therapy but a preferable one. Belghiti et al.[9] have argued that resection may be better than other non-surgical locoregional therapies, as it gives access to detailed pathologic examination of the tumor and the surrounding liver parenchyma. Resection may help identify patients with tumors apparently within the Milan criteria but with poor prognostic pathological features such as vascular invasion, poor histological grade, and the presence of unrecognized satellite nodules. In fact, some groups[10] have advocated utilization of pathological data obtained from resection to help select patients for expedited transplantation.

Resection and transplantation should be viewed as complimentary tools in the armamentarium to treat early HCC. Universal adoption of either strategy is unwarranted and overly simplistic. The use of different therapeutic approaches that incorporate hepatic resection or transplan-

tation should be dictated by the clinical situation. Factors will include not only graft availability and anticipated waiting times but also patient and tumor specific factors. By embracing an open-minded approach that acknowledges the value of both hepatic resection and transplantation, the surgeon can best serve the patient with early HCC and well-compensated cirrhosis.

References

1. Teh SH, Christein J, Donohue J, et al. Hepatic resection of hepatocellular carcinoma in patients with cirrhosis: model of end-stage liver disease (MELD) score predicts perioperative mortality. J Gastrointest Surg 2005;9:1207–1215. (discussion 1215). doi:10.1016/j.gassur.2005.09.008.
2. Cucchetti A, Ercolani G, Vivarelli M, et al. Impact of model for end-stage liver disease (MELD) score on prognosis after hepatectomy for hepatocellular carcinoma on cirrhosis. Liver Transpl 2006;12:966–971. doi:10.1002/lt.20761.
3. Cha CH, Ruo L, Fong Y, et al. Resection of hepatocellular carcinoma in patients otherwise eligible for transplantation. Ann Surg 2003;238:315–321. (discussion 321–313).
4. Izumi R, Shimizu K, Ii T, et al. Prognostic factors of hepatocellular carcinoma in patients undergoing hepatic resection. Gastroenterology 1994;106:720–727.
5. Poon RT, Fan ST, Lo CM, et al. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg 2002;235:373–382. doi:10.1097/00000658-200203000-00009.
6. Belghiti J, Cortes A, Abdalla EK, et al. Resection prior to liver transplantation for hepatocellular carcinoma. Ann Surg 2003;238:885–892. (discussion 892–883). doi:10.1097/01.sla.0000098621.74851.65.
7. Shah SA, Cleary SP, Tan JC, et al. An analysis of resection vs transplantation for early hepatocellular carcinoma: defining the optimal therapy at a single institution. Ann Surg Oncol 2007;14:2608–2614. doi:10.1245/s10434-007-9443-3.
8. Sarasin FP, Giostra E, Mentha G, Hadengue A. Partial hepatectomy or orthotopic liver transplantation for the treatment of resectable hepatocellular carcinoma? A cost-effectiveness perspective. Hepatology 1998;28:436–442. doi:10.1002/hep.510280222.
9. Belghiti J, Carr BI, Greig PD, et al. Treatment before liver transplantation for HCC. Ann Surg Oncol 2008;15:993–1000. doi:10.1245/s10434-007-9787-8.
10. Sala M, Fuster J, Llovet JM, et al. High pathological risk of recurrence after surgical resection for hepatocellular carcinoma: an indication for salvage liver transplantation. Liver Transpl 2004;10:1294–1300. doi:10.1002/lt.20202.

J Gastrointest Surg (2009) 13:1029–1036
DOI 10.1007/s11605-009-0843-5

SSAT PLENARY PRESENTATION

Minimally Invasive Surgical Treatment of Sigmoidal Esophagus in Achalasia

Matthew J. Schuchert · James D. Luketich · Rodney J. Landreneau · Arman Kilic · Yun Wang · Miguel Alvelo-Rivera · Neil A. Christie · Sebastien Gilbert · Arjun Pennathur

Received: 23 May 2007 / Accepted: 18 February 2009 / Published online: 27 March 2009

Abstract
Background The appropriate surgical intervention for sigmoidal esophagus in the setting of achalasia remains controversial. The objective of this study is to review our experience with minimally invasive myotomy (MIM) and minimally invasive esophagectomy (MIE) in the treatment of these patients.
Methods We reviewed the records of 30 patients (19 men, 11 women); mean age 59.1 years (range 25–83 years) who underwent MIM (n=24) or MIE (n=6). Primary variables included perioperative and long-term outcomes. Univariate and multivariate analyses were performed to identify clinical variables predictive of myotomy failure.
Results The operative mortality was zero and median hospital stay was 2 days (MIM) and 7 days (MIE). On follow-up (mean 30.5 months), nine (37.5%) patients undergoing primary MIM had failure requiring redo myotomy (n=1) or esophagectomy (n=8). Univariate analysis showed that previous myotomy and duration of symptoms were significant predictors of failure of MIM, with patient age trending toward significance. Multivariate analysis showed age and longer symptom duration to be significant.
Conclusions MIM affords symptomatic improvement in many patients. Age and symptom duration may be preoperative indicators of MIM failure. MIE offers similar symptom relief but is associated with a longer hospital stay. Further prospective studies are required to define the optimum treatment algorithm in the management of these patients.

Keywords Achalasia · Sigmoid esophagus · Minimally invasive · Myotomy · Esophagectomy

The Society for Surgery of the Alimentary Tract 48th Annual Meeting, Washington DC, May 19–23, 2007.

M. J. Schuchert (✉) · J. D. Luketich · R. J. Landreneau · A. Kilic · M. Alvelo-Rivera · N. A. Christie · S. Gilbert · A. Pennathur
Division of Thoracic and Foregut Surgery, Heart, Lung and Esophageal Surgery Institute, UPMC Health System, Shadyside Medical Building, Suite 715, 5200 Centre Avenue, Pittsburgh, PA 15232, USA
e-mail: schuchertmj@upmc.edu

Y. Wang
Department of Biostatistics, University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA

Introduction

Achalasia is an idiopathic motility disorder of the esophagus characterized by aperistalsis of the esophageal body and failure of complete relaxation of the lower esophageal sphincter (LES) during deglutition.[1] Treatment options are palliative in nature and are directed at decreasing the lower esophageal sphincter pressure (LESP) to promote enhanced esophageal emptying.[2] Though Heller myotomy with partial fundoplication can achieve excellent long-term outcomes in 80–90% of patients with achalasia,[3,4] the optimal therapy for patients with sigmoidal esophageal changes remains controversial (Fig. 1).

Several authors advocate myotomy as the primary treatment in patients with sigmoidal esophagus, reserving esophagectomy for myotomy failure and persistent symptoms.[5,6] Others recommend primary esophagectomy, citing concerns regarding the capacity of a dilated, sigmoidal

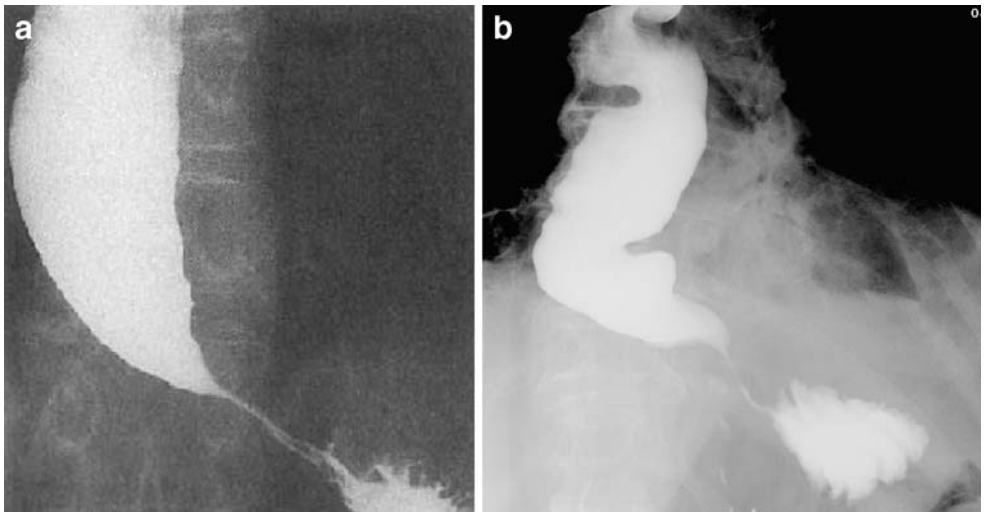

Figure 1 Radiographic features of achalasia. **a** Barium esophagram demonstrating classic "bird's beak" appearance consistent with achalasia. **b** Dilated and tortuous esophagus (sigmoidal esophagus) in a patient with chronic achalasia.

esophagus to empty efficiently even with a myotomy.[7–9] The aim of the current study is to review our experience with minimally invasive myotomy (MIM) and minimally invasive esophagectomy (MIE) in the treatment of patients with achalasia and sigmoidal esophagus.

Materials and Methods

Patients

Approval for this study was provided by the Institutional Review Board of the University of Pittsburgh. We performed a retrospective review of 250 patients undergoing minimally invasive Heller myotomy or MIE for achalasia at the University of Pittsburgh from 1992 to 2007. Sigmoidal esophageal changes were identified in 19 male and 11 female patients with a mean age of 59.1 years (range 25–83 years) (Table 1).

Table 1 Patient Demographics and Preoperative Data

	Primary myotomy (n=24)	Esophagectomy (n=6)	Significance (P value)
Age	61.3	50.2	NS
Gender	14 M, 10 F	5 M, 1 F	NS
Duration of symptoms (years)	18.6	19.0	NS
Preoperative resting LESP (mmHg)	28.1	20.0	NS
Prior endoscopic therapy (%)	79.2	100	NS
Previous myotomy (%)	8.3	16.7	NS
Dysphagia score	3.2	2.4	NS

LESP lower esophageal sphincter pressure

Preoperative Evaluation and Therapy

The diagnosis of achalasia was confirmed by barium esophagram demonstrating the classic appearance of achalasia (proximal esophageal dilation with a distal "bird's beak") and esophageal manometry (aperistalsis; LES with incomplete relaxation) when possible. In addition, each patient demonstrated sigmoidal esophageal changes by barium esophagram in varying geometrical configurations and with varying degrees of associated esophageal dilation. Preoperative manometry data is available in only 11 patients. Manometry was not required or was unable to be performed in the remaining patients due to difficulty in positioning the probe within the tortuous esophagus or to patient intolerance. All patients had a preoperative esophagogastroduodenoscopy to confirm the absence of other esophageal pathology prior to surgery. The most common presenting symptom was persistent or progressive dysphagia (95%), followed by regurgitation. Dysphagia scores were assessed preoperatively and postoperatively utilizing the following scale: 1=no dysphagia; 2=difficulty with hard solids; 3=difficulty with soft solids 4=difficulty with liquids; 5=cannot swallow saliva. Mean preoperative dysphagia score was 3.0. Mean duration of symptoms for the entire patient cohort was 18.7 years. Endoscopic therapy (balloon dilation, botulinum toxin injection, or both) was performed in 19 out of 24 (79.2%) patients prior to Heller myotomy and in six out of six (100%) patients prior to MIE. Prior myotomy had been performed in three (10%) patients—two in the myotomy group and one in the esophagectomy group.

Operative Technique

A minimally invasive approach was performed in all patients. Minimally invasive esophagomyotomy (±partial

Table 2 Postoperative Outcomes

	Primary myotomy (n=24)	Esophagectomy (n=6)	Significance (P value)
Median LOS (range)	2 (1–9)	7 (5–35)	0.025
Morbidity (%)	12.5	50	NS (0.09)
Mortality (%)	0	0	NS
Need for dilation (%)	37.5	66.7	NS
Mean improvement—dysphagia score	1.7	1.2	NS

LOS length of stay

fundoplication) was performed in 24 patients as described previously.[10] A partial fundoplication was performed in 22 out of 24 (91.7%) of the patients undergoing myotomy. In 17 (70.8%) patients, a posterior (Toupet) fundoplication was performed. An anterior (Dor) wrap was performed in five (20.8%) patients. Two patients (8.3%) underwent myotomy alone (Table 2). MIE was performed in six patients, as described previously.[11]

Postoperative Course

For MIM, patients were typically extubated in the operating room at the conclusion of the case. A barium swallow was performed on the first postoperative day and, if satisfactory, a clear liquid diet was initiated. Patients were typically discharged on the second postoperative day. Our current protocol is to evaluate the patients at 2 weeks for the first postoperative visit. Follow-up at 6 months, 1 year, and yearly thereafter is performed with repeat barium swallows. Manometry and esophageal transit studies are optional, based on surgeon and patient preference.

After MIE, patients remain nil per os with nasogastric tube decompression. Tube feeds are initiated at a low rate on postoperative day 3. A barium swallow is performed on postoperative day 5, after which a clear liquid diet is instituted. Patients are discharged home on a clear liquid diet and cycled night-time tube feeds. Patients are evaluated at 2 weeks, and their diet is advanced. The feeding tube is removed during their second postoperative visit if the diet is being tolerated well. Patients are then followed up yearly with repeat barium swallows.

Follow-Up

Follow-up data was successfully acquired in all patients. The primary postoperative outcome variables included length of stay, morbidity, mortality, and need for reoperation. Myotomy failure was defined as patients with no improvement in dysphagia score or those requiring reoperation (redo myotomy or esophagectomy). Postoperative dysphagia scores were assessed at each clinic or hospital visit and compared with preoperative values. Mean follow-up for all patients (MIM and MIE) was 25.3 months.

Statistical Analysis

Data were summarized with descriptive statistics (mean, standard deviation, median, and range for continuous variables, frequency, and percentage for categorical variables). A log rank test was used to assess the association between time to failure and age, duration of symptoms, previous myotomy, prior endoscopic treatment, and preoperative LESP. Univariate Cox regression model was used to assess the association between time to failure and age, duration of symptoms, and preoperative LESP as continuous variables, respectively. Multivariate Cox regression model was used to assess the association between time to failure and age, duration of symptom, and previous myotomy simultaneously.

Results

Perioperative Outcomes

Demographics and preoperative data are detailed in Table 1. Patients undergoing primary MIE were younger, had a higher rate of preoperative interventions, a lower LESP, and a higher incidence of "end-stage" sigmoidal megaesophagus on barium esophagram. None of these features attained statistical significance. Duration of symptoms and mean preoperative dysphagia scores were similar between the two groups. There were no perioperative deaths. MIM was associated with a similar improvement in symptoms compared with MIE, but had a significantly shorter length of hospital stay. There were trends towards less morbidity and reduced need for postoperative endoscopic interventions, though these did not attain statistical significance (Table 2). Complications were few and are detailed in Table 3. Pneumonia was the most common complication among

Table 3 Complications

Patient complications	Number
Minimally invasive myotomy (n=24)	
Pneumonia	2
Pneumothorax	1
Minimally invasive esophagectomy (n=6)	
Anastomotic leak	1
Hemothorax	1
Pleural effusion	1

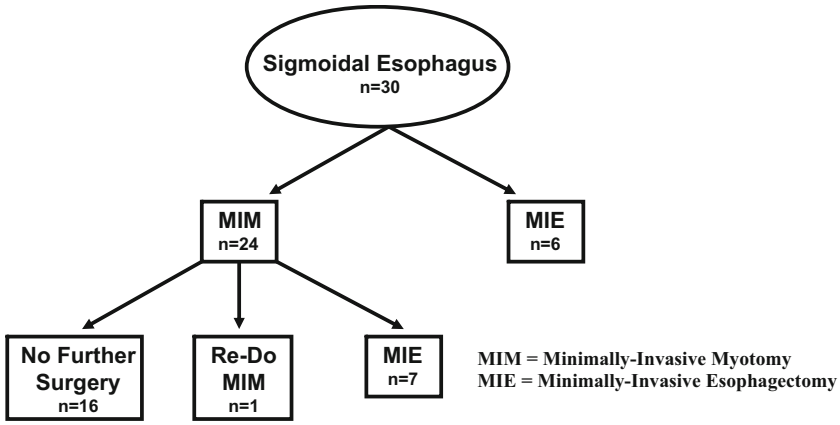

Figure 2 Clinical outcomes of patients with sigmoid esophagus.

the MIM group (8.3%). Complications in the MIE group included a contained anastomotic leak treated with opening of the cervical wound, a hemothorax necessitating drainage by video-assisted thoracoscopic surgery, and a pleural effusion.

Surgical Management of Sigmoidal Esophagus

From 1992 to 2007, 30 patients with sigmoidal esophageal changes in the setting of achalasia underwent surgical intervention. Among these, minimally invasive Heller myotomy was performed in 24 patients (Fig. 2). Partial fundoplication was performed in 22 (91.7%) of these patients (17 Toupet, five Dor). The remaining two patients underwent myotomy alone. Six patients received primary MIE. The principal criterion for primary esophagectomy was an end-stage sigmoidal esophagus in fit patients where long-term functionality of the esophagus was in doubt (Fig. 3). Among the 24 patients undergoing MIM, 15 patients (62.5%) had durable relief of dysphagia and required no further surgical intervention. Seven patients (29.2%) developed recurrent dysphagia and/or regurgitation, requiring subsequent esophagectomy. One patient required takedown of the partial wrap and extension of the myotomy, with improvement in her symptoms. One patient had no durable improvement after MIM and is considered a failure of therapy, but refused further surgical intervention and has been managed with periodic dilations (Fig. 2).

Analysis of Myotomy Failures

During follow-up (mean 30.5 months; range 0.3–105.4 months), nine patients (37.5%) undergoing MIM were considered clinical failures due to the need for subsequent operative intervention ($n=8$) or lack of symptomatic improvement ($n=1$). Mean time to myotomy failure was 18.4 months. Interestingly, there was no apparent correlation between preoperative radiographic findings and outcomes in either group. Similarly, there was no apparent correlation with surgical approach and rate of failure following myotomy. There were two failures with the Dor approach (40%), six with the Toupet approach (35.3%), and one with myotomy alone (50%).

A comparison of the clinical features between successful and failed myotomy is shown in Table 4. All patients who failed myotomy had prior endoscopic interventions. Both patients with a history of previous myotomy undergoing a redo myotomy failed and required subsequent esophagectomy. Myotomy failure was associated with a trend toward lower preoperative LESP (19.5 versus 33.8 mmHg) and longer duration of symptoms (24.8 versus 13.1 years) when compared with patients with successful outcomes after MIM (Table 4). Univariate analysis to assess the association between myotomy failure and age, duration of symptoms,

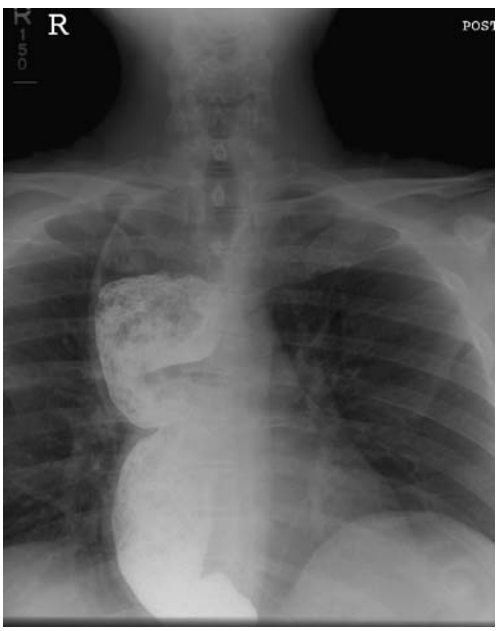

Figure 3 End-stage sigmoidal esophagus. Significant dilation is noted with food and fluid retention.

Table 4 Analysis of Failures After MIM

	Myotomy success (n=15)	Myotomy failure (n=9)	Significance (P value)
Age	66.2	53.1	NS (0.064)
Sex	9 M, 6 F	5 M, 4 F	NS
Symptom duration (years)	13.1	24.8	NS (0.098)
LESP (mmHg)	33.8	19.5	NS
Prior endoscopic therapy (%)	66.7	100	NS
Prior myotomy (%)	0	22.2	NS
Preoperative dysphagia score	3.2	3.1	NS

LESP lower esophageal sphincter pressure

prior myotomy, preoperative LESP, and prior endoscopic therapy was performed. Univariate analysis showed that previous myotomy and duration of symptoms were significant predictors of failure of MIM, with patient age demonstrating a strong trend toward significance. Multivariate analysis identified patient age and symptom duration as independent predictors of myotomy failure (Table 5).

Discussion

MIM has been established as a highly effective treatment modality in the management of patients with achalasia, with a greater than 80–90% long-term success rate.[12,13] The development of sigmoidal esophageal changes in the setting of achalasia presents a unique set of challenges in surgical management. As achalasia progresses, the esophagus can progressively dilate and acquire tortuous undulations due to persistent obstruction to forward flow, retained foodstuff, and pressurization from swallowed air.[8] These anatomic features further impair esophageal emptying and promote food retention and/or impaction, resulting in recurring dysphagia as well as regurgitation. The progressive nature of these findings has led some to believe that myotomy alone is unlikely to succeed long-term in patients with dilated, sigmoidal esophageal changes where a functionless esophagus fails to empty efficiently even after myotomy,

Table 5 Univariate and Multivariate Analyses

Variable	P value
Univariate analysis	
Sex	0.79[a]
Age	0.07[b]
Duration of symptom	0.04[b]
Preoperative LESP	0.18[b]
Previous myotomy	0.04[a]
Prior endoscopic treatment	0.16[a]
Multivariate analysis	
Age	0.02
Duration of symptoms	0.02

[a] Log rank test

[b] Likelihood ratio test

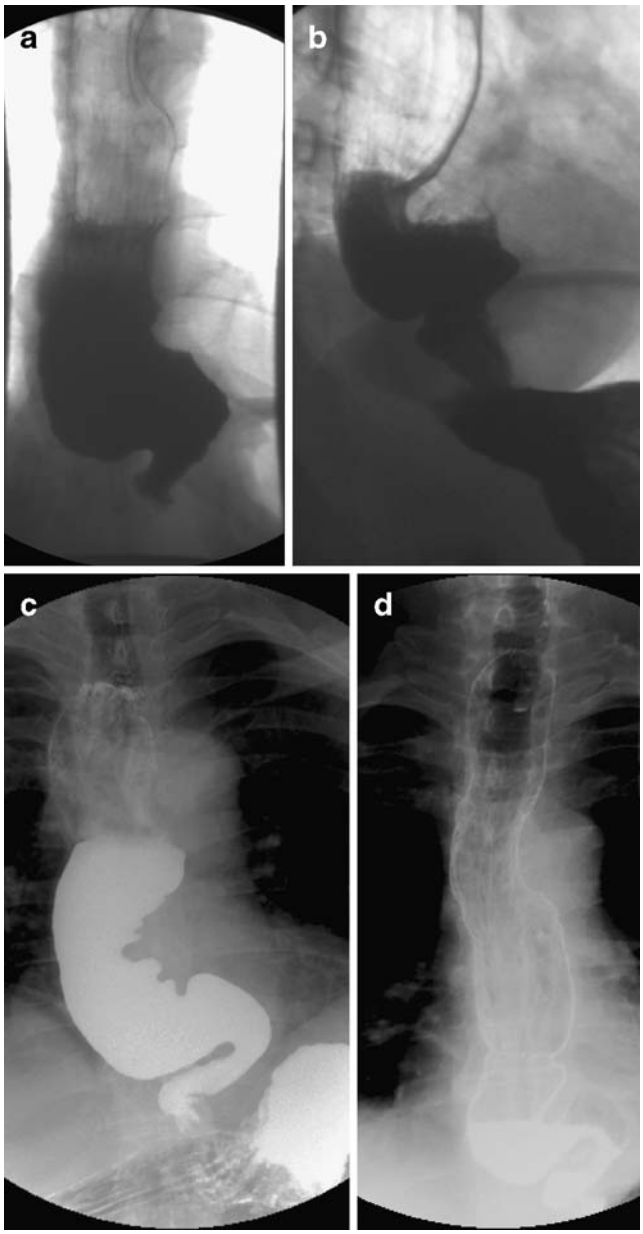

Figure 4 Radiographic improvement after Heller myotomy and relief of distal esophageal obstruction (**a**, **c** preoperative; **b**, **d** postoperative). **a** Sigmoidal esophagus prior to Heller myotomy. **b** Improved emptying of sigmoidal esophagus immediately following Heller myotomy. **c** Significant dilation and sigmoidal changes prior to Heller myotomy. **d** Decreased distension and sigmoidal angulation, as well as improved emptying, 3.5 years after Heller myotomy.

promoting the risk of retention esophagitis, regurgitation, and carcinoma.[9,14] From this perspective, esophagectomy provides a definitive "curative" solution for advanced or refractory achalasia with excellent relief of symptoms in the majority of patients.[9,15,16]

Concern is routinely raised regarding the morbidity and mortality of esophagectomy for benign disease. In experienced centers, mortality rates range from 1% to 5%.[17] MIE is a particularly useful technique in the setting of advanced achalasia. Several technical concerns encountered during open esophagectomy for achalasia include difficulty encircling the dilated esophagus, deviation of the esophagus into the right chest, enlarged aortoesophageal arteries, and the adherence of the exposed esophageal submucosa to the adjacent aorta subsequent to myotomy.[9] The enhanced visualization achieved with a laparoscopic/thoracoscopic approach can augment the successful management of each of these issues with acceptable morbidity and low mortality (1.4%).[11]

Several studies have shown, however, that esophageal resection may not be necessary in all patients with a sigmoid esophagus. Patti and colleagues evaluated the outcomes of seven patients with sigmoidal esophageal changes treated primarily with laparoscopic Heller myotomy and Dor fundoplication.[5] They were able to achieve good–excellent results in 100% of the patients with complete resolution or significant improvement in dysphagia, regurgitation, and chest pain. None of the patients in their study required further operative intervention. Mineo and coworkers evaluated 14 patients with achalasic sigmoid esophagus treated with an open or minimally invasive Heller myotomy and Dor fundoplication by the same surgeon.[6] In this series, ten out of 14 patients (71.4%) achieved good–excellent results with similar morbidities and hospital stays after the operation compared to those patients without a dilated esophagus. In addition, a substantial reduction in postoperative LESP and esophageal width was noted secondary to the relief of distal obstruction. Importantly, quality of life measures (SF-36) improved in all measured domains.

Currently, there are no randomized data available to definitively establish who should undergo primary myotomy or esophagectomy in the setting of advanced achalasia with sigmoid esophagus. The Practice Parameters Committee of the American College of Gastroenterology currently recommends graded pneumatic dilatation or laparoscopic myotomy as primary therapy for patients with achalasia (including early sigmoidal changes) and propose esophagectomy for those patients with megaesophagus (>8 cm) and those with low LESP with persistent symptoms.[18] In addition to sigmoid esophagus, several preoperative features have been postulated to impact negatively upon the results of myotomy including low preoperative LESP,[19,20] prior endoscopic therapy,[21,22] and longer duration of symptoms.[23] In the current series, each of these variables was seen more commonly in patients who failed primary myotomy (Table 4). Multivariate analysis confirmed age and duration of symptoms as independent risk factors for myotomy failure (Table 5).

Despite this, the majority (15 out of 24; 62.5%) of patients with sigmoidal esophagus in the present study achieved durable improvement in dysphagia and regurgitation, requiring no further operative intervention (redo myotomy or esophagectomy) at a mean follow-up of 30.5 months. In addition, myotomy was associated with reduced length of stay and a trend toward decreased morbidity compared with esophagectomy (Table 2). Similar to the observations of Mineo and associates,[6] the relief of distal obstruction not only improved patient symptoms, but was associated with improved anatomic features (decreased width and curvature, improved emptying) of the esophagus on barium esophagram in several cases (Fig. 4).

Conclusion

Minimally invasive Heller myotomy can be performed safely in patients with sigmoidal esophageal changes and can be successful in many patients with this condition. Significant symptomatic improvement can be achieved in approximately two thirds of these patients, without need for further operative intervention. Younger patients with longer duration of symptoms are at higher risk for myotomy failure, and consideration should be given to primary esophagectomy in this setting. Failure of myotomy in the setting of sigmoidal esophageal changes is likely multifactorial in nature, however, and the decision to perform primary myotomy or esophagectomy should thus be individualized based on patient characteristics as well as surgeon experience and judgment. Further prospective studies with longer-term follow-up are required to define the optimal treatment algorithm in these patients.

Acknowledgements The authors wish to acknowledge the important contributions of Diane Sabilla, Kathy Lovas, Theresa Krupka, and Darla Justus in database organization and management.

References

1. Lendrum FC. Anatomic features of the cardiac orifice of the stomach with special reference to cardiospasm. Arch Intern Med 1937;59:474–511.
2. Spiess AE, Kahrilas PJ. Treating achalasia: from whalebone to laparoscope. JAMA 1998;280:638–642.
3. Richards WO, Torquati A, Holzman MD, Khaitan L, Byrne D, Lutfi R, Sharp KW. Heller myotomy versus Heller myotomy with Dor fundoplication for achalasia: a prospective, randomized, double-blind clinical trail. Ann Surg 2004;240:405–415.

4. Patti MG, Fisichella PM, Perretta S, Galvani C, Gorodner MV, Robinson T, Way LW. Impact of minimally-invasive surgery on the treatment of esophageal achalasia: a decade of change. J Am Coll Surg 2003;196:698–705.
5. Patti MG, Feo CV, Diener U, Tamburini A, Arcerito M, Way LW. Laparoscopic Heller myotomy relieves dysphagia when the esophagus is dilated. Surg Endosc 1999;13:843–847.
6. Mineo TC, Pompeo E. Long-term outcome of Heller myotomy in achalasic sigmoid esophagus. J Thorac Cardiovasc Surg 2004;128:402–407.
7. Pinotti HW, Cecconello I, Mariano da Rocha J, Zilberstein B. Resection for achalasia of the esophagus. Hepatogastroenterology 1991;38:470–473.
8. Peters JH, Kauer WKH, Crookes PF, Ireland AP, Brenner CG, DeMeester TR. Esophageal resection with colon interposition for end-stage achalasia. Arch Surg 1995;130:632–637.
9. Devaney EJ, Lannettoni MD, Orringer MB, Marshall B. Esophagectomy for achalasia: patient selection and clinical experience. Ann Thorac Surg 2001;72:854–858.
10. Luketich JD, Fernando HC, Christie NA, Buenaventura PO, Keenan RJ, Ikramuddin S, Schauer PR. Outcomes after minimally-invasive esophagomyotomy. Ann Thorac Surg 2001;72:1909–1913.
11. Luketich JD, Alvelo-Rivera M, Buenaventura PO, Christie NA, McCaughan JS, Litle VR, Schauer PR, Close JM, Fernando HC. Minimally invasive esophagectomy: outcomes in 222 patients. Ann Surg 2003;238(4):486–494.
12. Patti MG, Pellegrini CA, Horgan S, Arcerito M, Omelanczuk P, Tamburini A, Diener U, Eubanks TR, Way LW. Minimally-invasive surgery for achalasia: an 8-year experience with 168 patients. Ann Surg 1999;230(4):587–594.
13. Rosemurgy A, Villadolid D, Thometz D, Kalipersad C, Rakita S, Albrink M, Johnson M, Boyce W. Laparoscopic Heller myotomy provides durable relief from achalasia and salvages failures after BoTox or dilation. Ann Surg 2005;241:725–735.
14. Peracchia A, Segalin A, Bardini R, Ruol A, Bonavina L, Baessato M. Esophageal carcinoma and achalasia: prevalence, incidence and results of treatment. Hepatogastroenterology 1991;38:514–516.
15. Banbury MK, Rice TW, Goldblum JR, Clark SB, Baker ME, Richter JE, Rybicki LA, Blackstone EH. Esophagectomy with gastric reconstruction for achalasia. J Thorac Cardiovasc Surg 1999;117:1077–1085.
16. Miller DL, Allen MS, Trastek VF, Deschamps C, Pairolero PC. Esophageal resection for recurrent achalasia. Ann Thorac Surg 1995;60:922–926.
17. Schuchert MJ, Luketich JD, Fernando HC. Complications of minimally-invasive esophagectomy. Semin Thorac Cardiovasc Surg 2004;16(2):133–141.
18. Vaezi MF, Richter JE. Diagnosis and management of achalasia. Am J Gastroenterol 1999;94(12):3406–3412.
19. Arain MA, Peters JH, Tambankar AP, Portale G, Almogy G, DeMeester SR, Crookes PF, Hagan JA, Bremner CG, DeMeester TR. Pre-operative lower esophageal sphincter pressure affects outcome of laparoscopic esophageal myotomy for achalasia. J Gastrointest Surg 2004;8(3):328–334.
20. Torquati A, Richards WO, Holzman MD, Sharp KW. Laparoscopic myotomy for achalasia: predictors of successful outcome after 200 cases. Ann Surg 2006;243:587–593.
21. Smith CD, Stival A, Howell DL, Swafford V. Endoscopic therapy for achalasia before Heller Myotomy results in worse outcomes than Heller myotomy alone. Ann Surg 2006;243(5):579–586.
22. Portale G, Costantini M, Rizzetto C, Guirroli E, Ceolin M, Salvador R, Ancona E, Zaninotto G. Long-term outcome of laparoscopic Heller–Dor surgery for esophageal achalasia: possible detrimental role of previous endoscopic treatment. J Gastrointest Surg 2005;9(9):1332–1339.
23. Schuchert MJ, Luketich JD, Landreneau RJ, Kilic A, Gooding WE, Alvelo-Rivera M, Christie NA, Gilbert S, Pennathur A. Minimally-invasive esophagomyotomy in 200 patients: factors influencing post-operative outcomes. Ann Thorac Surg 2008;85:1729–1734.

Discussion

969. Minimally Invasive Surgical Treatment of Sigmoid Esophagus in Achalasia. Paper presented by Matthew J. Schuchert, M.D., Pittsburgh, PA. E-mail: schuchertmj@upmc.edu

Discussion by Lee L. Swanstrom, M.D., Oregon
E-mail: lswanstrom@aol.com

Dr. L. Swanstrom (Portland, OR):

I would like to represent both some of my own questions as well as some comments by Blair Jobe, who was the original discussant and who is tied up at another session.

I would first like to compliment Dr. Schuchert and the folks from the University of Pittsburgh for their large series. It is one of the largest series that I presume will soon be in the literature and certainly represents their great experience in these very difficult cases. To recap, out of their 250 patients having minimally invasive surgery for achalasia, they had 30 who had a sigmoid esophagus, a very difficult end-stage finding. Of those, six had an esophagectomy as a primary treatment. There were several other salvage treatments of esophagectomy following myotomy. It should be noted that I think what is unusual with this is that the majority of these patients (25 out of 30) had previous treatment, which once again shows that this is an end-stage phenomenon.

Dr. Jobe commented that only 11 of these patients had preoperative manometry. He certainly stresses, and I concur, that preoperative motility testing is very valuable in these difficult cases. You have one-shot short of esophagectomy, so certainly every test that you can do would be good, including manometry and perhaps even pH testing if they have had previous myotomies or balloon dilatation to see if this could be related to GERD causing their failure.

Three questions were presented by Blair and then I have a couple of my own. One deals with manometry. How did you decide which approach to use as the primary therapy? In other words, what was your triage strategy in determining who went directly to esophagectomy versus myotomy? The second question is, please describe your technique for the myotomy. Was the myotomy carried down onto the stomach? Did you go to extra lengths carrying it proximally and distally? And how did you assess the completeness of the myotomy in the six failures that went on to esophagectomy? Three is, were any of the reinterventions after the primary therapy for GERD-related complications, particularly in those that did not have a fundoplication?

A couple of my own questions would be, do you advocate any techniques to correct the angulation of the distal esophagus? Do you perform an extended type II mediastinal dissection? And perhaps we should reconsider, especially if there were not GERD-related complications, not doing a fundoplication on these patients, because that, of course, adds a little bit of outflow resistance.

Thank you very much.

969. Minimally Invasive Surgical Treatment of Sigmoid Esophagus in Achalasia. Response by Matthew J. Schuchert, M.D., Pittsburgh, PA

Dr. Schuchert: Thank you very much, Dr. Swanstrom, for your insightful commentary and questions. We agree that preoperative manometry represents an important part of the work-up in patients in whom we are contemplating myotomy. Preoperative manometry was attempted in the majority of the patients undergoing myotomy in the current study. In cases where we could not get manometry, it was due to either difficulty with probe placement within a dilated, tortuous esophagus or due to patient refusal. We do agree that having all the information possible before making surgical decisions in these complex cases definitely is important and should be emphasized.

The principal determinant for deciding our approach, whether myotomy or esophagectomy, was somewhat subjective when you go back and review the charts and the thoughts of the individual surgeons. The most common reason was a dilated end-stage-appearing megaesophagus, where it was the opinion of the surgeon that is it was highly unlikely that a meaningful functional result could be achieved with myotomy alone. Esophagectomy was also considered in end-stage cases among younger patients with a longer expected life-span, who were deemed fit for esophagectomy. So those would be our main criteria, a burned-out mega esophagus and a younger, fit patient who might better tolerate primary esophagectomy. Going forward, what we have learned from the current analysis is that younger patients who have longer duration of symptoms (especially >15 years) may represent a high-risk group for long-term myotomy failure. Esophagectomy may be a reasonable option in these patients.

With regard to myotomy technique, after mobilizing the esophagogastric fat pad we extend our myotomy proximally at least 4–6 cm above the GE junction to reach a level of normal-appearing muscle. We pay particular attention to extending the myotomy onto the stomach by at least 1 to 2 cm, with very meticulous and careful dissection of the sling fibers of the proximal stomach. Intraoperatively we also perform endoscopy both before and after the myotomy to confirm visual release of the narrowed segment and abrogation of the associated "pop." We routinely perform a partial fundoplication after completion of the myotomy.

The majority of failures following myotomy in this series were due to refractory dysphagia. With respect to GERD-related failures, there was one patient after primary myotomy who developed significant GERD with associated stricture, both subjectively and objectively confirmed, who ended up requiring subsequent esophagectomy.

We do feel that there is some importance in correcting the angulation of the esophagus intraoperatively, and we do spend a significant amount of time with our mediastinal dissection to try to straighten out the esophagus when possible. We feel that this approach may help to improve the dynamics of emptying, and may help to resolve the sink-trap effect that can be seen above the diaphragm in these patients.

Whether or not to add a fundoplication after myotomy in these patients can be debated given the severity of their disease. It is our practice to perform a partial fundoplication in these patients to minimize the risk of postoperative GERD symptoms, as highlighted in the prospective, randomized trial by Richards and associates (Ann Surg 2004;240:405–415).

969. Minimally Invasive Surgical Treatment of Sigmoid Esophagus in Achalasia. Paper presented by Matthew J. Schuchert, M.D., Pittsburgh, PA. E-mail: schuchertmj@upmc.edu

Discussion by Nathaniel J. Soper, M.D., Illinois

E-mail: nsoper@nmh.org

Dr. N. Soper (Chicago, IL):

That was a great talk. I will make one follow-up question to Lee, and that is, the patient who had the reflux-associated stricture and problems, had that patient had a fundoplication at the initial myotomy?

969. Minimally Invasive Surgical Treatment of Sigmoid Esophagus in Achalasia. Response by Matthew J. Schuchert, M.D., Pittsburgh, PA

Dr. Schuchert: Yes. What ended up happening was that patient had a partial fundoplication at the time of the initial operation. This was taken down and an attempted redo myotomy was performed which failed, and the patient ultimately went on to esophagectomy.

Dr. Soper: The other question is I believe there were seven patients who had the initial myotomy and then went on to esophagectomy. Was that subsequent esophagectomy made more difficult by the myotomy? In other words, is there much harm done by initially trying a myotomy in the majority of these patients, among whom some may have to ultimately go on to esophagectomy?

Dr. Schuchert: The mediastinal dissection, myotomy and wrap does create some additional scarring at the level of the hiatus, but in none of the cases did that dissection significantly influence our ability to do the esophagectomy. So I would say that prior attempts at myotomy can make the dissection more challenging, but do not appear to have a significant impact on outcomes with subsequent esophagectomy.

J Gastrointest Surg (2009) 13:1037–1043
DOI 10.1007/s11605-009-0836-4

ORIGINAL ARTICLE

Esophagus Tissue Engineering: Hybrid Approach with Esophageal Epithelium and Unidirectional Smooth Muscle Tissue Component Generation *In Vitro*

Amulya K. Saxena · Kristina Kofler · Herwig Ainödhofer · Micheal E. Höllwarth

Received: 30 October 2008 / Accepted: 18 February 2009 / Published online: 10 March 2009

Abstract
Purpose The aim of this study was to engineer the two main components of the esophagus in vitro: (a) esophageal epithelium and (b) smooth muscle tissue. Furthermore, (a) survivability of esophageal epithelial cells (EEC) on basement membrane matrix (BMM)-coated scaffolds and (b) oriented smooth muscle tissue formation on unidirectional BMM-coated collagen scaffolds was investigated.
Methods Both EEC and smooth muscle cells (SMC) were sourced from Sprague–Dawley rats. The EEC were maintained in vitro and seeded onto BMM-coated 2-D collagen scaffolds. Similarly, smooth muscle cells were obtained using an explants technique and seeded on unidirectional 3-D BMM-coated collagen scaffolds. Cell–polymer constructs for EEC and SMC were maintained in vitro for 8 weeks.
Results Protocols to obtain higher yield of EEC were established. EEC formed a layer of differentiated epithelium after 14 days. EEC survivability on polymers was observed up to 8 weeks. Unidirectional smooth muscle tissue strands were successfully engineered.
Conclusion Esophageal epithelium generation, survivability of EEC on BMM-coated scaffolds, and engineering of unidirectional smooth muscle strands were successful in vitro. The hybrid approach of assembling individual tissue components in vitro using BMM-coated scaffolds and later amalgamating them to form composite tissue holds promises in the tissue engineering of complex organ systems.

Keywords Tissue engineering · Esophagus · Epithelium · Smooth muscle · Collagen · Hybrid · Basement membrane matrix

This research is funded by the European Union within the 6th Framework Program (EuroSTEC; LSHC-CT-2006–037409).

XXIst International Symposium on Pediatric Surgical Research, 2–4 October 2008, Leipzig, Germany

A. K. Saxena (✉) · K. Kofler · H. Ainödhofer · M. E. Höllwarth
Department of Pediatric and Adolescent Surgery,
Medical University of Graz,
Auenbruggerplatz-34,
8036 Graz, Austria
e-mail: amulya.saxena@meduni-graz.at

Introduction

Congenital malformation of the esophagus in form of esophageal atresia is relatively common and has an incidence of 1:3,000–5,000 births.[1] Surgical repair and bridging of the esophagus in these newborns by primary anastomosis is successful in the majority of cases; however, bridging of long-gap esophageal atresia still poses challenges in surgical management. In patients with long-gap atresia, surgical approaches such as (a) delayed repair (primary hitching of the esophagus end to the prevertebral fascia or the Foker technique), myotomy, and (b) esophageal replacement with either gastric, jejunum, or colon transposition have provided possible solutions.[2–4] However, these strategies are frequently associated with a high rate of short- and long-term complications that include leakage, stricture, elongation, and gastro-esophageal reflux.[5–7] Tissue engineering of the

esophagus could overcome these limitations and offer viable alternatives to these approaches.

The challenges in the tissue engineering of the esophagus lie in the anatomic complexity of this tubular organ.[8] Firstly, the esophagus transverses three anatomic planes: the neck, the thorax, and the abdomen. Since replacement of esophageal tissue will be required in the thoracic area, concerns relating to vascularization of tissue-engineered esophagus will have to be addressed; if substantial sizes of esophagus are engineered and replaced. Secondly, the esophagus performs two functions: (a) propulsive peristalisis of the swallowed bolus and (b) resisting of reflux of gastric juices by the lower and upper esophageal sphincter. As the thoracic part of the esophagus is mainly involved in bolus transport, the propulsive component which is dependant on elasticity of this organ will have to be addressed in attempts to engineer the esophagus. Thirdly, the esophagus presents histological variations according to localization, with (a) skeletal muscle in the cranial part, (b) mucous secreting cells for lubricating the esophagus, and (c) oriented smooth muscle (inner circular and outer longitudinal) through the caudal part. The heterogeneity of the esophagus in terms of location, function, and tissue variation have impeded the efforts in tissue engineering.

Experimental efforts have been made to replace the esophagus using tissue-engineering-based techniques. Replacement of esophagus in vivo has been performed with patch or circumferential implantation using synthetic as well as natural scaffolds: polyglycolic acid, acellular porcine aorta, small intestine submucosa, and a silicone/collagen hybrid.[9–13] When circumferential scaffolds using biomaterials were employed, they were found to be associated with complications ranging from stricture to dilation, including little or no muscle regeneration in these implants, which further raised questions on the propulsive ability of these grafts. Furthermore, studies using patch grafts (scaffolds) were more successful and demonstrated that coverage of 2–5 cm grafts by adjacent epithelium is a process that requires 3–4 weeks for complete epithelialization. However, when autologous epithelial cells were seeded into the grafts (scaffolds), epithelialization occurred within a period of 2 weeks after implantation and was observed to be associated with increased regeneration of the mesenchymal tissue.[14] Based on the success of scaffold epithelialization, studies further investigated the in vitro interaction of esophageal epithelial cells with scaffolds such as collagen and/or polyglycolic acid scaffolds.[15,16] Taking the results of these studies into account, our strategy to esophagus tissue engineering is based on the approach of assembling the individual hetrogenous components in vitro, which could be assimilated to construct a composite hybrid tissue for in vivo implantation.

The aim of this study was to engineer in vitro the two main components of the esophagus in rats: esophageal epithelium and smooth muscle tissue. Furthermore, to investigate (a) the survivability of esophageal epithelial cells (EEC) on basement membrane matrix (BMM)-coated scaffolds and determine cell migration when EEC were maintained on scaffold tubes, and (b) the possibility of oriented smooth muscle tissue formation on unidirectional scaffolds.

Methods

Epithelial Cell Isolation and Culture

Rat esophageal epithelial cells (REEC) were isolated by using an explants technique and modifying a previously published protocol.[17] Briefly, a rat esophagus was harvested from an adult female Sprague–Dawley rat as approved by the Animal Care and Use Committee at Ministry of Science and Research, Vienna, Austria. The esophagus was rinsed well in 4°C phosphate-buffered saline (Sigma-Aldrich, St. Louis, MO, USA) containing antibiotics (100 U/ml penicillin G sodium, 100 mg/ml streptomycin sulfate, and 0.25 mg/ml amphotericin B; Sigma-Aldrich) and incubated overnight at 4°C in dispase (50 caseinolytic units/ml; BD Biosciences, Bedford, MA, USA) containing antibiotics. The next day, the epithelium was mechanically separated from the connective tissue and cut longitudinally using an operating microscope or loops to magnify the structures. The epithelium was further cut in to 2–3 mm pieces. Tissue culture dishes (24-well plates) were coated with BMM (Matrigel, BD Biosciences) and incubated for 30 min. The esophageal pieces were then attached to the culture dish using BMM and incubated for further 30 min. Culture media were added, and the explants were incubated at 37°C and 5%CO_2. The culture media consisted of EpiLife basal media (Cascade Biologics, Portland, OR, USA) to which calcium was added to reach a concentration of 0.06 mM Ca++, supplemented with Human Keratinocyte Growth Supplement (HKGS, Cascade Biologics), bovine pituitary extract (0.2%), insulin (5 μg/ml), hydrocortisone (0.18 μg/ml), human epidermal growth factor (0.2 ng/ml), transferrin (5 μg/ml), triiodothyronine (6.51 ng/ml; Sigma-Aldrich), and glutamine–penicillin–streptomycin/amphotericin-B (Sigma-Aldrich). Dissociation of epithelial cells from the epithelium occurred after 48 h (Fig. 1). The explants were detached, and the cells were separated from the epithelium using mechanical dissociation by a 10-ml pipette. The solution was passed though a 50-μm filter, and the cells collected and re-suspended on the same tissue culture dishes previously used for explants attachment. Media was changed every 48 h, and the cells were maintained in culture until confluence was reached.

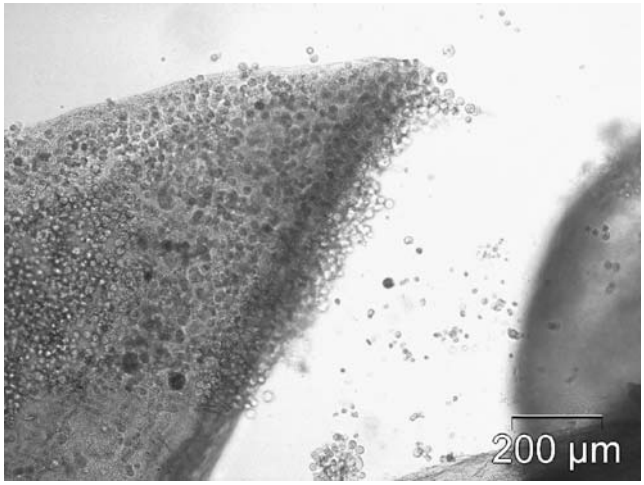

Figure 1 Esophgeal epithelial explant attached using BMM on 24-well plates. After 48 h, cells begin to detach from the explants (*spherical cells*) and can be seen migrating away on the BMM-coated tissue culture dishes (20x).

Smooth Muscle Cell Isolation and Culture

Rat smooth muscle cells (RSMC) were sourced from the aorta (due to the small size of the rat esophagus which was use to maximize epithelial cell counts), which was dissected and cut longitudinally to expose the luminal surface. This tunica intima was scrapped using a scalpel, and tunica adventitia was separated similarly from the tunica media. The tunica media was then placed in Dulbecco's modified essential medium (DMEM; 4.5 g/l glucose; Sigma-Aldrich) containing antibiotics (100 U/ml penicillin G sodium, 0.1 mg/ml streptomycin sulfate, and 2.5 μg/ml amphotericin B; Sigma-Aldrich) and incubated overnight. The next day, the tissue was cut into 2 mm pieces and placed in 24-well plates precoated with BMM. After incubation at 37°C and 10%CO_2 for 30 min to allow tissue attachment, media was added, DMEM (4.5 g/l glucose; Sigma-Aldrich) supplemented with 20% fetal bovine serum (Gibco, Invitrogen, Carlsbad, CA, USA), penicillin (100 U/ml), streptomycin (100 μg/ml), and amphotericin (2.5 μg/ml). Tissue was incubated for 7 days at 37°C without changing media to avoid detachment and allow cell growth (Fig. 2). Tissue explants were removed, and growth medium was then changed every 48 h, and when cell confluence was reached; the cells were passaged and replated at a density of 10,000 cells/cm^2 (Fig. 3).

Collagen Scaffold and Cell Seeding

OptiMaix™ collagen scaffolds (Matricel GmbH, Herzogenrath, Germany) 13 mm diameter were used as scaffolds for REEC and RSMC seeding. OptiMaix™ scaffolds provide a unique matrix for in vitro investigation which is the result of a patented manufacturing process which involves unidirectional solidification and freeze-drying of an aqueous dispersion containing 1.5 wt.% of porcine collagen (mainly type I) and low amounts of elastin.[18] Through this process, a controlled, homogeneous, and well-organized unidirectional pore structure with pore sizes between 25 and 100 μm can be produced (Fig. 4). Scaffolds were removed from sterile packaging and pre-coated with BMM for 1 h at 37°C.

REEC (seventh day) were seeded on the surface of OptiMaix-2D (2-D) scaffolds at a density of 100,000 cells/cm^2 using a drop-on seeding technique, while the RSMC (21st day) were seeded on OptiMaix-3D scaffolds with a drop-in seeding technique at a density of 250,000 cells/cm^2. The cells were allowed to adhere for 30 min before introducing media into the wells. Precaution was taken to provide media sufficient enough to cover the scaffold, in order to prevent its dislodgement from the culture plates initially. Media was changed every alternative day, and disks were removed in regular weekly intervals (1, 2, 3, 4, 5, 6, 7, and 8 weeks) for histochemical analysis. RSMC were also seeded on nondirectional collagen scaffolds (Symatese Biomateriaux, Chaponost, France) of identical dimensions to histologically compare the orientation of the tissue generated.

Results

The explant technique for isolation of REEC was repeated in ten rats and was successful for the recruitment of cells

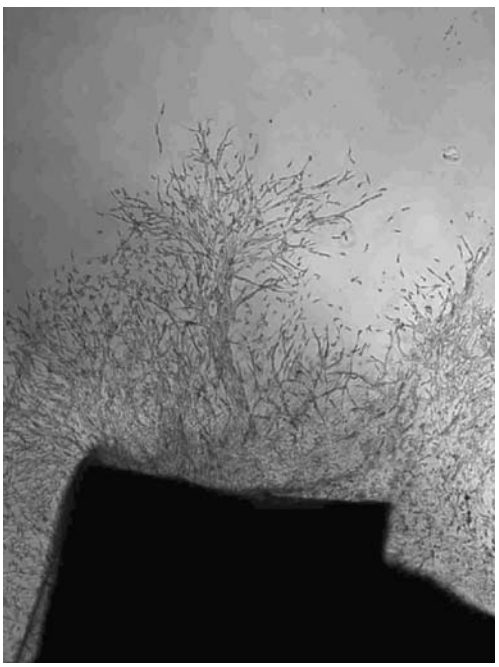

Figure 2 Smooth muscle cells migrating and proliferating from the tunica media explants attached to the tissue culture dish with BMM (10x).

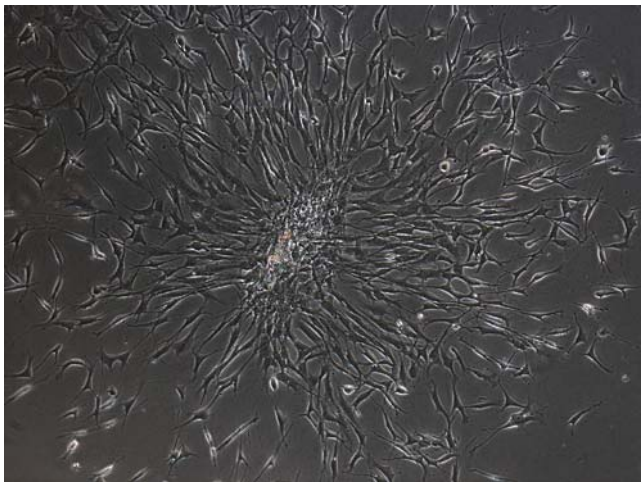

Figure 3 After smooth muscle cells reach confluence, the cells are passaged and replated (*above*) on BMM-coated tissue culture dishes for further proliferation (20x).

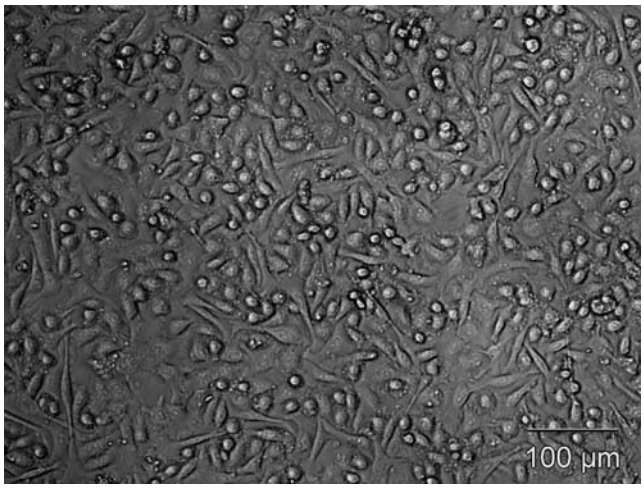

Figure 5 Esophageal epithelial cells after 7 days in culture exhibiting the cobble-stone morphology and confluence (40x).

from the epithelial layer which has advantages in overcoming cell loss that may occur due to the action of trypsin. After isolation, the REEC plated on BMM-coated culture dishes exhibited a cobblestone morphology characteristic of epithelial cells after 7 days in culture (Fig. 5). REEC differentiation was further observed, and after 14 days, differentiation to mature esophageal epithelium was complete (Fig. 6). During this time, REEC exhibited confluence and filled the entire wells with a single squamous epithelial layer (Fig. 4). Squamous epithelial cells were stained using cytokeratin marker CK-14 after 14 days in culture and confirmed the purity of REEC cultures with positive staining (no additional cell types were observed).

REEC were successfully seeded on the surface of BMM-coated OptiMaix™ 2-D scaffolds using the drop-on seeding technique. Constructs removed at 1, 2, 3, 4, 5, 6, 7, and 8 weeks of in vitro culture were investigated for cell viability and expression of CK-14. REEC seeded on scaffolds expressed CK-14 on all constructs investigated up to the eighth week of in vitro culture. REEC were found to survive in isolation as well as in groups scaffold even after 8 weeks (Fig. 7). Immunohistochemical markers confirmed the presence of only one cell type (REEC) on the scaffold, confirming the purity of the REEC on scaffolds.

RSMC were successfully seeded in the BMM-coated OptiMaix™ 3-D scaffolds using the drop-in seeding technique. Constructs removed at 1, 2, 3, 4, 5, 6, 7, and 8 weeks of in vitro culture were investigated for cell viability and expression of α-smooth muscle actin markers. RSMC expressed α-smooth muscle actin in all constructs investigated up to 8 weeks. Further proliferation and differentiation of RSMC to cover the

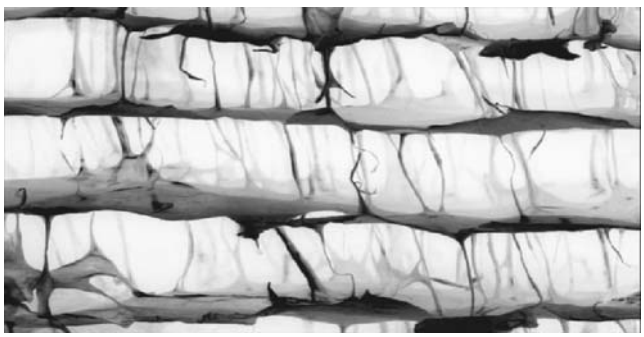

Figure 4 Light microscopic view of the unidirectional collagen scaffold employed for generation of oriented tissue structure (60x).

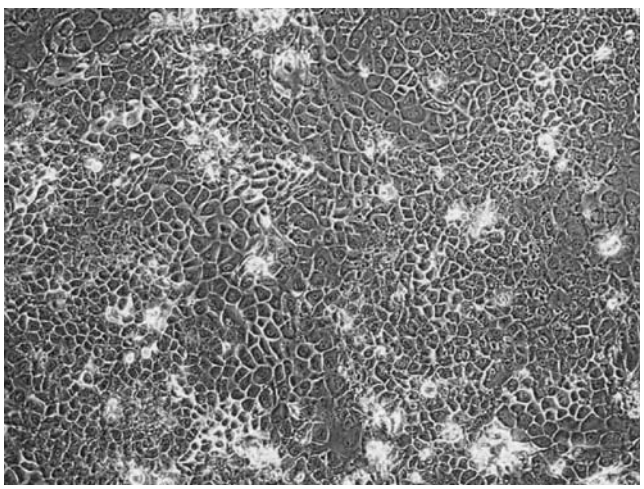

Figure 6 Esophageal epithelial cells after 14 days in culture demonstrating differentiation and mature esophageal epithelium sheet formation (20x).

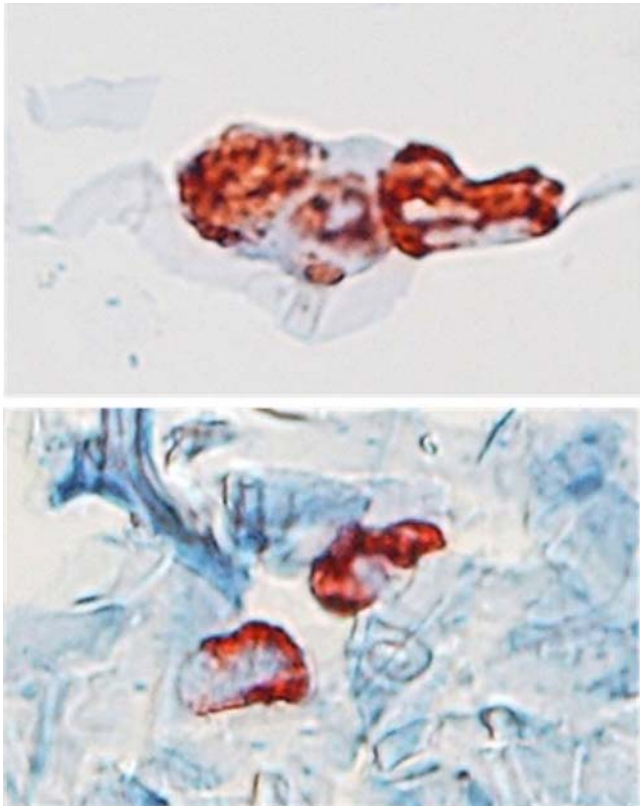

Figure 7 Cross-sectional view of esophageal epithelial cell clusters (above) and isolated cells (below) marked with cytokeratin-14 antibody (CK-14) demonstrating viability after 8 weeks in vitro on collagen scaffold (60x).

scaffold with cells and matrix was documented in constructs removed over successive weeks. When BMM-coated non-organized collagen scaffolds were compared to BMM-coated unidirectional collagen scaffolds, RSMC generated disorganized tissue on the non-organized scaffolds; however, oriented strands of smooth muscle tissue could be engineered when RSMC were seeded on the unidirectional scaffolds (Fig. 8).

Discussion

Tissue engineering of complex organs necessitates a hybrid approach which involves the generation of individual tissue grafts and assembling them to engineer the desired organ. In our attempts to tissue engineer the esophagus, this approach has been taken to generate the esophageal epithelium as well as the smooth muscle components primarily in vitro before assembling them for in vivo implantation. Initial work from our group has demonstrated the successful isolation and culture of REEC as well as the viability of these cells for 8 weeks on 3-D collagen scaffolds.[18] However, since the constructs will be implanted in vivo, cues should be placed on the scaffolds to promote not only vascularization but also support the attached primary cell and aid in its proliferation and differentiation. Furthermore, if the tissue-engineered esophagus is expected to function (transport food bolus), efforts must be concentrated on the engineering of oriented smooth muscle myoarchitecture to mimic the circular and longitudinal configurations found in the native organ.

BMM is effective for the attachment and differentiation of both normal and transformed anchorage-dependent epithelioid and other cell types which include neurons and vascular endothelial cells.[19–21] It also provides the substrate necessary for the study of angiogenesis both in vitro and in vivo.[22,23] Due to these properties, BMM-coated scaffolds should offer advantages of increased vascularization or vascular ingrowth when tested under in vivo condition and was the rationale for investigating the interaction of REEC and RSMC with BMM-coated scaffold in vitro. In REEC, BMM-coated tissue culture plates (24-well plates) promoted

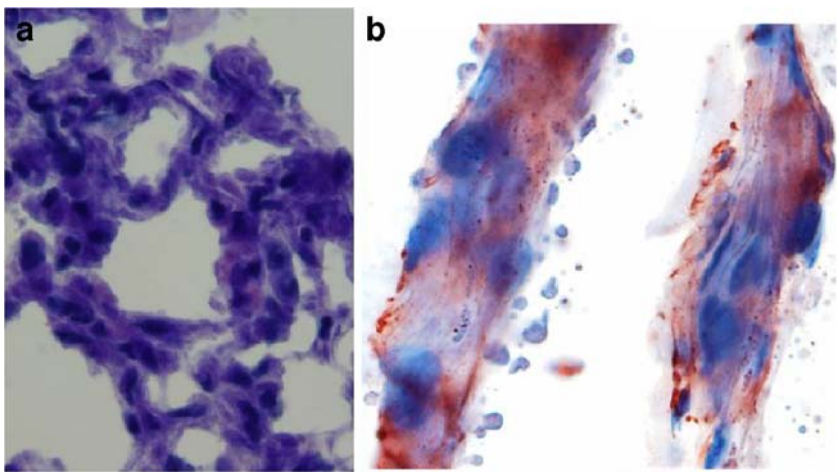

Figure 8 a Non-organized smooth muscle tissue generation on non-organized collagen. **b** Oriented smooth muscle strands generated on unidirectional collagen polymer (marked with α-smooth muscle actin antibody) (60x).

the recruitment of cells from the explants and offered a substrate for the proliferation and differentiation of cells to form sheets of esophageal epithelium. Scaffolds seeded with BMM also anchored the REEC, and viability of individual cells or clusters was unaltered for a period of 8 weeks. Similarly, BMM effectively promoted the attachment of the explants and expansion of RSMC. On coated collagen scaffolds, BMM facilitated organization of RSMC in 3-D toward growth as well as tissue formation. The in vitro investigations with BMM have demonstrated positive interactions with both the cell types (REEC and RSMC) required for esophageal tissue engineering and offer the basis to investigate these constructs now under in vivo conditions.

Isolation of REEC and culture was described by our group in a previous report where trypsin was employed to dissociate cells from the rat epithelium.[24] Due to the size of the rat esophagus obtained for isolation of the REEC, it was important to maximize the cell recruitment for culture. Esophageal explant was the alternative technique that was opted to isolate the cells and maximize isolated cell counts. BMM gels were employed to attach the explants on the tissue culture dishes which were also pre-coated with BMM to permit cell outgrowth or spread. Both these objectives were achieved using the explant technique. Since REEC attached to the BMM-coated plates while the explants were still gelled to the dishes, after explant removal, titration, and filtration, the REEC isolated from the explant reprocessing were replated on the same dishes to maximize cell counts.

Scaffold morphology was also chosen bearing in mind the histology of the native esophagus. Esophageal epithelial cells require a 2-D scaffold for attachment and sheet formation.[25] OptiMaix™ 2-D scaffolds were employed for REEC attachment since they offer an almost uniform and relatively flat outer surface for epithelial cell seeding and attachment. Porous scaffolds with uneven scaffold surfaces are undesirable for REEC since this leads to cells dispersal and hampers epithelial layer formation due to disconnectivity of the dispersed cells along the scaffold crevices. In the present investigation with REEC on OptiMaix™ 2-D, low-density seeding was performed to evaluate the viability of cells under in vitro conditions, both as individual cells and clusters. For the generation of sheets of esophageal epithelial sheets on scaffolds when using a small animal model, cell pooling is necessary to obtain sufficient cell counts to cover the entire scaffold surface.

Generation of smooth muscle tissue using smooth muscle cells on scaffolds has been demonstrated in previous reports.[26,27] However, tubular tissues such as esophagus rely on the organized and oriented layers of this muscle to maintain the proper structure and well as intended function. Our investigations using unidirectional collagen scaffolds for tissue engineering of oriented smooth muscle strands demonstrates the effective use of polymer technology in meeting the requirements of the tissue-engineered constructs to match the original myoarchitecture. Despite this initial success, further strides in polymer engineering technology will be necessary for functional organs such as the esophagus in terms of application of elastic scaffolds or shape memory scaffolds to enable the return of tissue engineered esophagus to its normal shape once a bolus has passed through. Plastic scaffolds in the future will be one of the limiting factors in functional organs. Recent advances in elastic polymer engineering technology with development of scaffolds such as caprolactone, polydioxanone-elastin blends, or collagen-hybridized elastic poly L:-lactide-co-epsilon-caprolactone may provide the breakthroughs associated with scaffold kinetics.[28–30]

Conclusion

Hybrid approach to cell-scaffold attachment using basement membrane matrix and in vitro generation of individual components was successful for esophageal epithelium and smooth muscle, the two components required for the tissue engineering of the esophagus. Strands of smooth muscle could be generated using unidirectional scaffold. The hybrid approach of in vitro tissue assembly and delayed combination of the components in a structured form holds the key to success in esophagus tissue engineering.

Acknowledgment We thank Prof. Wout Feitz (Radboud University Medical Centre, Nijmegen, The Netherlands), Dr. Ingo Heschel (Matricel GmbH, Herzoganrath, Germany) along with Mrs. Anna Kuess (Medical University of Graz, Austria) for the valuable contributions toward this study.

References

1. Clark DC. Esophageal atresia and tracheoesophageal fistula. Am Fam Physician. 1999;59:910–916.
2. Cusick EL, Batchelor AA, Spicer RD. Development of a technique for jejunal interposition in long-gap esophageal atresia. J Pediatr Surg 1993;28:990–994. doi:10.1016/0022-3468(93)90499-B.
3. Raffensperger JG, Kuck SR, Reynolds M, Schwartz D. Intestinal bypass of the esophagus. J Pediatr Surg 1996;31:38–46. doi:10.1016/S0022-3468(96)90316-4.
4. Spitz L, Ruangtrakool R. Esophageal substitution. Semin Pediatr Surg 1998;7:130–133.
5. Cauchi JA, Buick RG, Gornall P, Simms MH, Parikh DH. Oesophageal substitution with free and pedicled jejunum: short- and long-term outcomes. Pediatr Surg Int 2007;23:11–19. doi:10.1007/s00383-006-1770-0.
6. Arul GS, Parikh D. Oesophageal replacement in children. Ann R Coll Surg Engl 2008;90:7–12. doi:10.1308/003588408X242222.

7. Spitz L. Esophageal atresia—lessons I have learned in a 40-year experience. J Pediatr Surg 2006;41:1635–1640. doi:10.1016/j.jpedsurg.2006.07.004.
8. Saxena AK, Kofler K, Ainoedhofer H, Kuess A, Höllwarth ME. Complexity of approach and demand for esophagus tissue engineering. Tissue Eng Part A 2008;14:829.
9. Kajitani M, Wadia Y, Hinds MT, Teach J, Schwartz KR, Gregory KW. Successful repair of esophageal injury using an elastin based biomaterial patch. ASAIO J 2001;47:342–345. doi:10.1097/00002480-200107000-00009.
10. Badylak S, Meurling S, Chen M, Spievack A, Simmons-Byrd A. Resorbable bioscaffold for esophageal repair in a dog model. J Pediatr Surg 2000;35:1097–1103. doi:10.1053/jpsu.2000.7834.
11. Takimoto Y, Nakamura T, Yamamoto Y, Kiyotani T, Teramachi M, Shimizu Y. The experimental replacement of a cervical esophageal segment with an artificial prosthesis with the use of collagen matrix and a silicone stent. J Thorac Cardiovasc Surg 1998;116:98–106. doi:10.1016/S0022-5223(98)70247-8.
12. Isch JA, Engum SA, Ruble CA, Davis MM, Grosfeld JL. Patch esophagoplasty using AlloDerm as a tissue scaffold. J Pediatr Surg 2001;36:266–268. doi:10.1053/jpsu.2001.20685.
13. Grikscheit T, Ochoa ER, Srinivasan A, Gaissert H, Vacanti JP. Tissue-engineered esophagus: experimental substitution by onlay patch or interposition. J Thorac Cardiovasc Surg 2003;126:537–544. doi:10.1016/S0022-5223(03)00032-1.
14. Natsume T, Ike O, Okada T, Shimizu Y, Ikada Y, Tamura K. Experimental studies of a hybrid artificial esophagus combined with autologous mucosal cells. ASAIO Trans 1990;36:M435–437.
15. Sato M, Ando N, Ozawa S, Miki H, Kitajima M. An artificial esophagus consisting of cultured human esophageal epithelial cells, polyglycolic acid mesh, and collagen. ASAIO J 1994;40:M389–392. doi:10.1097/00002480-199407000-00028.
16. Miki H, Ando N, Ozawa S, Sato M, Hayashi K, Kitajima M. An artificial esophagus constructed of cultured human esophageal epithelial cells, fibroblasts, polyglycolic acid mesh, and collagen. ASAIO J 1999;45:502–508. doi:10.1097/00002480-199909000-00025.
17. Oda D, Savard CE, Eng L, Sekijima J, Haigh G, Lee SP. Reconstituted human oral and esophageal mucosa in culture. In Vitro Cell Dev Biol Anim 1998;34:46–52. doi:10.1007/s11626-998-0052-7.
18. Saxena AK, Ainoedhofer H, Höllwarth ME. Esophagus tissue engineering: In-vitro generation of esophageal epithelial cell sheets and viabilty on scaffold. J Pediatr Surg. In press.
19. Debnath J, Muthuswamy SK, Brugge JS. Morphogenesis and oncogenesis of MCF-10A mammary epithelial acini grown in three-dimensional basement membrane cultures. Methods 2003;30:256–268. doi:10.1016/S1046-2023(03)00032-X.
20. Biederer T, Scheiffele P. Mixed-culture assays for analyzing neuronal synapse formation. Nat Protocols 2007;2:670–676. doi:10.1038/nprot.2007.92.
21. McGuire PG, Orkin RW. Isolation of rat aortic endothelial cells by primary explant techniques and their phenotypic modulation by defined substrata. Lab Invest 1987;57:94–105.
22. Maeshima Y, Manfredi M, Reimer C, Holthaus KA, Hopfer H, Chandamuri BR, Kharbanda S, Kalluri R. Identification of the anti-angiogenic site within vascular basement membrane-derived tumstatin. J Biol Chem 2001;276:15240–15248. doi:10.1074/jbc.M007764200.
23. Kisucka J, Butterfield CE, Duda DG, Eichenberger SC, Saffaripour S, Ware J, Ruggeri ZM, Jain RK, Folkman J, Wagner DD. Platelets and platelet adhesion support angiogenesis while preventing excessive hemorrhage. Proc Natl Acad Sci USA 2006;103:855–860. doi:10.1073/pnas.0510412103.
24. Saxena AK, Ainoedhofer H, Baumann P, Kristler M, Höllwarth ME. In-vitro investigation of esophageal cell organization and collagen scaffold interaction. Tissue Eng Part A 2008;14:747.
25. Beckstead BL, Pan S, Bhrany AD, Bratt-Leal AM, Ratner BD, Giachelli CM. Esophageal epithelial cell interaction with synthetic and natural scaffolds for tissue engineering. Biomaterials 2005;26:6217–6228. doi:10.1016/j.biomaterials.2005.04.010.
26. Pattison MA, Wurster S, Webster TJ, Haberstroh KM. Three-dimensional, nano-structured PLGA scaffolds for bladder tissue replacement applications. Biomaterials 2005;26:2491–2500. doi:10.1016/j.biomaterials.2004.07.011.
27. Schnell AM, Hoerstrup SP, Zund G, Kolb S, Sodian R, Visjager JF, Grunenfelder J, Suter A, Turina M. Optimal cell source for cardiovascular tissue engineering: venous vs. aortic human myofibroblasts. Thorac Cardiovasc Surg 2001;49:221–225. doi:10.1055/s-2001-16113.
28. Lim JI, Yu B, Lee YK. Fabrication of collagen hybridized elastic PLCL for tissue engineering. Biotechnol Lett 2008;30:2085–2090. doi:10.1007/s10529-008-9808-0.
29. Sell SA, McClure MJ, Barnes CP, Knapp DC, Walpoth BH, Simpson DG, Bowlin GL. Electrospun polydioxanone-elastin blends: potential for bioresorbable vascular grafts. Biomed Mater 2006;1:72–80. doi:10.1088/1748-6041/1/2/004.
30. Duling RR, Dupaix RB, Katsube N, Lannutti J. Mechanical characterization of electrospun polycaprolactone (PCL): a potential scaffold for tissue engineering. J Biomech Eng 2008;130:011006. doi:10.1115/1.2838033.

J Gastrointest Surg (2009) 13:1044–1051
DOI 10.1007/s11605-009-0839-1

ORIGINAL ARTICLE

Effectiveness of *HSV-tk* Suicide Gene Therapy Driven by the *Grp78* Stress-Inducible Promoter in Esophagogastric Junction and Gastric Adenocarcinomas

Armen Azatian · Hong Yu · Wande Dai · Fiona I. Schneiders · Natalia K. Botelho · Reginald V. N. Lord

Received: 25 January 2009 / Accepted: 18 February 2009 / Published online: 10 March 2009

Abstract
Background The thymidine kinase gene of the herpes simplex virus (*HSV-tk*) is a suicide gene when administrated with the prodrug ganciclovir (GCV). This study investigated the effectiveness of *HSV-tk* activation as gene therapy for gastroesophageal junction and gastric adenocarcinomas using either the stress-inducible *Grp78* promoter or the murine leukemia virus long-terminal repeat (LTR) promoter.
Methods The *HSV-tk* gene, controlled by either the *Grp78* promoter or the LTR promoter, was transduced into the gastroesophageal junction adenocarcinoma cell line SK-GT-5 and the gastric adenocarcinoma cell line MKN-74. Cell viability after exposure to varying concentrations of GCV was compared. The same cell lines were used to develop a nude mouse model for studies of the *HSV-tk*/GCV effect in vivo. The effect of intraperitoneal GCV injection on growth of the subcutaneous tumors was measured. HSV-TK expression was measured by Western blot and reverse transcription polymerase chain reaction.
Results Cell viability in vitro was significantly lower in the *HSV-tk* expressing (*HSV-tk*+) cells compared to control (no *HSV-tk*) cells after exposure to GCV. MKN-74tk+ cells were more sensitive to GCV killing than SK-GT-5tk+ cells. After culture with 1 μg/ml GCV for 10 days, MKN-74/tk cells were totally killed, whereas most SK-GT-5/tk cells survived. Cell viability was significantly lower under glucose starvation conditions when *HSV-tk* expression was regulated by the *Grp78* promoter compared with the LTR promoter. MKN-74 tumors formed with *HSV-tk*+ cells in nude mice were eliminated after administration of GCV for 3 weeks, but GCV had no effect on tumors formed from *HSV-tk*− cells. Eradication of tumor formed with *Grp78*-tk cells was faster than that with LTR-tk cells. HSV-TK protein and mRNA were expressed in the transduced, but not the non-transduced tumors.
Conclusion *HSV-tk* xwith ganciclovir suicide gene therapy results in significant cell killing in gastroesophageal junction and gastric adenocarcinoma cells both in vitro and in vivo, but complete tumor elimination only occurred with the gastric adenocarcinoma cell tumors. The most effective approach in this study used the *Grp78* promoter in glucose-starvation stress conditions.

Keywords Gastroesophageal junction adenocarcinoma · Gastric adenocarcinoma · Gastric neoplasms · Gene therapy · *HSV-tk* · *Grp78*

Introduction

With the exception of patients identified through surveillance programs, most patients with gastroesophageal junction or

Armen Azatian and Hong Yu are equal co-first authors.

A. Azatian · H. Yu · W. Dai · R. V. N. Lord
Department of Surgery,
University of Southern California Keck School of Medicine,
Los Angeles, CA 90033, USA

F. I. Schneiders · N. K. Botelho · R. V. N. Lord
St. Vincent's Centre for Applied Medical Research and
Department of Surgery, St. Vincent's Hospital,
University of New South Wales,
Sydney 2010, Australia

R. V. N. Lord (✉)
Suite 606, St. Vincent's Clinic, 438 Victoria Street, Darlinghurst,
Sydney, NSW 2010, Australia
e-mail: rvlord@stvincents.com.au

Present Address:
H. Yu
Vascular Biology Institute, University of Miami, and Bruce W.
Carter Miami Veterances Affairs Medical Center,
1201 NW 16th St, Miami, FL 33125, USA

gastric cancer present with advanced disease, and in contrast to the recent reduction in mortality for patients with cancer in general, outcome statistics for patients with esophagogastric cancers remain poor and largely unchanged.[1] Despite the more than 80% decline in gastric cancer incidence over the past 50 years, there were an estimated one million new cases worldwide in 2007, and gastric cancer is the second most common cause of cancer death worldwide in males and the fourth most common cause of cancer death in females (www.cancer.org/downloads/STT/Global_Cancer_Facts_and_Figures_2007.pdf). These unfavorable statistics reflect the failure of conventional treatments for most patients and increase the importance of investigating novel therapies such as gene therapy.

The thymidine kinase gene of the herpes simplex virus (*HSV-tk*) is a suicide gene when administrated with the prodrug ganciclovir (GCV). *HSV-tk*, but not mammalian *TK*, is able to phosphorylate GCV to its monophosphate, which is then further converted into GCV triphosphate and incorporated into cellular DNA. Incorporation of GCV triphosphate into cellular DNA results in termination of DNA synthesis and cell death. In addition to achieving direct killing of tumor cells expressing *HSV-tk*, a bystander effect caused by diffusion of toxic GCV triphosphate to adjacent cells causes the death of neighboring cells that do not express *HSV-tk*.[2] The bystander effect can enable complete tumor eradication in animal models when only 10–20% of the tumor cells carry the *HSV-tk* gene.[2]

Successful application of the suicide gene approach in vivo requires targeted gene delivery and maximization of expression of the suicide gene in the tumor. A frequently used vector for the transfer of the *HSV-tk* gene is a murine leukemia virus (MuLV)-derived retroviral vector whose promoter in its long-terminal repeat (LTR) can provide constitutive expression of a foreign gene in vitro. However, the viral promoters are often inactivated and expression of the genes is eventually abolished in vivo.[3] Furthermore, under glucose-free conditions in a fast-growing solid tumor devoid of nutrient due to insufficient blood supply, the viral promoter in LTR can be suppressed and thus unable to sustain foreign gene expression.[4] Non-specific and unregulated expression of the suicide gene in normal cells can also be problems. To circumvent these difficulties, we used the glucose-regulated protein 78 (*Grp78*) promoter in this study in an effort to target gene expression and selectively eliminate cancer cells. *GRP78* is a stress-inducible protein that is strongly induced by the conditions that persist within poorly vascularized solid tumors: glucose deprivation, chronic anoxia, and acidic pH.[5]

This study investigated and compared the in vitro and in vivo effectiveness of *HSV-tk*/GCV suicide gene therapy in gastroesophageal junction and gastric body adenocarcinomas. Very few gene therapy studies have been reported for junctional or esophageal adenocarcinoma, with esophageal cancer studies focusing on squamous cell carcinoma[6–9] and gastric cancer studies focusing on the non-junctional/non-cardia gastric cancers.[8] The limited number of esophageal adenocarcinoma gene therapy studies have unfortunately mostly used inappropriate cell lines or animal models, reflecting the paucity of suitable models.[10–14] There have been many gastric cancer gene therapy studies with significant progress, if only at the preclinical stage,[8] but none using the promising *HSV-tk*/GCV approach with the *Grp78* promoter as in the current study.

Materials and Methods

Cell Culture The human gastroesophageal junction adenocarcinoma cell line SK-GT-5[15] (kindly provided by Dr. Nasser Altorki) and human gastric adenocarcinoma cell line MKN-74 (generously provided by Dr. David Beer)[16] were cultured in RPMI medium (Gibco BRL Gaithersburg, MD, USA) supplemented with 10% fetal bovine serum (FBS; HyClone, Logan, UT, USA) and 2 mM glutamine (Gibco BRL). SK-GT5 has a point mutation (D281E) on its p53 gene,[16] whereas MKN-74 has no p53 mutation.[16] SK-GT-5 is often reported as an esophageal adenocarcinoma cell line, but the original description by Altorki et al.[15] refers to a gastric cardia or junctional adenocarcinoma, unlike SK-GT-4, which is a Barrett's esophageal adenocarcinoma.

Human 293T/17 cells (CRL11268)[17] were obtained from American Type Culture Collection and were maintained in Dulbecco's modified Eagle's medium (DMEM, Gibco BRL) supplemented with 10% FBS and 2 mM glutamine. The 293/GPG cell line, a vesicular stomatitis virus G glycoprotein (VSV-G) pseudotyped MuLV packaging cell line, was kindly provided by Dr. Ory.[18] 293/GPG was maintained in DMEM medium as described above with additional 1 μg/ml tetracycline (Sigma-Aldrich, St. Louis, MO, USA), 2 μg/ml puromycin (Sigma-Aldrich), 0.3 mg/ml G418 (Gibco BRL), and 100× MEM sodium pyruvate (Gibco BRL) and has constantly expressed gag-pol genes and tet promoter-controlled VSV-G genes. All cells were maintained in a humidified 37°C incubator with 5% CO_2.

Retroviral Production and Cell Transduction The retroviral vector plasmids G1TkSvNa and G1NaGrpTk, kindly provided by Dr. Amy Lee,[19] carry the HSV TK gene controlled by the LTR promoter and the *Grp78* promoter, respectively. The replication-incompetent VSV-G pseudotyped MuLV G1TkSvNa vector was first generated from 293T/17 cells after a transient three-plasmid (G1TkSvNa, CVG, and HIT60) transfection, as described previously.[20] The viral supernatants from the transient transfection were used to transduce packaging cell line 293/GPG. The pool of the transduced 293/GPG cells (named as 293/GPG/

G1TkSvNa), without selection, was used as a stable vector producer since the transduction efficiency of VSV-G pseudotyped MLV vector is higher than 90%.[20]

To transduce 293/GPG package cells with the amphotropic MuLV G1NaGrpTk vector supernatant from producer cell line PE501,[19] the amphotropic viral supernatant mixed with 8 μg/ml polybrene was plated onto 293/GPG cells on a 60-mm plate for 2 h at 37°C. The transduced cells were cultured with fresh medium for 2 days at 37°C and then diluted into a concentration of four cells per milliliter and plated onto a 96-well plate to form single colonies. Twelve single colonies were picked and amplified in six-well plates, and the supernatants were collected after culture with medium without tetracycline. The viral titers of the supernatants were measured. The clone that generated the highest titer was used as the producer cell line, named as 293/GPG/G1NaGrpTk, for the VSV-G pseudotyped MuLV vector.

To produce the VSV-G pseudotyped viral vectors from the producer cell lines of 293/GPG/G1TkSvNa or 293/GPG/G1NaGrpTk, the cells were cultured separately in DMEM medium with tetracycline to 90% confluence, washed with phosphate-buffered saline (PBS) and then further cultured in fresh DMEM as aforementioned but without tetracycline. At every 24 h, retroviral supernatants were collected and replaced with fresh culture medium. The collected culture medium (up to 72 h) was filtered through a 0.45-mm pore size filter (Pall Gelman, Ann Arbor, MI, USA) and stored at −80°C for further use. The viral titers were between 10^6 and 10^7 colony formation unit per milliliter, analyzed by neomycin resistance assay.

Transductions of SK-GT5 and MKN-74 cell lines with viral vectors were as described[20] (no. 957) by mixing the cells with viral supernatants with 8 μg polybrene for 2 h, followed by G418 (1.2 mg/ml, Gibco BRL) selection. Seven days after the culture with G418, the pools of surviving cells, named as SK-GT5/LTR-tk, SK-GT5/Grp-tk, MKN-74/LTR-tk, and MKN-74/Grp-tk, were used for the following GCV killing and in vivo animal study.

In Vitro GCV Sensitivity Assay Each cell line, SK-GT5, SK-GT5/LTR-tk, SK-GT5/Grp-tk, MKN-74, MKN-74/LTR-tk, and MKN-74/Grp-tk, was plated in duplicate at 5×10^4 cells/well in a 24-well plate. After 24-h culture, the cells were incubated with medium containing GCV (Cytovene, Syntex Laboratories, Inc., Palo Alto, CA, USA) at concentrations of 0, 1, 3, 10, and 30 μg/ml. Fresh GCV was added daily to the culture, and cells in a well were counted every other day using the Trypan Blue dye exclusion method. For glucose starvation treatment, culture media were changed on the second day of plating to the glucose-free DMEM supplemented with dialyzed FBS. After 30-h culture in glucose-free medium, the cells were incubated with regular medium containing GCV. GCV was added daily and cells counted every other day.

In Vivo Tumor Formation and GCV Treatment The cell suspensions were prepared by trypsinizing cells from a confluent plate, washing the cells three times in PBS, and resuspending 5×10^7 cells in 1 ml of PBS (Fig. 1). The cell suspension (0.1 ml, 5×10^6 cells) was injected subcutaneously in the flank area of Nu/Nu mice (all male, 4–6 weeks old, 20–25 g at time of tumor cell injection). Six flanks from three sets of mice were injected with six kinds of cell suspensions: SK-GT5, SK-GT5/LTR-tk, SK-GT5/Grp-tk, MKN-74, MKN-74/LTR-tk, and MKN-74/Grp-tk. Each cell line had seven mice injected. Tumors were measured with a caliper daily. Tumor volumes were calculated from the formula: $volume(mm^3) = (width)2 \times (length) \times 0.5$.[4,21] Two weeks after cell inoculation, five of the seven mice in each group received daily intraperitoneal injections of GCV at a dosage of 100 mg/kg of body weight until tumor disappeared or the mouse died. The two control mice in each group inoculated with an identical dose of cells were injected with saline (0.75% NaCl, 100 ml/kg).

Western Blot Analysis of In Vitro HSV-tk Protein Expression Western blot analysis was performed to determine the HSV-tk protein expression in vitro and from homogenized tumors in vivo. The cells on culture plates were lysed as described elsewhere (Sambrook, Molecular Cloning). The supernatant of the lysis was separated on denaturing sodium dodecyl sulfate-polyacrylamide gels and transferred onto nitrocellulose membrane. After blocking overnight at 4°C with 5% nonfat dry milk in TBS-T (20 mM Tris–HCl, 137 mM NaCl, 0.1% Tween 20), the membrane was incubated with the polyclonal rabbit anti-HSV-TK antibody (1:600 dilution, obtained from Dr. W. Summers, Yale University School of Medicine, New Haven, CT, USA) or monoclonal mouse anti-β-actin antibody (1:1,000 dilution, Sigma Chemical) for 1 h at room temperature and, after

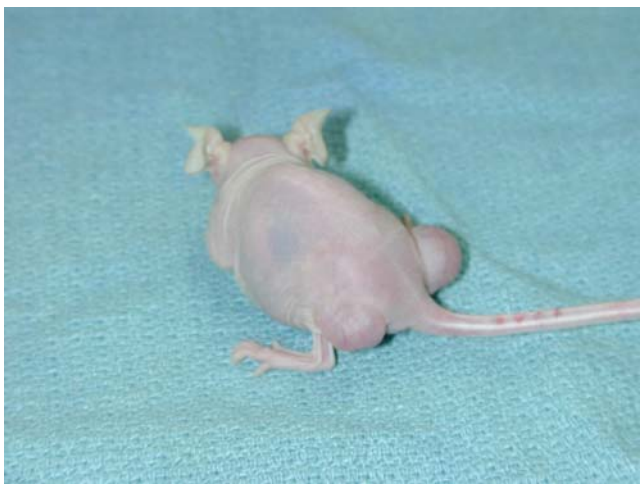

Figure 1 Esophagogastric adenocarcinoma xenografts growing subcutaneously on both flanks in a nude mouse.

washing, with the second antibody, horseradish peroxidase-conjugated sheep anti-mouse or rabbit IgG antibody (1:1,000 dilution, Amersham Pharmacia Biotech, Inc.) for 1 h. Specific protein bands (HSV-TK at 45 kDa, anti-β-actin at 42 kDa) were detected by an enhanced chemiluminescence kit (Amersham Pharmacia Biotech, Inc.). Amount of HSV-TK was quantitated by densitometry and normalized against that of actin serving as an internal loading control.

Reverse Transcription/Polymerase Chain Reaction Quantification of In Vivo *HSV-tk* mRNA Expression

RNA was extracted from sections of formalin-fixed paraffin-embedded (FFPE) xenografts using an FFPE RNA extraction kit (AusDiagnostics, Sydney, Australia). Primers for *HSV-tk* [human herpesvirus 2 thymidine kinase (tk) gene; AF466703] and NONO ("non-POU domain containing, octamer-binding"; NM_007363) as reference gene were designed with the help of Primer 3 software, leading to an "inner" amplicon of 70–90 bp and restricting the size of the "outer" amplicon to <150 bp. The following primers for *HSV-tk* were used in the multiplexed tandem PCR (MT-PCR) assay: First round outer primers, forward 'CTCGCCGGCAGCAAGAAG', reverse 'AGCAGTTG CGTGGTGGTGG' and second round inner primers, forward 'CAGCAAGAAGCCACGGAAGT', reverse 'CATCCCGT GAGGACCGTCTAT'. The amplified "outer" *HSV-tk* amplicon covers the region from base 92 to 206, and the "inner" *HSV-tk* amplicon covers the region from base 100 to 180. The amplified "outer" NONO amplicon covers the region from base 831 to base 935, and the "inner" NONO amplicon covers the region from base 841 to base 925.

First round multiplexed amplification:

RNA was added to an outer primer mixture at a final concentration of 0.2 μM of each primer, MT-PCR step 1 MasterMix (Quantace, Finchley, UK) and step 1 additives (Quantace) in a total volume of 20 μl. Each tube was placed in a Rotor-Gene thermal cycler (RG6000, Corbett Life Science, Sydney, Australia) and heat-treated as follows: 2 min at 55°C (reverse transcription), 5 min at 95°C (RT denaturation) followed by 20 cycles of 10 s at 95°C, 20 s at 60°C and 20 s at 72°C. This completed the multiplex PCR step.

Second round quantification amplifications:

The product from the multiplexed amplification (final dilution in reaction 1:75) was added to MT-PCR step 2 MasterMix (Quantace) and step 2 additives (Quantace) diluted in water. An aliquot of 15 μl of PCR mixture was then added to 0.1-ml PCR tubes (Corbett Life Science) containing 5 μl of inner primer mixes (0.4 μM final concentration in reaction). The tubes were loaded into a RG6000 thermal cycler and PCR was performed for 35 cycles of 1 s at 95°C, 10 s at 60°C, and 10 s at 72°C. Fluorescence was measured at the end of each 72°C extension step. Melt was performed at 72–95°C.

The presence of the correct length PCR product was checked on a Bioanalyzer DNA separation chip (Agilent, Santa Clara, CA, USA).

Results

Tumor Cells with *HSV-tk* Were Sensitive to GCV Killing In Vitro

The human esophagogastric adenocarcinoma cell lines were transduced with retroviral vectors carrying *HSV-tk* gene. The transduced cells exhibited equivalent plating efficiencies and growth rates. As shown in Fig. 2a, cell viability in vitro was significantly lower in the *HSV-tk*-expressing cells than those without *HSV-tk* after exposure to different concentrations of GCV. Only a small minority of cells transduced with *HSV-tk* survived after exposure to 10 μg/ml GCV,

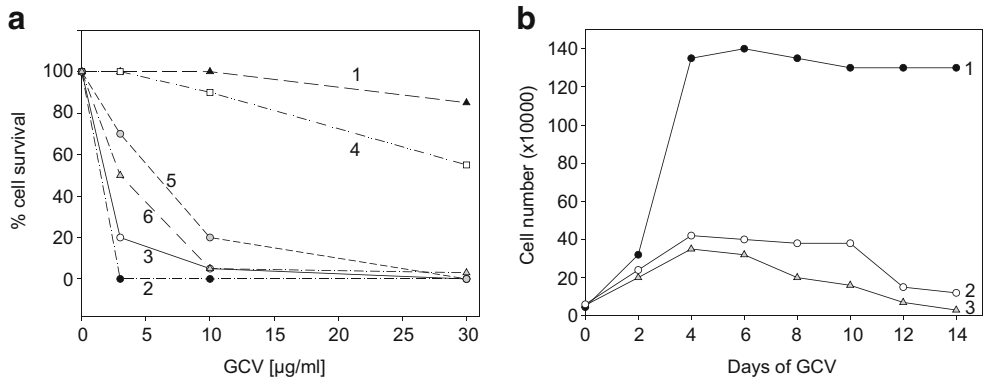

Figure 2 **a** In vitro ganciclovir (*GCV*) sensitivity assay. Cell survival (%) after 14 days of exposure to different concentrations of GCV. *1* MKN-74; *2* MKN-74-*Grp78-HSV-TK*; *3* MKN-74-LTR-*HSV-TK*; *4* SK-GT-5; *5* SK-GT-5-*Grp78-HSV-TK*; *6* SK-GT-5-LTR-*HSV-TK*. **b** Time course of GCV killing of MKN-74 cells. Cell number (×1,000 cells/ml) after 14 days of GCV (1 μg/ml) exposure in glucose containing medium. *1* MKN-74; *2* MKN-74-LTR-*HSV-TK*; *3* MKN-74-*Grp78-HSV-TK*.

whereas most non-transduced cells survived exposure to 30 μg/ml GCV (Fig. 2a).

Figure 2a also shows that the MKN-74 gastric adenocarcinoma cells transduced with the TK gene were more sensitive to GCV killing than the SK-GT-5 gastroesophageal junction adenocarcinoma cells. The sensitivity of MKN-74 cells to *HSV-tk* suicide gene therapy is further shown in the time course experiment in which untransduced MKN-74 cells and MKN-74 cells transduced with either the LTR or *Grp78* promoter were incubated with medium containing GCV at 1 μg/ml (Fig. 2b). As shown, cell death occurred at this low GCV concentration in *HSV-tk*-expressing cells.

Grp78 Promoter Effect in a Glucose-Free Environment

When cells were cultured in media with glucose, cell survival was similar for the *HSV-tk* transduced cells (Fig. 3a). MKN-74 was again more sensitive to GCV killing at lower GCV concentrations (Fig. 3a). When the cells were cultured in media free of glucose, the cells (both MKN-74 and SK-GT-5) transduced with *Grp78*-tk were more sensitive to GCV than those with LTR-tk. (Fig. 3b).

Eradication of Tumor In Vivo By GCV Treatment

The six cell lines were injected subcutaneously into the flanks of mice to allow formation of tumor. After the tumor was formed, the mice received an abdominal injection of GCV daily for 3 weeks. As shown in Fig. 4a, b, tumor sizes were significantly reduced for the cells transduced with *HSV-tk* gene. The tumor eradication in the cells transduced with the *Grp78*-tk gene promoter was faster than in those with LTR-tk gene. The tumors formed with MKN-74/HSV-tk gastric adenocarcinoma cells were completely eradicated (Fig. 4a), whereas tumors with SK-GT-5/HSV-tk gastroesophageal junction adenocarcinoma cells were not completely eradicated (Fig. 4b).

HSV-TK Protein Expression

To test the efficacy of the LTR and the *Grp78* promoter to drive expression of the HSV-TK protein, total cell lysates were prepared from individual cell lines under normal culture and glucose-starved conditions and from tumors recovered from nude mice. The Western blot showed that there was no detectable HSV-TK in the non-transduced MKN-74 cells (Fig. 5, lane 1). In all *HSV-tk* transduced cells, there was HSV-TK expression under both normal culture conditions and glucose-starved conditions. There was no discernable increase in HSV-TK protein levels in glucose-starved cells even in the cells with *HSV-tk* gene driven by the *Grp78* promoter. As shown in Fig. 3 for MKN-74, more HSV-TK were detected in cells with the LTR promoter (Fig. 5, lanes 2 and 3) than with the *Grp78* promoter (Fig. 5, lanes 4 and 5), suggesting that LTR is a stronger promoter than *Grp78* in vitro. However, there were more HSV-TK in MKN-74/*Grp78*-tk tumor (Fig. 5, lane 7) than that in MKN-74/LTR-tk (Fig. 5, lane 6) tumor recovered from mice.

HSV-tk mRNA Expression

As shown in Fig. 6, *HSV-tk* PCR product was present in the tumors transduced with *HSV-tk*, but not in the non-transduced tumors, demonstrating that mRNA expression of the *HSV-tk* suicide gene was present after transduction.

Discussion

This study provides encouraging data for the effectiveness of a gene therapy strategy directed against gastric and gastroesophageal junction adenocarcinomas. We showed that using a HSV vector to introduce the HSV thymidine kinase gene, followed by administration of the prodrug

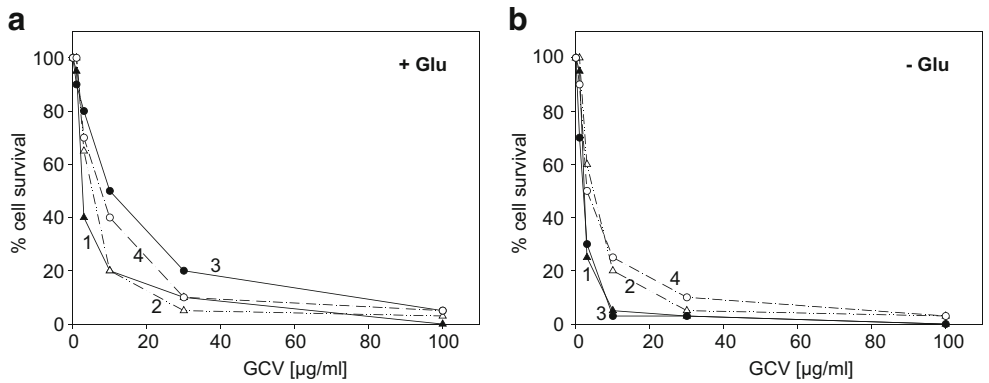

Figure 3 Promoter effect on cell killing in a glucose supplemented medium (**a**) and in a glucose-free medium (**b**). Transduced cells (5×10^4 cells/well in a 24-well plate) were incubated with glucose-supplemented medium containing GCV at the concentrations shown for 10 days. Surviving cells were normalized to the number of cells cultured without GCV at day 10 (5×10^5). *1* MKN-74-*Grp78-HSV-TK*; *2* MKN-74-LTR-*HSV-TK*; *3* SK-GT-5-*Grp78-HSV-TK*; *4* SK-GT-5-LTR-*HSV-TK*.

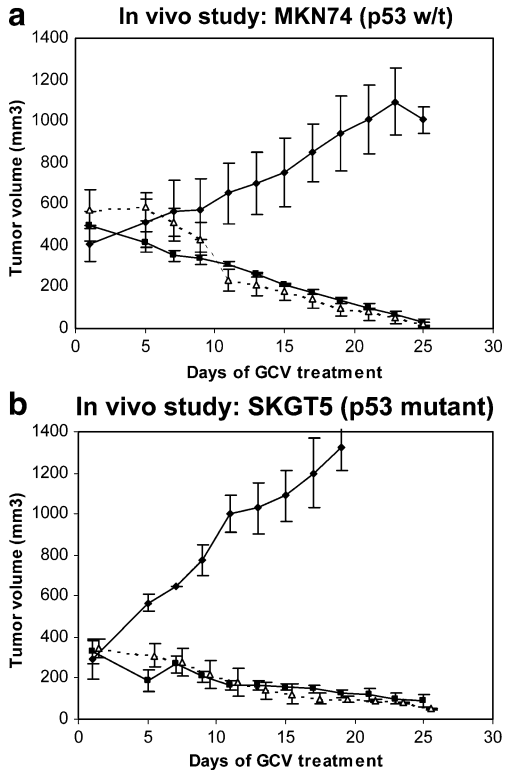

Figure 4 Eradication of MKN-74 tumors (**a**) and SK-GT-5 tumors (**b**) by GCV treatment. **a** MKN-74 (*diamond*, *N*=5 tumors), MKN-74/LTR-tk (*circle*, *N*=4), and MKN-74/Grp-tk (*triangle*, *broken line*, *N*=5). **b** SK-GT5 (*diamond*, *N*=4), SK-GT5/LTR-tk (*circle*, *N*=3), SK-GT5/Grp-tk (*triangle*, *broken line*, *N*=3). Cells were inoculated subcutaneously in nude mice for approximately 2 weeks. The mice were treated with GCV daily at a dosage of 100 mg/kg of body weight after tumor size reached ~400 mm^3. Biperpendicular tumor measurements were taken for 25 days. The *error bars* stand for standard error of sample numbers shown in *parenthesis*.

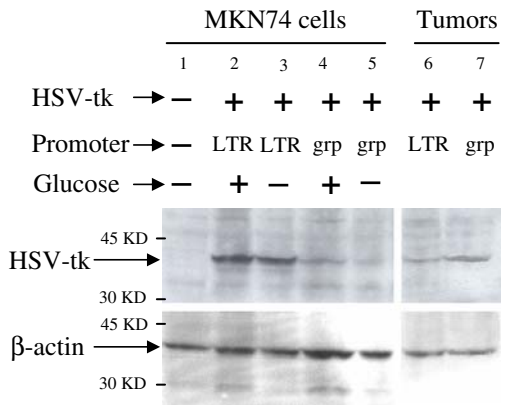

Figure 5 HSV-tk protein expression in MKN-74 cells and tumors. Cell lysates from MKN-74, MKN-74/LTR-tk, or MKN-74/Grp-tk, and homogenized tumors formed 2 weeks after injecting MKN-74/LTR-tk, MKN-74/Grp-tk cells into nude mice, were subjected to Western blot analysis with antibodies against HSV-tk and β-actin. The cells were grown under normal culture medium (*plus symbol*) or glucose-starved (*minus symbol*) conditions for 24 h.

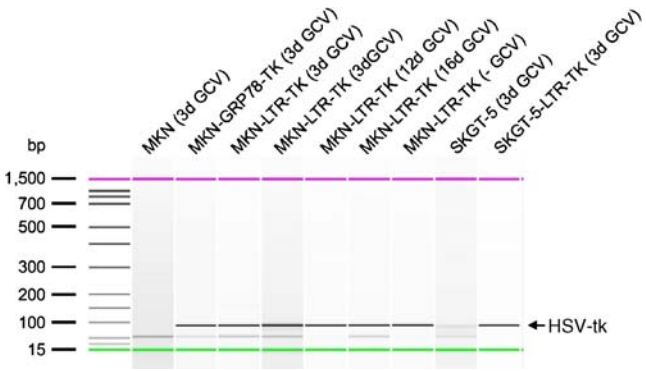

Figure 6 Electropherogram showing *HSV-TK* in the transduced cell tumors generated in nude mice but not in the non-transduced cell tumors (*lanes 1* and *8*). Fifteen- and 1,500-bp markers are also shown, as well as non-specific PCR products (probably primer dimers) at 54 bp.

GCV, significant cell death in vitro and significant tumor regression in vivo can be obtained. The gastric adenocarcinoma cells (MKN-74) were more sensitive to the gene therapy than the gastroesophageal junction adenocarcinoma cells (SK-GT-5) in this study. This was observed in the cell line studies and also in the nude mouse xenograft tumor studies; the gastric cancer tumors were completely eradicated using either promoter, whereas the gastroesophageal junction cancer tumors were not completely eradicated.

The reason for the differing sensitivities of gastric compared to gastroesophageal junction adenocarcinomas in this study is not known and only reflects the findings in two cell lines derived from two individuals. No previous reports are available with which to compare our gastroesophageal junction adenocarcinoma results, and there are also very few previous reports of gene therapy in esophageal adenocarcinoma. Those that have been published are mostly limited in scope or have significant methodological problems. In two separate studies, Marsman et al. showed only limited transduction efficiency using adenoviral vectors in esophageal adenocarcinoma cell lines (OE-19 and OE-33), in a substitute for Barrett's esophagus (Caco-2 cells), and in the questionable esophagojejunostomy rat model.[11,12,22] Heideman et al.[13] investigated the epithelial cell adhesion molecule (EpCAM) as a gene therapy target using cell lines (TE-1 and TE-2) that have been shown to be derived from an esophageal squamous cell carcinoma rather than an esophageal adenocarcinoma. Further demonstrating the poor availability of suitable esophageal adenocarcinoma cell lines, Gupta et al.[10] also used adenoviral vectors in cell lines (Bic-1 and Seg-1) that have subsequently been identified as not esophageal adenocarcinoma cells (Dr. David Beer, University of Michigan, open letter to the scientific community, 2008).

In contrast to the situation for esophageal or junctional adenocarcinoma, many studies have investigated gene therapy strategies for gastric cancer, including several that used an *HSV-tk*/GCV suicide gene strategy.[8] Tang et al.[23] transduced the *HSV-tk* gene using a GINaTK retroviral vector, resulting in up to 47% reduction in tumor volume (no. 6206). Importantly, they observed a bystander effect in which the *HSV-tk*/GCV toxic metabolite is taken up from transduced to neighboring non-transduced cells via gap junctions in the cell membrane. The bystander effect is thought to explain the effectiveness, despite incomplete and inefficient gene transfer to the cancer cells, of the *HSV-tk*/GCV suicide gene strategy. The bystander effect was not estimated in the present study but is likely be responsible for the complete tumor eradication observed with the MKN-74 cell tumors.

Nakaya et al.[24] reported the effectiveness adenovirus-mediated expression of *HSV-tk* by an alpha-fetoprotein (AFP) enhancer/promoter element in an AFP-expressing gastric adenocarcinoma cell line but not an AFP-negative gastric cancer cell line. In duplicate publications, Zhang et al.[25,26] reported that using the recombinant retroviral expression vector PLXSN co-expressing both HSVtk and the cytokine TNF-alpha genes resulted in significantly greater reduction in tumor size in vivo compared to using the vector expressing either gene alone, but tumor eradication was not reported and the significant in vivo effect was not observed *in vitro*.[25,26]

Grp78 was a weaker promoter than LTR in vitro in all conditions but a stronger promoter in vivo, and HSV-tk expression in tumors was higher when the gene was controlled by *Grp78*. Glucose-regulated protein 78 is a stress-inducible protein which is strongly induced during glucose deprivation, chronic anoxia, and the acidic environment present in poorly vascularized solid tumors.[5] This ability makes it ideal for gene therapy in which the aim is to selectively kill tumor cells without affecting normal tissues. Our findings indicate that gastric adenocarcinoma can be added to the list of human tumors for which eradication of sizable tumors has been demonstrated using the *Grp78* promoter to enhance *HSV-tk*/GCV effectiveness under glucose-starvation conditions.[4,19]

A possible explanation for the different results with the gastric versus gastroesophageal junction adenocarcinoma cells in this study is p53 mutation status. MKN-74 cells are reported to have no mutations on the p53 gene, while the SK-GT-5 cells have a p53 point mutation (D281E, at 281 amino acids from Asp to Glu).[16] Matsubara et al.[27] have shown that esophageal squamous cancer cells with mutated p53 were resistant to phosphorylated GCV, whereas the tumor formed using a wild-type p53 cell line was totally eradicated with *HSV-tk*/GCV treatment, and many other studies support the potential pharmacogenetic importance of p53 status.[28] Studies in other cancer types, however, report that wt p53 may not necessarily improve the efficacy of *HSV-tk*/GCV suicide gene therapy in vivo.[29] The importance of p53 mutation status would ideally be established by assessing further cell lines, preferably with transduction of wild-type p53 into the p53 mutant cells to assess for reversal of GCV resistance, before clinical trials are undertaken for these cancer types.

These results indicate that clinical trials for foregut adenocarcinoma could be considered. Human clinical trials have not been reported for either gastric cancer[30] or esophageal/junctional adenocarcinoma. *HSV-tk* with ganciclovir suicide gene therapy has been used for up to phase 3 clinical trials for patients with other tumor types, especially malignant glioma[31] and prostate cancers,[32,33] although results have so far been disappointing, with no significant improvement in survival. One advantage for esophagogastric cancers is that direct delivery via endoscopically should be efficient, although imaging-guided injection or even operation would likely be required for delivery to metastatic disease. External beam radiation therapy, which induces relative tissue hypoxia, could theoretically be used to help activate the *Grp78* promoter.

Acknowledgment This study is supported by STOP Cancer Foundation, Los Angeles, Cancer Institute NSW, NSW Cancer Council, and the National Health and Medical Research Council.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. CA Cancer J Clin 2007;57(1):43–66. doi:10.3322/canjclin.57.1.43.
2. Culver KW, Ram Z, Wallbridge S, et al. In vivo gene transfer with retroviral vector-producer cells for treatment of experimental brain tumors. Science 1992;256(5063):1550–1552. doi:10.1126/science.1317968.
3. Palmer TD, Rosman GJ, Osborne WR, Miller AD. Genetically modified skin fibroblasts persist long after transplantation but gradually inactivate introduced genes. Proc Natl Acad Sci U S A 1991;88(4):1330–1334. doi:10.1073/pnas.88.4.1330.
4. Dong D, Dubeau L, Bading J, et al. Spontaneous and controllable activation of suicide gene expression driven by the stress-inducible grp78 promoter resulting in eradication of sizable human tumors. Hum Gene Ther 2004;15(6):553–561. doi:10.1089/10430 3404323142006.
5. Lee AS. GRP78 induction in cancer: Therapeutic and prognostic implications. Cancer Res 2007;67(8):3496–3499. doi:10.1158/0008-5472.CAN-07-0325.
6. Roth JA. Gene therapy in thoracic oncology. Ann Thorac Surg 2008;85(5):1837–1838. doi:10.1016/j.athoracsur.2006.09.079.
7. Shimada H, Matsushita K, Tagawa M. Recent advances in esophageal cancer gene therapy. Ann Thorac Cardiovasc Surg 2008;14(1):3–8.
8. Sutter AP, Fechner H. Gene therapy for gastric cancer: Is it promising? World J Gastroenterol 2006;12(3):380–387.

9. Buskens CJ, Marsman WA, Bosma PJ, van Lanschot JJB. The current state of cancer gene therapy and its application in esophageal carcinoma. Dig Surg 2005;22(4):222–233. doi:10.1159/000088052.
10. Gupta VK, Park JO, Kurihara T, et al. Selective gene expression using a DF3/MUC1 promoter in a human esophageal adenocarcinoma model. Gene Ther 2003;10(3):206–212. doi:10.1038/sj.gt.3301867.
11. Marsman WA, Buskens CJ, Wesseling JG, et al. Gene therapy for esophageal carcinoma: The use of an explant model to test adenoviral vectors ex vivo. Cancer Gene Ther 2004;11(4):289–296. doi:10.1038/sj.cgt.7700680.
12. Marsman WA, Wesseling JG, El Bouch A, et al. Adenoviral serotypes in gene therapy for esophageal carcinoma. J Surg Res 2007;140(1):50–54. doi:10.1016/j.jss.2006.12.006.
13. Heideman DA, Snijders PJ, Craanen ME, et al. Selective gene delivery toward gastric and esophageal adenocarcinoma cells via EpCAM-targeted adenoviral vectors. Cancer Gene Ther 2001;8(5):342–351. doi:10.1038/sj.cgt.7700313.
14. Buskens CJ, Marsman WA, Wesseling JG, et al. A genetically retargeted adenoviral vector enhances viral transduction in esophageal carcinoma cell lines and primary cultured esophageal resection specimens. Ann Surg 2003;238(6):815–824. doi:10.1097/01.sla.0000098622.47909.c0.
15. Altorki N, Schwartz GK, Blundell M, et al. Characterization of cell lines established from human gastric-esophageal adenocarcinomas. Biologic phenotype and invasion potential. Cancer 1993;72(3):649–657. doi:10.1002/1097-0142(19930801)72:3<649::AID-CNCR2820720305>3.0.CO;2-L.
16. Nabeya Y, Loganzo F Jr, Maslak P, et al. The mutational status of p53 protein in gastric and esophageal adenocarcinoma cell lines predicts sensitivity to chemotherapeutic agents. Int J Cancer 1995;64(1):37–46. doi:10.1002/ijc.2910640109.
17. DuBridge RB, Tang P, Hsia HC, et al. Analysis of mutation in human cells by using an Epstein–Barr virus shuttle system. Mol Cell Biol 1987;7(1):379–387.
18. Ory DS, Neugeboren BA, Mulligan RC. A stable human-derived packaging cell line for production of high titer retrovirus/vesicular stomatitis virus G pseudotypes. Proc Natl Acad Sci U S A 1996;93(21):11400–11406. doi:10.1073/pnas.93.21.11400.
19. Chen X, Zhang D, Dennert G, et al. Eradication of murine mammary adenocarcinoma through HSVtk expression directed by the glucose-starvation inducible grp78 promoter. Breast Cancer Res Treat 2000;59(1):81–90. doi:10.1023/A:1006398918227.
20. Yu H, Eton D, Wang Y, et al. High efficiency in vitro gene transfer into vascular tissues using a pseudotyped retroviral vector without pseudotransduction. Gene Ther 1999;6(11):1876–1883. doi:10.1038/sj.gt.3301019.
21. Zhou Q, Sherwin RP, Parrish C, et al. Contortrostatin, a dimeric disintegrin from *Agkistrodon contortrix contortrix*, inhibits breast cancer progression. Breast Cancer Res Treat 2000;61(3):249–260. doi:10.1023/A:1006457903545.
22. Oberg S, Lord RV, Peters JH, et al. Is adenocarcinoma following esophagoduodenostomy without carcinogen in the rat reflux-induced? J Surg Res 2000;91(2):111–117. doi:10.1006/jsre.2000.5908.
23. Tang Q, Zhang D, Wan M, Jin L. Experimental study of the RV-HSV-TK/GCV suicide gene therapy system in gastric cancer. Cancer Biother Radiopharm 2007;22(6):755–761. doi:10.1089/cbr.2007.346.
24. Nakaya H, Ishizu A, Ikeda H, et al. In vitro model of suicide gene therapy for alpha-fetoprotein-producing gastric cancer. Anticancer Res 2003;23(5A):3795–3800.
25. Zhang JH, Wan MX, Pan BR, Yu B. Cytotoxicity of HSVtk and hrTNF-alpha fusion genes with IRES in treatment of gastric cancer. Cancer Lett 2006;235(2):191–201. doi:10.1016/j.canlet.2004.10.054.
26. Zhang JH, Wan MX, Pan BR, Yu B. Cytotoxicity of HSVtk and hrTNF-alpha fusion genes with IRES in treatment of gastric cancer. Cancer Biol Ther 2004;3(11):1075–1080.
27. Matsubara H, Kawamura K, Sugaya M, et al. Differential efficacy of suicide gene therapy by herpes simplex virus-thymidine kinase gene reflects the status of p53 gene in human esophageal cancer cells. Anticancer Res 1999;19(5B):4157–4160.
28. Shimada H, Matsubara H, Ochiai T. p53 gene therapy for esophageal cancer. J Gastroenterol 2002;37(Suppl 14):87–91.
29. Craperi D, Vicat JM, Nissou MF, et al. Increased bax expression is associated with cell death induced by ganciclovir in a herpes thymidine kinase gene-expressing glioma cell line. Hum Gene Ther 1999;10(4):679–688. doi:10.1089/10430349950018751.
30. Fumoto S, Nishi J, Nakamura J, Nishida K. Gene therapy for gastric diseases. Curr Gene Ther 2008;8(3):187–200. doi:10.2174/156652308784746431.
31. King GD, Curtin JF, Candolfi M, et al. Gene therapy and targeted toxins for glioma. Curr Gene Ther 2005;5(6):535–557. doi:10.2174/156652305774964631.
32. Nasu Y, Saika T, Ebara S, et al. Suicide gene therapy with adenoviral delivery of HSV-tK gene for patients with local recurrence of prostate cancer after hormonal therapy. Mol Ther 2007;15(4):834–840.
33. Ayala G, Satoh T, Li R, et al. Biological response determinants in HSV-tk+ ganciclovir gene therapy for prostate cancer. Mol Ther 2006;13(4):716–728. doi:10.1016/j.ymthe.2005.11.022.

J Gastrointest Surg (2009) 13:1052–1057
DOI 10.1007/s11605-009-0847-1

SSAT POSTER PRESENTATION

Utilization of Preoperative Patient Factors to Predict Postoperative Vitamin D Deficiency for Patients Undergoing Gastric Bypass

Judy Jin · Thomas A. Stellato · Peter T. Hallowell · Margaret Schuster · Kristen Graf · Scott Wilhelm

Received: 23 November 2008 / Accepted: 18 February 2009 / Published online: 13 March 2009

Abstract
Introduction Vitamin D deficiency occurring after gastric bypass procedures can predispose patients to calcium and parathyroid hormone (PTH) level abnormalities. The aim of the study is to identify preoperative patient risk factors for postoperative vitamin D deficiency.
Methods We retrospectively reviewed patients who underwent Roux-en-Y gastric bypass procedures between 2005 and 2006. Patient demographics, laboratory values of calcium, vitamin D, and PTH were followed at quarterly intervals for 1 year.
Results One hundred forty-five patients were included in the study. The mean age for the group was 44 years with an average body mass index of 49.5 kg/m^2. Eighty-six percent of patients were female and 23% was African–American. Forty-two percent of the patients had vitamin D deficiency (<20 ng/mL) either preoperatively or at year 1. The mean calcium levels decreased from 9.39 to 9.16 mg/dL ($p<0.001$) while the mean PTH levels increased from 25.7 to 43.9 ng/mL ($p<0.001$). A logistic regression model recognized preoperative vitamin D levels, race, and bypass limb length to be the only significant factors ($p<0.05$) for postoperative vitamin D deficiency.
Conclusion It is important to recognize patients who are at risk for vitamin D deficiency before surgery so that early intervention could be in place to minimize further postoperative deficiency.

Keywords Vitamin D deficiency · Risk factors · Roux-en-Y gastric bypass · Calcium · Parathyroid hormone · PTH

Background

The number of bariatric operations performed in the USA has increased approximately sixfold in the last decade.[1] While many surgical weight reduction procedures are available, the Roux-en-Y gastric bypass remains the most common procedure performed because it combines restrictive, malabsorptive, and hormonal components. While malabsorption from the gastric bypass assists in weight loss, it does have detrimental effects and can result in vitamin D and sometimes calcium deficiencies. These deficiencies can then trigger an upregulation in the parathyroid hormone (PTH) levels, resulting in secondary hyperparathyroidism. This is of concern because calcium and vitamin D homeostasis, along with PTH, may have a long-term impact on bone integrity. In the setting of malabsorption, a vicious cycle may start: first, vitamin D deficiency leads to a decrease in intestinal calcium absorption, and second, with reduced circulating calcium level, parathyroid hormone is increased to accelerate the rate of bone resorption in an effort to compensate for the low serum calcium level. If vitamin D deficiency persists, parathyroid hormone will continue to rise, and bone resorption can lead to osteopenia and potentially osteoporosis. The phenomenon of intestinal calcium and vitamin D malabsorption after gastric bypass

This paper had been presented as a poster at the DDW meeting May 2008, San Diego, CA, USA.

J. Jin · T. A. Stellato · P. T. Hallowell · M. Schuster · K. Graf · S. Wilhelm (✉)
Department of Surgery, Case Western Reserve University School of Medicine, University Hospitals Case Medical Center, Cleveland, OH, USA
e-mail: scott.wilhelm@uhhs.com

Table 1 Patient Demographics

Age (years)	44±10	
Gender	Male	14%
	Female	86%
Race	African–American	23%
	Caucasian	76%
BMI (kg/m2)		49.5
Bypass length	Short	61%
	Long	39%

surgeries has been documented in the recent years[2–4] and the need for postoperative supplementation of vitamin D and calcium has been stressed by many clinicians. However, vitamin D deficiency can be present in obese patients even before the gastric bypass procedures take place.[5] Therefore, it is equally, if not more important, to identify these "at risk patients" during preoperative screening so that intervention can take place before the effects of additional malabsorption take place. Using our institutional database from the gastric bypass population, we evaluated the pattern of postoperative changes in calcium, vitamin D, and parathyroid hormone levels in these patients. We then identified patients with postoperative vitamin D deficiency at 1 year after the gastric bypass procedures and investigated potential preoperative patient factors that predispose these patients to postoperative deficiency.

Methods

We retrospectively reviewed the data of morbidly obese patients who underwent Roux-en-Y gastric bypass procedures for weight reduction at University Hospitals Case Medical Center between January 2005 and October 2006. Institutional review board approval was obtained prior to study. Demographic data included patient age, gender, race, and preoperative body mass index (BMI). The length of the Roux limb was documented as either a long LL (~165 cm) or a short SL (~75 cm) limb. Roux limb length was determined by the operating bariatric surgeon based on patient's BMI. When the patient's BMI is greater than 50 kg/m^2, the patient will undergo long limb bypass; otherwise short limb bypass is the preferred operation at our institution.

Postoperatively, the standard of care is for all patients to receive a starting dose of elemental calcium (1,000 mg) and vitamin D (400–800 I.U.) supplementation daily. On subsequent visits, the amount of vitamin D supplementation was adjusted based on biochemical laboratory determination and could vary at the surgeon's discretion.

Preoperative values of calcium (normal 8.5–10.1 mg/dl), alkaline phosphatase (normal 33–110 U/dl), 25-hydroxy-vitamin D (25(OH) D) (normal 20–57 ng/mL), and PTH (normal 10–53 pg/mL) were collected and reviewed in each patient. After the bypass procedure, all patients returned to the clinic 2 weeks postoperatively, then quarterly for the first year, and yearly thereafter for serum analysis of aforementioned biochemical markers. When the preoperative values of vitamin D and PTH were not available in patients, the 2-week postoperative laboratory values were used as the baseline levels for the analysis. The follow-up period for all patients in the study was 1 year. In our study, vitamin D deficiency was defined as 25(OH) D≤20 ng/mL while secondary hyperparathyroidism was defined as having PTH>53 pg/mL without abnormal serum calcium level.

Statistical analysis was performed using the R program.[6] Data were expressed as mean ± standard deviations. Comparisons between groups were determined using paired Student's t test for continuous variables and Fisher's exact test (FET) for categorical values. Pearson correlation was used to quantify linear associations between variables. The multivariate prediction model was built using a backward stepwise logistic regression. A p value of <0.05 was considered statistically significant.

Results

We identified 195 patients during the study period; 50 patients were not included due to incomplete follow-up. The remaining 145 patients were included in the study. Overall patient demographics are shown in Table 1. The average age for the group was 44±10 years (range 19–64). Majority of the patients were Caucasian female. The mean Preoperative BMI was 49.5 kg/m^2 (range 36.4–74.6), and 39% of the patients underwent LL bypass. At 1 year, the mean postoperative BMI was significantly reduced to

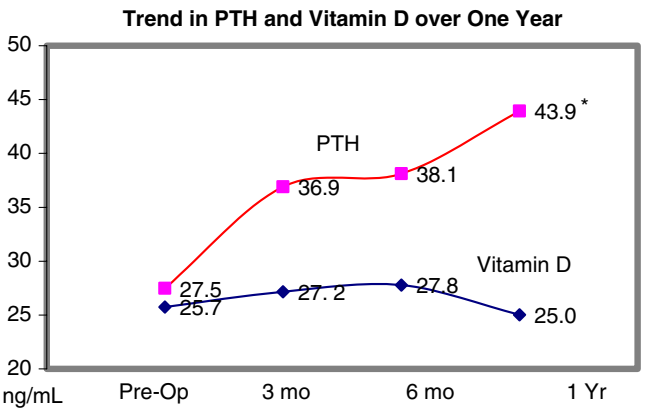

Figure 1 The trend in vitamin D, PTH, and calcium over 1 year after gastric bypass procedure.

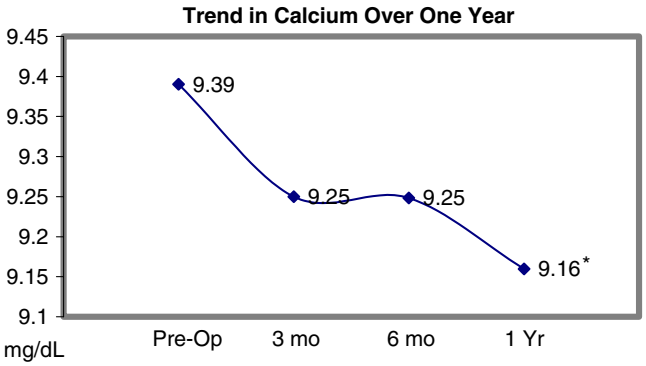

Figure 2 The trend in vitamin D, PTH, and calcium over 1 year after gastric bypass procedure.

31.8 kg/m^2 (range 19.8–51, $p<0.001$); this represented a mean excess weight loss of 73% based on a targeted BMI of 24 kg/m^2.

The trends in calcium, vitamin D, and PTH are depicted in Figs. 1 and 2. The mean preoperative calcium level was 9.39±0.52 mg/dL. Fifteen patients (10%) had abnormal calcium levels, and 40% ($n=6$) of them were hypocalcemic (<8.5 mg/dL). Over the 1-year follow-up, the calcium level exhibited a downward trend, and the mean level decreased significantly to 9.16±0.40 mg/dL ($p<0.001$). Seven (5%) patients had abnormal calcium levels at 1 year; 85% were hypocalcemic. Alkaline phosphatase levels did not change significantly over the 1-year follow-up (91→93 U/dL, $p=0.46$).

The PTH levels increased significantly from 27.5 to 43.9 pg/mL over 1 year ($p<0.001$). Ten patients (7%) had secondary hyperparathyroidism (>53 pg/mL) before undergoing gastric bypass procedure, and the rate in this population was increased to 38 (26%) patients at 1 year. This almost fourfold increase in patients with secondary hyperparathyroidism was statistically significant (FET, $p=0.0004$).

The mean vitamin D level was 25.7 ng/mL at baseline. There was minimal change in the mean level after the gastric bypass procedure, and at 1 year, the vitamin D level was 25.0 ng/mL ($p=0.54$). While the mean vitamin D levels were within the normal range at both time points, 41% of the patients had vitamin D deficiency (<20 ng/mL) prior to the gastric bypass procedure. This proportion increased slightly to 42% after surgery (FET, $p=0.90$). Preoperatively, vitamin D and PTH (Fig. 3) exhibited an inverse but not statistically significant relationship ($r=-0.11$, $p=0.12$). One year after surgery, vitamin D and PTH continued to exhibit an inverse but now a much stronger and statistically significant relationship ($r=-0.22$, $p=0.009$). Preoperative vitamin D levels and patient BMIs also had an inverse relationship ($r=-0.15$, $p=0.06$) which became more pronounced after surgery ($r=-0.24$, $p=0.0038$). Vitamin D and calcium levels, however, did not appear to have any significant relationship either before or after the bypass procedure.

We compared patients with vitamin D deficiency 1 year after surgery to patients without vitamin D deficiency using various preoperative patient factors. On univariate analysis (Table 2), postoperative vitamin D deficiency was associated with higher preoperative BMI (51.1 vs 48.4 kg/m^2, $p=0.037$), African–American race (FET, $p=0.0002$), long limb bypass (FET, $p=0.017$), lower preoperative calcium levels (9.27 vs. 9.47 mg/dL, $p=0.018$) and lower preoperative vitamin D levels (19.9 vs. 30.0 ng/mL, $p<0.0001$). Age, gender, and preoperative PTH levels did not appear to affect postoperative vitamin D values.

A multivariate logistic regression model was built to predict postoperative vitamin D deficiency using the aforementioned preoperative patient factors. The final model was reached by using bootstrap validation with backward AIC-based variable deletion scheme. Preoperative vitamin D levels <16 ng/mL, African–American race, and long limb bypass (Table 3) were recognized to be the only independent risk factors for postoperative vitamin D deficiency. Area under the receiver operating characteristic curve was 0.836.

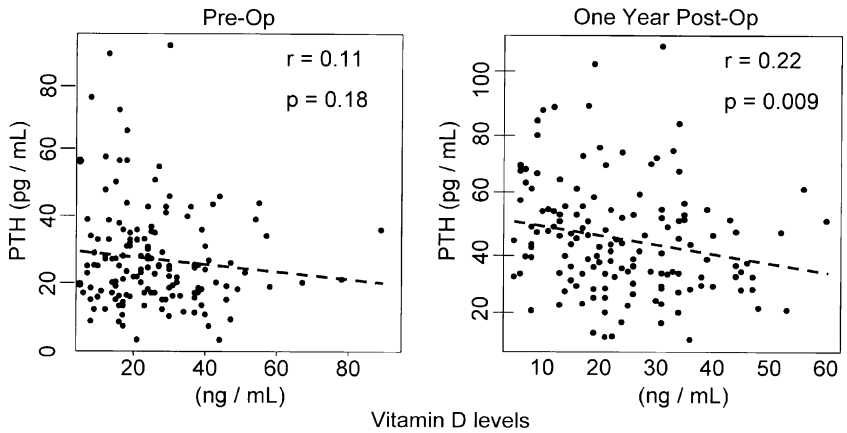

Figure 3 Relationship between PTH and vitamin D levels prior to and 1 year after gastric bypass procedure.

Table 2 Determination of Preoperative Risk Factors that Predispose Patients to Postoperative Vitamin D Deficiency Using Univariate Analysis

	Vitamin D deficient (n=61)	Non-vitamin D deficient (n=84)	P value
Age (years)	43	45	0.38
Gender (M vs. F)	8/53	12/72	0.52
Race (C vs. AA)	47/24	74/10	0.0002
Pre-Op BMI (kg/m^2)	51.0	48.4	0.037
Limb length (short vs. long)	30/31	58/36	0.017
Pre-Op Vitamin D (ng/mL)	19.9	30.0	<0.001
Pre-Op PTH (pg/mL)	29.6	26.0	0.17
Pre-Op Calcium (mg/dL)	9.27	9.48	0.018

Discussion

Vitamin D deficiency appears to be a prevalent problem in the obese population. In this study, almost half of the patients undergoing gastric bypass procedures had underlying vitamin D deficiency prior to the procedure. This phenomenon continued to persist even after surgery despite daily vitamin D and calcium supplementation. These results suggest that the currently recommended regimen of supplementation is not adequate to compensate for the additional malabsorptive loss as a result of the bypass surgery. To prevent worsening postoperative vitamin deficiency and optimizing postoperative outcomes, we believe it is important to identify patients who are at risk for vitamin D deficiency before surgery so that aggressive therapy could be initiated both before and after the procedure has taken place. To study this, we evaluated potential preoperative patient factors for their predictability of postoperative vitamin D deficiency. While many patient factors appeared to play a role in univariate analysis, preoperative vitamin D levels <16 ng/mL, long bypass limb length, and African–American race were the only independent risk factors based on our multivariate logistic regression analysis.

Chronic vitamin D deficiency has a significant effect on the overall calcium homeostasis in the body. Based on our study, patients with Preoperative vitamin D levels <16 ng/mL are almost seven times more likely to continue their vitamin D deficiency postoperative when compared with patients who have levels above that. Thirty-four patients in this study had preoperative vitamin D levels than less 16 ng/mL. Seventy-one percent of these 34 patients continued to have vitamin D deficiency after surgery despite oral supplementation. It is important for clinicians to recognize that this subset of patients will have more difficulty in normalizing their vitamin D levels. At most institutions, the common vitamin D supplementation is 400 I.U.; this may be increased to 800 I. U. daily when a patient is discovered to have postoperative vitamin D deficiency. This regimen is based mostly on requirements of healthy, nonobese patients and does not take into account the loss through malabsorption after surgery. To date, there has been no study attempting to correlate vitamin D dosages to the correction of its deficiency in the gastric bypass population. Due to the paucity of data, the trend of supplementing these patients at suboptimal doses is continued. A recent study by DiGiorgi et al.[7] showed improved vitamin D levels (17±8 to 25±12 ng/mL) from preoperatively to 1 year after surgery. These patients received 800–1,200 I.U. of vitamin D daily, higher than what was being given at our institution; this dosage may have contributed to the improvement. However, the number of patients available for follow-up at 12 months in that study (n=118) was less than half of the patients (n=249) presented at preoperative screening, a common limitation in longitudinal studies. Another study[8] compared the effect of two levels of vitamin D supplementation: 700 I.U. vitamin D daily versus 50,000 I.U. ergocalciferol weekly. While no difference was shown between the two regimens at 1 year post-surgery, the group that received ergocalciferol had much lower mean preoperative vitamin D levels (31.7 versus 62.8 ng/mL), hence, the more aggressive treatment. As a result, prospective study is absolutely necessary to investigate the appropriate dosage of vitamin D supplementation to eliminate or minimize postoperative deficiency. This will allow for the proper treatment to be initiated before the gastric bypass procedure takes place.

Table 3 Factors Independently Predictive of Postoperative Vitamin D Deficiency on Multivariate Analysis

	Odds ratio	95% confidence interval	P value
African–American Race	10.5	2.0–55.2	0.006
Long limb bypass	2.58	1.1–6.1	0.03
Preop Vitamin D <16 ng/mL	6.67	1.75–25.0	0.01

Patients with preoperative BMI>50 kg/m^2 usually undergo longer intestinal bypass to achieve greater weight loss in order to reach their ideal body weight. At our institution, the Roux limb is 90 cm longer (165 vs. 75 cm) in patients with BMI>50 kg/m^2. This additional length of bypass can put patients at even greater risk for malabsorption caused by poor mixing of the bile salts required for fat soluble vitamin D absorption.[9] The results from our study confirm this hypothesis. Patients with longer limb lengths are 2.5 times more likely to develop postoperative vitamin D deficiency. This is in agreement with the study performed by Johnson et al.[4]; however, the difference between their limb lengths were not specified in the study. Another study by Youssef et al.[10] looked at different Roux limb lengths and their effect on vitamin D deficiency, although there was an increased proportions of patients with vitamin D deficiency at higher limb length (150 cm), the difference was not statistically significant compared with the other limb lengths (75, 100, 125 cm). This study reported at least a potential trend that patient with longer limb length >125 cm may be at greater risk for worsening vitamin D deficiency. Although BMI was not determined to be an independent risk factor on multivariate analysis, we believe it could still be used as an easily identifiable risk factor since the determination of the limb bypass length is intricately linked to patient's BMI.

The most impressive finding in the study was that an African–American female patient undergoing gastric bypass procedure is ten times more likely to develop postoperative vitamin D deficiency than her Caucasian counterpart. This prevalence is not only seen in adults but in children as well. Black children are 14 times more likely to have vitamin D levels <30 ng/mL.[11] African–American patients tended to have lower baseline vitamin D levels for several reasons. Prior studies have indicated that increased melanin production in the African–American patients may limit the amount of cutaneous vitamin D absorbed through the sunlight. In this particular study, northern latitude with further decreased sunlight exposure can aggravate the problem even more.[12] In addition, the oral intake of vitamin-D-fortified dairy products is lower in the African–American patients because of higher prevalence of lactose intolerance. In a recent study on healthy postmenopausal African–American patients who are borderline obese (BMI= 29 kg/m^2), 2,000 I.U. of vitamin D daily was recommended to patients with vitamin D level less than 45 ng/mL in order to reach an optimal level of 50 ng/mL.[13] This dosage is much higher than the general recommendation for vitamin D supplement in the post-gastric bypass population.

There are several limitations to this study. First, this study has a relatively small population. The generality of the results are, thus, limited by the sample size. However, the patients included in this study had completed data so as to make comparison between groups and time periods more meaningful. We also did not have information on markers of bone turnover including serum bone-specific alkaline phosphatase, osteocalcin, and urine *n*-telopeptide cross-links of type 1 collage. While the African–American patients have much more severe vitamin D deficiency, they have been shown to have a more efficient calcium economy and higher resistance of cortical bone loss to elevated levels of PTH.[14] Without information on specific bone markers, we are unable to verify this finding.

Vitamin D deficiency appears to be the initiating event that sets off the cascade of endocrine feedback response involving several body organ systems.[15] Secondary hyperparathyroidism as a result of chronic vitamin D deficiency can potentially cause unbalanced resorptive bone loss leading to osteopenia and osteoporosis in adults. This is especially important in the gastric bypass population because these patients are predominantly female and perimenopausal who are already at risk for bone loss. While weight reduction is the primary goal of the gastric bypass procedure, minimizing or avoiding metabolic sequelae of the procedure is equally important. To be able to identify risk factors for vitamin D deficiency preoperatively is, therefore, important for the long-term well-being of these patients. In our study, it is apparent that a large portion of these patients have vitamin D deficiency before surgery. If untreated, these patients go on to have worsening deficiency after surgery. Even with supplementation, it is difficult to correct this abnormality. We have identified three independent patient characteristics that are considered high risk that we believe will be useful for clinicians at initial screening. Once vitamin D deficiency is recognized, clinicians should aggressively treat these patients before undergoing the gastric bypass procedure to ensure a more optimal long-term outcome. In the future, we believe that prospective study is needed to look for the optimal dose of vitamin D and calcium supplement to avoid or correct preexisting vitamin D deficiency.

References

1. Trus TL, Pope GD, Finlayson SR. National trends in utilization and outcomes of bariatric surgery. Surg Endosc 2005;19(5):616–620. doi:10.1007/s00464-004-8827-8.
2. Carlin AM, Rao DS, Meslemani AM, et al. Prevalence of vitamin D depletion among morbidly obese patients seeking gastric bypass surgery. Surg Obes Relat Dis 2006;2(2):98–103. discussion 104 doi:10.1016/j.soard.2005.12.001.
3. Carlin AM, Rao DS, Yager KM, et al. Effect of gastric bypass surgery on vitamin D nutritional status. Surg Obes Relat Dis 2006;2(6):638–642. doi:10.1016/j.soard.2006.09.003.
4. Johnson JM, Maher JW, DeMaria EJ, et al. The long-term effects of gastric bypass on vitamin D metabolism. Ann Surg 2006;243(5):701–704. discussion 704–705 doi:10.1097/01.sla.0000216773.47825.c1.

5. Ybarra J, Sanchez-Hernandez J, Gich I, et al. Unchanged hypovitaminosis D and secondary hyperparathyroidism in morbid obesity after bariatric surgery. Obes Surg 2005;15(3):330–335. doi:10.1381/0960892053576758.
6. Team RDCR. A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2007.
7. Digiorgi M, Daud A, Inabnet WB, et al. Markers of bone and calcium metabolism following gastric bypass and laparoscopic adjustable gastric banding. Obes Surg 2008;18(9):1144–1148.
8. Nelson ML, Bolduc LM, Toder ME, et al. Correction of preoperative vitamin D deficiency after Roux-en-Y gastric bypass surgery. Surg Obes Relat Dis 2007;3(4):434–437. doi:10.1016/j.soard.2007.02.007.
9. Lo CW, Paris PW, Clemens TL, et al. Vitamin D absorption in healthy subjects and in patients with intestinal malabsorption syndromes. Am J Clin Nutr 1985;42(4):644–649.
10. Youssef Y, Richards WO, Sekhar N, et al. Risk of secondary hyperparathyroidism after laparoscopic gastric bypass surgery in obese women. Surg Endosc 2007;21(8):1393–1396. doi:10.1007/s00464-007-9228-6.
11. Weng FL, Shults J, Leonard MB, et al. Risk factors for low serum 25-hydroxyvitamin D concentrations in otherwise healthy children and adolescents. Am J Clin Nutr 2007;86(1):150–158.
12. Webb AR, Holick MF. The role of sunlight in the cutaneous production of vitamin D3. Annu Rev Nutr 1988;8:375–399. doi:10.1146/annurev.nu.08.070188.002111.
13. Talwar SA, Aloia JF, Pollack S, Yeh JK. Dose response to vitamin D supplementation among postmenopausal African–American women. Am J Clin Nutr 2007;86(6):1657–1662.
14. Perry HM 3rd, Horowitz M, Morley JE, et al. Aging and bone metabolism in African–American and Caucasian women. J Clin Endocrinol Metab 1996;81(3):1108–1117. doi:10.1210/jc.81.3.1108.
15. Jin J, Robinson AV, Hallowell PT, et al. Increases in parathyroid hormone (PTH) after gastric bypass surgery appear to be of a secondary nature. Surgery 2007;142(6):914–920. discussion 914–920 doi:10.1016/j.surg.2007.09.023.

J Gastrointest Surg (2009) 13:1058–1063
DOI 10.1007/s11605-009-0840-8

ORIGINAL ARTICLE

Laparoscopy-Assisted Distal Gastrectomy with D2 Lymph Node Dissection Following Standardization—A Preliminary Study

Masanori Tokunaga · Naoki Hiki · Tetsu Fukunaga · Kyoko Nohara · Hiroshi Katayama · Yoshimasa Akashi · Shigekazu Ohyama · Toshiharu Yamaguchi

Received: 2 January 2009 / Accepted: 18 February 2009 / Published online: 7 March 2009

Abstract
Background Laparoscopy-assisted distal gastrectomy (LADG) with standard D2 dissection is a complex procedure usually performed only by experienced surgeons, and the feasibility of this procedure still remains unclear.
Method Patients who underwent LADG at the Cancer Institute Hospital between April 2006 and October 2008 were recruited for this study. Early surgical outcomes were compared between patients who underwent complete D2 dissection (complete D2 group; n=42) and those who underwent D1 + beta dissection (D1 + beta group; n=179) to determine the feasibility of laparoscopic D2 lymph node dissection.
Results In complete D2 group, the operation time was longer (253±10 vs 224±4 min; P=0.005), and the number of retrieved lymph nodes was larger (41±2 vs 35±1; P=0.002) compared with those in D1 + beta group. The other early surgical outcomes monitored for the two groups were not different between groups.
Conclusions LADG with complete D2 lymph node dissection can be performed safely if the procedure is standardized and an experienced laparoscopic surgeon performs the surgery. To be accepted as a standard treatment for advanced gastric cancer, well-designed prospective trial is necessary.

Keywords Laparoscopy-assisted gastrectomy · Gastric cancer · D2 lymph node dissection

Introduction

Laparoscopy-assisted gastrectomy (LAG) is increasingly performed in Japan since the first case of laparoscopy-assisted distal gastrectomy (LADG) with Billroth I reconstruction was reported.[1] Several advantages of LAG compared with conventional open gastrectomy have been documented,[2–8] including reductions in bleeding and pain and reduced disturbance of respiratory function. However, LAG has limitations for lymph node dissection,[7] and at present in Japan, generally accepted laparoscopic lymph node dissection is D1 and D1 + beta lymph node dissection (D1 + station 7, 8a, 9 lymph nodes dissection), while complete laparoscopic D2 lymph node dissection is performed by experienced surgeons.[7,9–13]

A large randomized controlled trial conducted in Europe failed to prove the efficacy of conventional open gastrectomy with D2 lymph node dissection due to the high morbidity and mortality rate.[14–17] By comparison, in Japan, the procedure for conventional open gastrectomy with complete D2 lymph node dissection (D1 + station 7, 8a, 9, 11p, 12a, 14v lymph node dissection) is well established and accepted as a standard practice for the treatment of advanced gastric cancer.[18–20] Therefore, the feasibility of LAG with D2 lymph node dissection should be investigated so that LAG is accepted as a standard treatment for advanced gastric cancer.

It is difficult to perform LAG with complete D2 lymph node dissection since this type of surgery involves major vessel and pancreatic tissue exposure, and there is, therefore, an increased risk of major vessel injury and postoperative

M. Tokunaga · N. Hiki (✉) · T. Fukunaga · K. Nohara · H. Katayama · Y. Akashi · S. Ohyama · T. Yamaguchi
Department of Gastroenterological Surgery,
Cancer Institute Hospital,
Japanese Foundation for Cancer Research,
3-10-6 Ariake, Koto-ku,
Tokyo 135-8550, Japan
e-mail: naoki.hiki@jfcr.or.jp

pancreas-related infections associated with the procedure. Therefore, the establishment of standardized procedures for D1 + beta lymph node dissection might be an initial step towards the introduction of complete laparoscopic D2 lymph node dissection. In our institute where these procedures have been standardized,[21] the number of laparoscopic D2 lymph node dissections is gradually increasing. In the present study, the early surgical outcomes of laparoscopic D2 lymph node dissection was investigated, and these surgical outcomes were compared with those following D1 + beta lymph node dissection. The feasibility of laparoscopic D2 lymph node dissection following standardization of LAG with D1 + beta lymph node dissection was thereby determined.

Patients and Methods

Patients who were treated with LADG with extraperigastric lymph node dissection performed by one of the two specialists (F.T. or H.N.) at the Cancer Institute Hospital between April 2006 and October 2008 were included in the study. All patients had histologically proven adenocarcinoma prior to surgery, and all surgeries were conducted with a curative intent.

Patients' characteristics, including gender, age, body mass index, and preoperative comorbidity, were collected from their respective clinical records. Information on the operation procedure, operation time, intraoperative bleeding, intraoperative complications, degree of lymph node dissection, and number of retrieved lymph nodes were collected from surgical charts. The postoperative clinical course, such as the day of first flatus, the day of first oral intake, postoperative morbidity, mortality, and the duration of the postoperative hospital stay were also collected from clinical records. All data collection was performed retrospectively.

Indication for LADG with D2 Lymph Node Dissection

Laparoscopy-assisted distal gastrectomy with D2 lymph node dissection is indicated in patients with cT2N0 or cT1N1 gastric cancer. LADG with D2 lymph node dissection is also indicated even in patients with cT1N0 early gastric cancer if tumor invasion to proper muscle layer (T2a) or first tier lymph node metastasis was suspected intraoperatively.

Numbering of Lymph Node Station and Degree of Lymph Node Dissection

The number of each lymph node station was assigned according to the Japanese Classification of Gastric Carcinoma.[22] Stations 1 to 6 were perigastric lymph nodes while 7, 8a, 9, 11p, 12a, and 14v were second-tier lymph nodes and were located along the left gastric artery, the common hepatic artery, the celiac axis, the proximal half of the splenic artery, the proper hepatic artery, and the surface of the superior mesenteric vein at the lower border of the pancreas, respectively. D1 + beta lymph nodes were defined as regional lymph nodes with some additional second-tier lymph nodes (stations 7, 8a, and 9). Conversely, all second-tier lymph nodes were dissected during complete D2 lymph node dissection (Fig. 1).

Conversion from LADG to Conventional Open Gastrectomy

Laparoscopy-assisted distal gastrectomy was converted to conventional open gastrectomy if intraoperative findings showed (1) advanced gastric cancer was obviously exposed the serosal membrane, (2) positive second-tier lymph nodes following frozen examination of retrieved lymph nodes, (3) uncontrollable bleeding or adhesion, and (4) any other difficulties in performing laparoscopic surgery.

Operation Procedures of LAG with Complete D2 Lymph Node Dissection

We previously reported our standardized laparoscopic procedure for LAG with D1 + beta lymph node dissection;

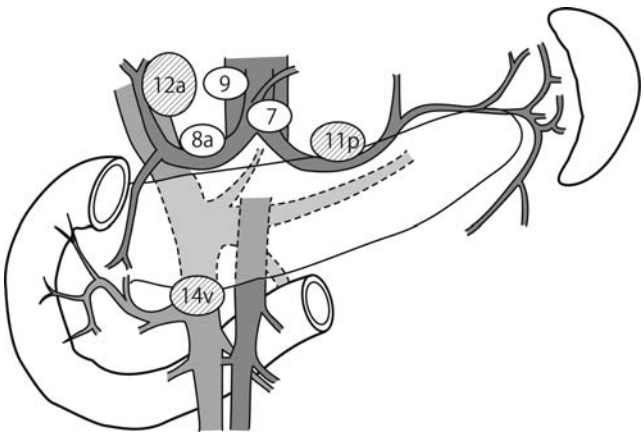

Figure 1 Extragastric lymph node station. D1 + beta lymph node dissection includes station 7, 8a, and 9 lymph node (*open oval*) retrieval. In distal gastrectomy with D2 lymph node dissection, station 11p and 12a lymph node (*shaded oval*) have to be dissected as well as station 7, 8a, and 9 lymph nodes. Moreover, station 14v lymph node (*shaded oval*) should also be dissected in patient with lower third gastric cancer.

thus techniques for station 11p, 12a, and 14v lymph node dissection were highlighted in this manuscript.[21]

Dissection of Station 6 and 14v Lymph Nodes

The origin of the right gastroepiploic vein and the surface of the superior mesenteric vein at the lower border of the pancreas were exposed for the dissection of station 14v lymph nodes. The right gastroepiploic artery and vein were divided separately at its origin using a clip (Lapro-Clip™; single absorbable ligating clip cartridge, Covidien) and Ligasure (Covidien), then station 6 and 14v lymph node dissection were completed.

Dissection of Station 5 and 12a Lymph Nodes

The origin of the right gastric artery and vein was exposed using AutoSonix™ ULTRA SHEARS™. The left border of the proper hepatic artery and portal vein was also exposed, and station 12a lymph nodes were completely dissected. The right gastric artery and vein were then divided using clips and Ligasure at its origin.

Dissection of Station 7, 8a, 9, and 11p Lymph Nodes

The pancreatic capsule was dissected using AutoSonix™ ULTRA SHEARS™ at the line of the superior pancreatic border. The splenic artery and its origin were exposed, and the surface of splenic vein was also exposed toward the pancreatic tail as far as the root of the posterior gastric artery, then station 11p lymph node was completely retrieved. Next, the left gastric artery and vein were divided at their origins, respectively. Subsequently, common hepatic artery and celiac axis were exposed; thus, station 7, 8a, and 9 lymph node dissection were also completed.

Comparison of Early Surgical Outcomes

In the present study, operation time, intraoperative bleeding, the number of retrieved lymph nodes, the day of first flatus, the day of first oral intake, postoperative morbidity, mortality, and the duration of the postoperative hospital stay were compared between patients who underwent LADG with complete D2 lymph node dissection (complete D2 group) and patients who underwent LADG with D1 + beta lymph node dissection (D1 + beta group). Surgery-related complications included intra-abdominal bleeding, anastomotic leakage, anastomotic bleeding, enteric injury, pancreas related infection, intra-abdominal abscess, and other complications related to the surgical procedure itself. Complications unrelated to surgery included respiratory and cardiovascular complications.

Statistic Analyses

All continuous data are presented as the mean ± standard error. Statistical analyses were performed using the chi-square test, Fisher's exact test, Student's *t* test, and Mann–Whitney *U* test. $P<0.05$ was considered significant.

Results

Between April 2006 and October 2008, 221 patients underwent LADG with lymph node dissection performed by one of the two specialists (F.T. or H.N) at the Cancer Institute Hospital. Of these, 179 patients underwent LADG with D1 + beta lymph node dissection (D1 + beta group), and 42 patients underwent LADG with complete D2 lymph node dissection (complete D2 group).

The patients' characteristics and operative findings are given in Tables 1 and 2. Younger patients were more frequently observed in the complete D2 group. The operation time was significantly longer, and the number of retrieved lymph nodes was significantly larger for the complete D2 group compared to the D1 + beta group (253± 10 vs 224±4 min; $P=0.005$ and 41±2 vs 35±1; $P=0.002$,

Table 1 Characteristics of Patients

	Complete D2	D1 + beta	*P* value
Number of patients	42	179	
Gender			
Male/Female	29/13	118/61	0.699
Age (years)			
Mean	56±2	64±1	0.001
Range	36–78	37–90	
Body mass index (kg/m2)	22±0	24±1	0.403
Pathological stage			
IA	17 (40)	147 (82)	
IB	13 (31)	19 (11)	
II	9 (21)	10 (6)	
IIIA	2 (5)	2 (1)	
IIIB	1 (2)	1 (1)	<0.001
Preoperative complication			
Hypertension	5 (14)	49 (27)	0.077
Diabetes	3 (7)	21 (11)	0.390
Ischemic heart disease	0	4 (2)	0.328
Asthma	0	11 (6)	0.099
Cerebral infarction	1 (2)	4 (2)	0.954
Previous laparotomy			
Yes	5	56	
No	37	123	0.012

Data are presented as mean ± SE

Table 2 Operative Data of Patients

	Complete D2	D1 + beta	*P* value
Operation time (min)	253±10	224±4	0.005
Bleeding (ml)	73±5	57±7	0.392
Number of retrieved lymph nodes	41±2	35±1	0.002
Conversion	1 (2)	6 (3)	0.746
Transfusion, *n* (%)	0	0	–

Data are presented as mean ± SE

respectively). Intraoperative bleeding was not different between groups, and intraoperative transfusion was not required in any of the patients in the present study. Conversion to open gastrectomy was required in six patients of D1 + beta group (three patients for further lymph node dissection, two patients due to severe intra-abdominal adhesion, and one patient for total gastrectomy due to positive proximal margin). In complete D2 group, one patient required conversion to open surgery due to uncontrollable bleeding from the gastrocolic trunk, which happened during station 14v lymph node dissection.

The postoperative clinical course of patients in both groups is given in Table 3. The incidence of surgery-related complication was similar, and postoperative mortality was not observed. Re-operation was not required in any patient in this study.

Discussion

Open gastrectomy with D2 lymph node dissection is a standard surgical procedure for advanced gastric cancer. The procedure is widely accepted in Japan despite a large randomized controlled study conducted in Europe that failed to prove the efficacy of D2 lymph node dissection.[14,16,17] LAG has been widely accepted as a treatment for early gastric cancer, and many advantages, including reduced pain and bleeding, less postoperative respiratory disturbance, early bowel movement, and short postoperative hospital stay, have been reported.[2–8] Nevertheless, laparoscopic D2 lymph node dissection has not been widely investigated since it is considered to be technically difficult. LAG with D2 lymph node dissection is performed only in a few institutes by highly experienced surgeons.[7,9–12,23,24] Furthermore, the quality of lymph node dissection differs between institutes, and the operation time for LAG with D2 lymph node dissection was generally longer than that for conventional open gastrectomy with D2 lymph node dissection.[7,9,11]

Approximately 50 operations are required to complete a surgeons' learning curve in LAG.[2,25,26] Moreover, we previously reported that standardization of each laparoscopic procedure resulted in favorable early surgical outcomes such as shortened operation time or less intraoperative

Table 3 Postoperative Clinical Course

	Complete D2	D1 + beta	P value
Postoperative complications			
Surgery-related complications, *n* (%)	2 (5)	16 (9)	0.373
Intraabdominal bleeding, *n* (%)	0	1 (1)	0.627
Anastomotic leakage, *n* (%)	0	2 (1)	0.491
Anastomotic bleeding, *n* (%)	1 (2)	1 (1)	0.262
Pancreas related infection, *n* (%)	1 (2)	3 (2)	0.758
Intraabdominal abscess, *n* (%)	0	5 (3)	0.273
Bowel obstruction, *n* (%)	0	0	–
Superficial surgical site infection, *n* (%)	0	3 (2)	0.398
Others, *n* (%)	0	1 (1)	0.627
Surgery unrelated complications	0	6 (3)	0.229
Respiratory complications, *n* (%)	0	2 (1)	0.491
Cardiovascular complications, *n* (%)	0	1 (1)	0.627
Others, *n* (%)	0	3 (2)	0.398
Re-operation	0	0	–
Postoperative hospital stay (days)	12±1	13±1	0.346
Time until start of oral intake (days)	2±0	2±0	0.471
Time until first flatus (days)	3±0	2±0	0.549

Data are presented as mean ± SE

bleeding, even if specialists for LAG (more than 200 cases of experience) performed surgery.[21] The present study was conducted following the standardization period; in other words, feasibility of laparoscopic D2 lymph node dissection following standardization could be investigated as a preliminary study.

As expected, the operation time for the complete D2 group was longer (by about 30 min) than for the D1 + beta group, due in part to the additional lymph nodes that required dissection. Thus, in patients with middle third gastric cancer, D2 lymph node dissection is achieved by the removal of station 11p (along with the splenic artery) and 12a (along with the proper hepatic artery) lymph nodes as well as D1 + beta lymph node dissection. In addition, station 14v (surface of superior mesenteric vein at the level of lower border of pancreas) lymph nodes were dissected if the tumor was located in the lower third of the stomach.

The quality of lymph node dissection is occasionally determined from the number of retrieved lymph nodes.[7,11] In the present study, the number of retrieved lymph nodes was significantly larger for the complete D2 group than for the D1 + beta group. This difference might be a result of the aggressive lymph node dissection, including dissection from the suprapancreatic area, for the complete D2 group.

The higher frequency of postoperative morbidity following complete D2 lymph node dissection was of some concern, since a European randomized trial reported a higher frequency of postoperative morbidity after D2 lymph node dissection compared with those following either D0 or D1 lymph node dissection.[15,16] Intraoperative bleeding and postoperative pancreas-related infections were of particular concern for the complete D2 group since the procedure requires the exposure of major vessels and the pancreas capsule, both of which could be injured during the procedure. In the present study, one patient of complete D2 group required conversion due to uncontrollable bleeding even though all operations were performed by experienced surgeons. However, the incidence of postoperative morbidity and mortality was not different, and any other intraoperative complication was not observed. We consider, therefore, laparoscopic D2 lymph node dissection can be performed safely. However, since it is a technically difficult procedure, standardization of the laparoscopic procedure is required, and experienced surgeons should carry out the surgery.

The current study has some limitation, however, since the long-term outcome has not been evaluated, and the number of patients who underwent complete D2 dissection is relatively low. Continued monitoring of patients is required to determine the long-term efficacy of laparoscopic D2 lymph node dissection, thereby enabling its acceptance as a standard surgical procedure for advanced gastric cancer. Moreover, well-designed prospective study comparing LADG with D2 lymph node dissection and conventional open gastrectomy with D2 lymph node dissection is required as a next step.

In conclusion, LADG with complete D2 lymph node dissection is a safe procedure, provided experienced surgeons perform the surgery following standardization. To be accepted as a standard treatment, well-designed prospective study is warranted in the future.

References

1. Kitano S, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. Surg Laparosc Endosc 1994;4:146–148.
2. Kim MC, Jung GJ, Kim HH. Learning curve of laparoscopy-assisted distal gastrectomy with systemic lymphadenectomy for early gastric cancer. World J Gastroenterol 2005;11:7508–7511.
3. Adachi Y, Suematsu T, Shiraishi N, Katsuta T, Morimoto A, Kitano S, Akazawa K. Quality of life after laparoscopy-assisted Billroth I gastrectomy. Ann Surg 1999;229:49–54. doi:10.1097/00000658-199901000-00006.
4. Adachi Y, Shiraishi N, Shiromizu A, Bandoh T, Aramaki M, Kitano S. Laparoscopy-assisted Billroth I gastrectomy compared with conventional open gastrectomy. Arch Surg 2000;135:806–810. doi:10.1001/archsurg.135.7.806.
5. Mochiki E, Nakabayashi T, Kamimura H, Haga N, Asao T, Kuwano H. Gastrointestinal recovery and outcome after laparoscopy-assisted versus conventional open distal gastrectomy for early gastric cancer. World J Surg 2002;26:1145–1149. doi:10.1007/s00268-002-6286-8.
6. Mochiki E, Kamiyama Y, Aihara R, Nakabayashi T, Asao T, Kuwano H. Laparoscopic assisted distal gastrectomy for early gastric cancer: Five years' experience. Surgery 2005;137:317–322. doi:10.1016/j.surg.2004.10.012.
7. Miura S, Kodera Y, Fujiwara M, Ito S, Mochizuki Y, Yamamura Y, Hibi K, Ito K, Akiyama S, Nakao A. Laparoscopy-assisted distal gastrectomy with systemic lymph node dissection: a critical reappraisal from the viewpoint of lymph node retrieval. J Am Coll Surg 2004;198:933–938. doi:10.1016/j.jamcollsurg.2004.01.021.
8. Huscher CG, Mingoli A, Sgarzini G, Sansonetti A, Di Paola M, Recher A, Ponzano C. Laparoscopic versus open subtotal gastrectomy for distal gastric cancer: five-year results of a randomized prospective trial. Ann Surg 2005;241:232–237. doi:10.1097/01.sla.0000151892.35922.f2.
9. Noshiro H, Nagai E, Shimizu S, Uchiyama A, Tanaka M. Laparoscopically assisted distal gastrectomy with standard radical lymph node dissection for gastric cancer. Surg Endosc 2005;19:1592–1596. doi:10.1007/s00464-005-0175-9.
10. Uyama I, Sugioka A, Fujita J, Komori Y, Matsui H, Hasumi A. Laparoscopic total gastrectomy with distal pancreatosplenectomy and D2 lymphadenectomy for advanced gastric cancer. Gastric Cancer 1999;2:230–234. doi:10.1007/s101200050069.
11. Ziqiang W, Feng Q, Zhimin C, Miao W, Lian Q, Huaxing L, Peiwu Y. Comparison of laparoscopically assisted and open radical distal gastrectomy with extended lymphadenectomy for gastric cancer management. Surg Endosc 2006;20:1738–1743. doi:10.1007/s00464-006-0031-6.
12. Kim MC, Kim HH, Jung GJ. Surgical outcome of laparoscopy-assisted gastrectomy with extraperigastric lymph node dissection for gastric cancer. Eur J Surg Oncol 2005;31:401–405. doi:10.1016/j.ejso.2004.11.007.

13. Nakajima T. Gastric cancer treatment guidelines in Japan. Gastric Cancer 2002;5:1–5. doi:10.1007/s101200200000.
14. Hartgrink HH, van de Velde CJ, Putter H, Bonenkamp JJ, Klein Kranenbarg E, Songun I, Welvaart K, van Krieken JH, Meijer S, Plukker JT, van Elk PJ, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H, Sasako M. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. J Clin Oncol 2004;22:2069–2077. doi:10.1200/JCO.2004.08.026.
15. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT, van Elk P, Obertop H, Gouma DJ, Taat CW. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet 1995;345:745–748. doi:10.1016/S0140-6736(95)90637-1.
16. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, Cook P. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial.The Surgical Cooperative Group. Lancet 1996;347:995–999. doi:10.1016/S0140-6736(96)90144-0.
17. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, Sydes M, Fayers P. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer 1999;79:1522–1530. doi:10.1038/sj.bjc. 6690243.
18. Kodera Y, Schwarz RE, Nakao A. Extended lymph node dissection in gastric carcinoma: where do we stand after the Dutch and British randomized trials? J Am Coll Surg 2002;195:855–864. doi:10.1016/S1072-7515(02)01496-5.
19. Maruyama K, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. World J Surg 1987;11:418–425. doi:10.1007/BF01655804.
20. Lee SW, Shinohara H, Matsuki M, Okuda J, Nomura E, Mabuchi H, Nishiguchi K, Takaori K, Narabayashi I, Tanigawa N. Preoperative simulation of vascular anatomy by three-dimensional computed tomography imaging in laparoscopic gastric cancer surgery. J Am Coll Surg 2003;197:927–936. doi:10.1016/j.jamcoll surg.2003.07.021.
21. Hiki N, Fukunaga T, Yamaguchi T, Nunobe S, Tokunaga M, Ohyama S, Seto Y, Yoshiba H, Nohara K, Inoue H, Muto T. The benefits of standardizing the operative procedure for the assistant in laparoscopy-assisted gastrectomy for gastric cancer. Langenbecks Arch Surg 2008;393:963–971. doi:10.1007/s00423-008-0374-7.
22. Japanese Gastric Cancer A. Japanese Classification of Gastric Carcinoma—2nd English Edition. Gastric Cancer 1998;1:10–24.
23. Huscher CG, Mingoli A, Sgarzini G, Brachini G, Binda B, Di Paola M, Ponzano C. Totally laparoscopic total and subtotal gastrectomy with extended lymph node dissection for early and advanced gastric cancer: early and long-term results of a 100-patient series. Am J Surg 2007;194:839–844. doi:10.1016/j.amjsurg.2007.08.037, discussion 844.
24. Azagra JS, Ibanez-Aguirre JF, Goergen M, Ceuterick M, Bordas-Rivas JM, Almendral-Lopez ML, Moreno-Elola A, Takieddine M, Guerin E. Long-term results of laparoscopic extended surgery in advanced gastric cancer: a series of 101 patients. Hepatogastroenterology 2006;53:304–308.
25. Lee SI, Choi YS, Park DJ, Kim HH, Yang HK, Kim MC. Comparative study of laparoscopy-assisted distal gastrectomy and open distal gastrectomy. J Am Coll Surg 2006;202:874–880. doi:10.1016/j.jamcollsurg.2006.02.028.
26. Fujiwara M, Kodera Y, Miura S, Kanyama Y, Yokoyama H, Ohashi N, Hibi K, Ito K, Akiyama S, Nakao A. Laparoscopy-assisted distal gastrectomy with systemic lymph node dissection: a phase II study following the learning curve. J Surg Oncol 2005;91:26–32. doi:10.1002/jso.20166.

J Gastrointest Surg (2009) 13:1064–1070
DOI 10.1007/s11605-009-0837-3

ORIGINAL ARTICLE

The Effect of Obesity on the Outcome of Laparoscopic Antireflux Surgery

Jacob A. Chisholm · Glyn G. Jamieson · Carolyn J. Lally · Peter G. Devitt · Philip A. Game · David I. Watson

Received: 9 November 2008 / Accepted: 18 February 2009 / Published online: 4 March 2009

Abstract
Background Obesity has long been considered to be a predisposing factor for gastroesophageal reflux. It is also thought to predispose patients to a poorer clinical outcome following antireflux surgery. This study examined the effect of body mass index (BMI) on clinical outcomes following laparoscopic antireflux surgery.
Methods Patients were included if they had undergone a laparoscopic fundoplication, their presurgical BMI was known, and they had been followed for at least 12 months after surgery. The clinical outcome was determined using a structured questionnaire, and this was applied yearly after surgery. Patients were divided into four groups according to BMI: normal weight (BMI<25), overweight (BMI 25–29.9), obese (BMI 30–34.9), and morbidly obese (BMI≥35). The most recent clinical outcome data was analyzed for each BMI group.
Results Patients, 481, were studied. One hundred three (21%) had a normal BMI, 208 (43%) were overweight, 115 (24%) were obese, and 55 (12%) were morbidly obese. Mean follow-up was 7.5 years. Conversion to an open operation and requirement for revision surgery were not influenced by preoperative weight. Operating time was longer in obese patients (mean 86 vs 75 min). Clinical outcomes improved following surgery regardless of BMI.
Conclusions Preoperative BMI does not influence the clinical outcome following laparoscopic antireflux surgery. Obesity is not a contraindication for laparoscopic fundoplication.

Keywords Laparoscopic fundoplication · Obesity · Gastro-esophageal reflux

Financial disclosure: None of the authors have a financial interest in the outcome of this study. The study was not sponsored by a commercial entity.

J. A. Chisholm · C. J. Lally · D. I. Watson (✉)
Department of Surgery, Flinders Medical Centre,
Flinders University,
Room 3D211,
Bedford Park, South Australia 5042, Australia
e-mail: david.watson@flinders.edu.au

G. G. Jamieson · C. J. Lally · P. G. Devitt · P. A. Game
Discipline of Surgery, University of Adelaide,
Adelaide, South Australia, Australia

Introduction

Obesity has long been known to be a risk factor for the development of gastroesophageal reflux disease (GORD). It is also thought to be associated with an increased risk of a poorer clinical outcome following antireflux surgery, specifically due to recurrent reflux or paraoesophageal hiatus herniation.

A number of studies have investigated the relationship between obesity and outcome following laparoscopic fundoplication procedures,[1–5] although the data from these studies have been confusing, with some studies suggesting that obesity is associated with a poorer outcome,[1,2] whereas others have not replicated these findings.[3–5] Unfortunately, only one of these studies[4] included a sufficient number of morbidly obese patients to enable the influence of obesity on outcome to be determined with certainty, and no study assessed the influence of obesity on longer-term outcomes.

There now seems to be an increasing trend to use anti-obesity operations as treatment for reflux in the obese. This

Table 1 Correlation Between BMI and Outcome

BMI versus	*r* Value	*p* Value
Age	0.04	0.428
Operation time	0.10	0.032
Satisfaction	0.02	0.712
Heartburn	−0.001	0.982
Liquid dysphagia	0.03	0.564
Solid dysphagia	0.02	0.658

is partly because it is suggested that anti-obesity operations are an effective antireflux procedure and partly because of some of the reports which claimed that the outcome of antireflux surgery is worse in the obese. Against this background, we sought to evaluate a larger cohort of patients who had undergone longer-term follow-up following laparoscopic antireflux surgery to better determine whether or not obesity is linked to outcome following laparoscopic fundoplication for gastro-esophageal reflux.

Methods

Since October 1991, all patients who underwent a laparoscopic fundoplication by surgeons in the Departments of Surgery at the University of Adelaide and Flinders University of South Australia have had perioperative and follow-up data entered prospectively into a computerized database (Filemaker Pro version 9.3; Filemaker, Santa Clara, CA, USA). These patients were then followed prospectively following surgery, and a structured clinical questionnaire was used each year to evaluate their outcome. For this study, we identified patients from the database who met the following criteria: minimum 12 months follow-up data available, and preoperative height and weight data available for calculation of body mass index (BMI).

All patients underwent preoperative investigation with esophageal manometry and endoscopy. 24-h pH monitoring was performed for patients who did not have typical symptoms of gastroesophageal reflux and ulcerative esophagitis demonstrated by endoscopy. In general, patients were selected for either partial or full fundoplication within the context of one of three prospective randomized trials.[6–8] A smaller subset underwent partial fundoplication because of either patient or surgeon preference, the latter usually because of poor esophageal body motility.

Our technique for laparoscopic Nissen fundoplication has been previously described.[9] A loose 1.5- to 2-cm wrap was constructed with a 52F intra-esophageal bougie in situ. The anterior wall of the gastric fundus was used to construct the fundoplication, and the short gastric vessels were not divided in the majority of cases. The technique for laparoscopic anterior 180° fundoplication has also been described in detail elsewhere.[10] It involved hiatal dissection and repair, suturing of the anterior wall of the gastric fundus, and the right lateral wall of the distal esophagus to the right hiatal pillar and the apex of the esophageal hiatus.

The database used to collect information, included the following details: age at the time of operation, operating time, postoperative complications, type of fundoplication performed, conversion from laparoscopic to an open procedure, and the timing and reasons for any revisional surgery. Follow-up data was collected at yearly intervals following surgery using a structured questionnaire. The questionnaire used visual analogue scales to assess heartburn (0=no symptoms, 10=severe symptoms), dysphagia to liquids, dysphagia to solids, and overall satisfaction (0=very unsatisfied, 10=highly satisfied) following surgery. The questionnaire also included a series of yes/no questions which enquired about the patient's ability to belch, the presence of abdominal bloating symptoms, the ability to relieve bloating by belching, and the patient's assessment as to whether he or she thought the correct decision had been made to undergo surgery. For this study, the most recent follow-up data was extracted and analyzed.

Patients were divided into BMI groups according to the WHO classification: normal weight (BMI<25), overweight (BMI 25–29.9), obese (BMI 30–34.9), and morbidly obese

Table 2 Comparison of Outcomes Across BMI Groups

	BMI classification				
	Normal weight (*n*=103)	Overweight (*n*=208)	Obese (*n*=115)	Morbidly obese (*n*=55)	*P* value
Age	50 (47, 53)	50 (47, 51)	51 (48, 53)	52 (48, 56)	0.753
Operation time (min)	75 (68, 81)	83 (77, 89)	86 (78, 93)	87 (75, 99)	0.155
Satisfaction score	7.9 (7.4, 8.5)	8.4 (8.0, 8.7)	8.2 (7.7, 8.7)	8.1 (7.4, 8.8)	0.558
Heartburn score	1.6 (1.1, 2.1)	1.3 (1.0, 1.6)	1.6 (1.2, 2.1)	1.4 (0.7, 2.0)	0.579
Liquid dysphagia score	1.1 (0.6, 1.5)	1.2 (0.9, 1.5)	1.2 (0.8, 1.6)	1.2 (0.6, 1.8)	0.794
Solid dysphagia score	2.1 (1.6, 2.6)	2.0 (1.7, 2.4)	2.1 (1.7, 2.6)	2.6 (1.7, 3.4)	0.874

All figures represented as mean (95% confidence intervals). Statistical testing using ANOVA

Table 3 Yes/No Outcomes Versus BMI

	Normal weight	Overweight	Obese	Morbidly obese	*P* (chi)
"Made correct decision to have operation"	80 (79%)	183 (88%)	102 (90%)	47 (85%)	0.083
Abdominal bloating	54 (55%)	114 (58%)	68 (65%)	31 (60%)	0.516
Able to relieve bloating	51 (50%)	117 (59%)	71 (64%)	36 (65%)	0.139
Able to belch	73 (74%)	145 (70%)	78 (74%)	42 (76%)	0.734

(BMI 35 or greater), and the outcome determined for each category of BMI. Statistical analysis was performed using commercially available statistical software (GraphPad InStat, version 3.06 for Windows Vista, GraphPad Software, San Diego California USA, www.graphpad.com). Spearman rank correlation, ANOVA, and chi-squared tests were used to determine the significance of any differences between the study groups. Statistical significance was determined if *P* values were less than 0.05. Data collection was approved by the Royal Adelaide Hospital Clinical Research Ethics Committee, and the Flinders Clinical Research Ethics Committee.

Results

Details for 1,925 patients were entered into the database between October 1991 and February 2008. Patients, 481, met the inclusion criteria for this study. Of these, 278 (58%) were men, and 203 (42%) were women. Mean age at the time of surgery was 50.3 years (range 16–91). Mean follow-up was 7.5 years (range 1–15 years). There were 103 (21%) patients with a normal BMI, 208 (43%) were overweight, 115 (24%) were obese, and 55 (12%) were morbidly obese. Mean follow-up was 8.0 years (range 1–15 years) in patients with a normal BMI, 7.6 years (range 1–15 years) in the overweight group, 6.6 years (range 1–15 years) in the obese, and 5.9 years (range 1–15 years) in the morbidly obese. Three hundred twenty-two (67%) underwent a laparoscopic Nissen fundoplication, and 148 (31%) underwent a laparoscopic anterior partial fundoplication. Another 11 patients (2%) underwent a 270° posterior fundoplication. All surgeons undertaking antireflux surgery were equally likely to undertake either a Nissen or partial fundoplication, and they were equally likely to operate on obese patients. The choice of fundoplication type was not influenced by BMI.

Conversion to an open surgical operation and the requirement for revisional surgery were not influenced by preoperative weight. Eighteen (4%) patients underwent conversion from a laparoscopic to an open procedure. Three of these were of normal weight, seven were overweight, six were obese, and two were morbidly obese. Forty-eight (10%) patients underwent revisional surgery during follow-up. Thirteen of these patients had a normal weight, 17 were overweight, nine were obese, and nine were morbidly obese. Eighteen of these operations were for troublesome dysphagia following hiatal narrowing,[11] 11 were for paraoesophageal hiatus herniation,[12] and 14 were revised to treat recurrent reflux. A bleeding short gastric blood vessel (one case), wound dehiscence (one case), gastric perforation secondary to carbonated drinks (one case),[13] troublesome bloating (one case), and perforation of the esophagus (one case) accounted for the remaining revisions.

Table 1 summarizes correlations between BMI and visual analogue scale outcomes for heartburn, dysphagia, and overall satisfaction, as well as age at operation and operation time. A statistically significant, but clinically weak (r=0.10) correlation was demonstrated between increasing BMI and the length of the operation. There were no significant associations between BMI and the other outcomes measured.

When patients were divided into the different BMI groups (Table 2), longer operating times were found as weight increased (not statistically significant). No association was demonstrated between satisfaction, heartburn, liquid dysphagia, solid dysphagia, and BMI when analyzed by BMI groups. Overall, patients with a higher BMI had a similar clinical outcome to other patients. The responses to the yes/no questions are summarized in Table 3. There were no significant differences between the four BMI groups for these questions.

Table 4 summarizes further analysis of "failure" for the four clinical outcome scores analyzed in this study. A poor outcome was arbitrarily determined to be a satisfaction score of 0 to 6 and a heartburn, liquid dysphagia, or solid dysphagia

Table 4 "Symptomatic Failure" vs BMI

	Normal weight	Overweight	Obese	Morbidly obese	*P* (Chi)
Satisfaction score=0–6	21 (21%)	31 (15%)	16 (14%)	11 (20%)	0.448
Heartburn score=4–10	18 (18%)	29 (14%)	21 (18%)	6 (11%)	0.523
Liquid dysphagia score=4–10	15 (15%)	31 (15%)	19 (17%)	9 (17%)	0.960
Solid dysphagia score=4–10	24 (23%)	54 (26%)	33 (29%)	20 (37%)	0.295

Table 5 Comparison of Outcome Across BMI Groups in Patients who Underwent an Anterior Partial Fundoplication

	BMI classification			
	Normal weight (n=32)	Overweight (n=65)	Obese/morbidly obese (n=51)	p Value
Age (years)	56 (50, 62)	53 (50, 57)	56 (52, 60)	P=0.674
Operation time (min)	82 (71, 93)	80 (69, 92)	90 (78, 101)	P=0.083
Satisfaction score	9.0 (8.3, 9.6)	8.0 (7.3, 8.7)	7.5 (6.6, 8.4)	P=0.103
Heartburn score	2.1 (1.2, 3.0)	1.8 (1.2, 2.5)	2.1 (1.3, 2.9)	P=0.601
Liquid dysphagia score	0.2 (−0.1, 0.5)	0.4 (0.1, 0.7)	1.1 (0.5, 1.7)	P=0.024*
Solid dysphagia score	1.2 (0.5, 1.9)	1.4 (0.9, 1.9)	1.8 (1.1, 2.6)	P=0.743

All figures represented as mean (95% confidence intervals). Statistical testing using ANOVA

*Dunn's multiple comparisons post-test: $P<0.05$ for normal weight vs obese; $P>0.05$ for all other comparisons

score of 4 to 10. For each of these parameters, there were no significant differences between the four BMI groups.

The clinical outcomes for patients who underwent an anterior partial fundoplication vs a Nissen fundoplication were determined separately (Tables 5, 6, 7, 8). For this analysis, only three BMI groups were used, with the obese and the morbidly obese groups combined to ensure a sufficient sample size in each group. In the normal weight group, 32 patients underwent an anterior partial fundoplication, and 70 a Nissen fundoplication; in the overweight group, 65 underwent an anterior fundoplication, and 139 a Nissen fundoplication; and in the obese/morbidly obese group, 51 underwent an anterior fundoplication, and 113 a Nissen fundoplication. There was a significantly higher liquid dysphagia score in obese patients who underwent an anterior partial fundoplication, compared to normal weight patients (Table 4). The outcomes for patients who underwent a Nissen fundoplication were similar across all weight ranges (Table 6).

Answers to the yes/no questions in the patients who underwent an anterior partial fundoplication were similar in all weight groups (Table 7). Answers to the yes/no questions in the patients who underwent a Nissen fundoplication demonstrated a significantly better overall satisfaction in obese patients, compared to normal weight patients (Table 8).

Clinical outcomes were assessed according to sex (Tables 9, 10, 11, 12). For this analysis, again only three BMI groups were used, combining obese and morbidly obese to ensure an adequate sample size. In the normal weight group, there were 53 males and 50 females; in the overweight group 142 were males, and 66 were females; and in the obese/morbidly obese group, there were 83 males and 87 females. The outcomes for male patients were similar across all weight ranges (Table 9). The outcomes for female patients were also similar across all weight ranges (Table 10). Answers to the yes/no questions in male patients were similar in all weight groups (Table 11). In the female patients, significantly better overall satisfaction was demonstrated in the obese patients compared with normal weight patients (Table 12).

Discussion

Subjectively, as surgeons, we know that operating on the obese patient is more difficult. Intuitively, we might expect

Table 6 Comparison of Outcomes Across BMI Groups for Nissen Fundoplications

	BMI classification			
	Normal weight (n=70)	Overweight (n=139)	Obese/morbidly obese (n=113)	p Value
Age (years)	48 (45, 52)	47 (45, 50)	49 (47, 52)	0.497
Operation time (min)	71 (63, 80)	84 (77, 91)	83 (75, 91)	0.045*
Satisfaction score	7.4 (6.7, 8.2)	8.4 (8.0, 8.8)	8.3 (7.8. 8.8)	0.083
Heartburn score	1.3 (0.7, 1.9)	1.1 (0.7, 1.4)	1.3 (0.8, 1.7)	0.802
Liquid dysphagia score	1.3 (0.8, 1.8)	1.6 (1.2, 2.0)	1.2 (0.8, 1.6)	0.283
Solid dysphagia score	2.4 (1.7, 3.0)	2.3 (1.9, 2.8)	2.5 (2.0, 3.1)	0.832

All figures represented as mean (95% confidence intervals). Statistical testing using ANOVA.

*Dunn's multiple comparisons post-test: $P>0.05$ for all comparisons

Table 7 Yes/No Outcomes versus BMI in Patient who Underwent an Anterior Partial Fundoplication

	Normal weight	Overweight	Obese/morbidly obese	*P* (chi)
"Made correct decision to have operation"	28 (90%)	59 (91%)	43 (86%)	0.696
Abdominal bloating	16 (55%)	28 (47%)	25 (58%)	0.540
Able to relieve bloating	23 (77%)	38 (69%)	35 (78%)	0.569
Able to belch	23 (79%)	51 (86%)	40 (91%)	0.368

Table 8 Yes/No Outcomes versus BMI in Patients who Underwent a Nissen Fundoplication

	Normal weight	Overweight	Obese/morbidly obese	*P* (chi)
"Made correct decision to have operation"	51 (73%)	122 (88%)	100 (89%)	0.005
Abdominal bloating	38 (55%)	86 (64%)	74 (67%)	0.253
Able to relieve bloating	48 (74%)	81 (61%)	60 (56%)	0.054
Able to belch	49 (71%)	89 (66%)	77 (70%)	0.747

Table 9 Comparison of Outcomes Across BMI Groups in Male Patients

	BMI classification			
	Normal weight (n=53)	Overweight (n 142)	Obese/morbidly obese (n=83)	p Value
Age (years)	46 (43, 50)	47 (44, 49)	46 (43, 49)	P=0.912
Operation time (min)	73 (64, 82)	84 (77, 92)	87 (77, 96)	P=0.169
Satisfaction score	8.0 (7.2, 8.8)	8.4 (8.0, 8.8)	8.3 (7.7, 8.9)	P=0.502
Heartburn score	1.3 (0.6, 2.0)	1.2 (0.8, 1.5)	0.8 (0.5, 1.2)	P=0.781
Liquid dysphagia score	1.0 (0.4, 1.6)	1.1 (0.8, 1.4)	0.6 (0.3, 1.0)	P=0.208
Solid dysphagia score	1.8 (1.1, 2.6)	1.9 (1.5, 2.3)	1.8 (1.3, 2.4)	P=0.768

Table 10 Comparison of Outcomes Across BMI Groups in Female Patients

	BMI classification			
	Normal weight (n=50)	Overweight (n=66)	Obese/morbidly obese (n=87)	p Value
Age (years)	55 (51, 60)	56 (53, 59)	56 (53, 59)	P=0.976
Operation time (min)	76 (66, 86)	81 (71, 90)	86 (77, 95)	P=0.406
Satisfaction score	7.8 (6.9, 8.6)	8.2 (7.6, 8.9)	7.8 (7.2, 8.4)	P=0.553
Heartburn score	1.9 (1.2, 2.7)	1.6 (1.0, 2.2)	2.2 (1.6, 2.9)	P=0.358
Liquid dysphagia score	1.2 (0.5, 1.9)	1.4 (0.9, 2.0)	1.7 (1.2, 2.3)	P=0.217
Solid dysphagia score	2.4 (1.6, 3.1)	2.2 (1.5, 2.9)	2.8 (2.2, 3.4)	P=0.443

Table 11 Yes/No Outcomes Versus BMI in Male Patients

	Normal weight	Overweight	Obese/morbidly obese	*P* (chi)
"Made correct decision to have operation"	44 (83%)	128 (91%)	71 (87%)	0.295
Abdominal bloating	29 (56%)	76 (58%)	48 (62%)	0.743
Able to relieve bloating	37 (73%)	85 (64%)	51 (65%)	0.536
Able to belch	39 (75%)	91 (69%)	56 (72%)	0.751

that the clinical outcomes following laparoscopic antireflux surgery would be worse in obese patients. Furthermore, increased intra-abdominal pressure secondary to obesity is thought to promote complications such as postoperative hiatal herniation. The increased difficulty in performing such surgery in obese patients is confirmed by the significantly longer operating times that our study has demonstrated. Despite this, other measures of clinical outcome were not affected, and conversion to an open procedure and the need for revisional surgery were also unaffected by BMI.

Previous studies that have looked at this issue have revealed conflicting results. In general, most of these studies have also been hampered by relatively small cohorts of obese and morbidly obese patients, and shorter follow-up than in our current study. In a retrospective study of 224 patients, Perez et al.[1] found a correlation between recurrent reflux and BMI, independent of the type of fundoplication performed. In that study, 31% of patients who were obese (BMI>30) developed recurrent reflux, compared with 4.5% of patients in the normal weight range (BMI<25).

In support of this conclusion, Morgenthal et al.[2] determined the outcome following laparoscopic fundoplication for 174 patients and also showed that morbidly obese patients (BMI≥35) were more likely to have a poor outcome after surgery. In their study, failure was defined as the need for any revisional operation, dissatisfaction with the outcome, or the reporting of any severe symptoms at follow-up. Unfortunately, only 90 of the 174 patients had sufficient information available to allow the preoperative BMI to be calculated, and only seven (8%) were classified as morbidly obese, of which three (43%) were considered failures. Based on these results, these authors now no longer offer a laparoscopic Nissen fundoplication to morbidly obese patients. Such patients are encouraged to lose weight, and the option of bariatric surgery is discussed.

In contrast, several studies have demonstrated that antireflux surgery can be successfully performed in obese patients. D'Alessio et al.[3] prospectively assessed 257 patients who underwent laparoscopic Nissen fundoplication for gastro-esophageal reflux. Similar complication rates were reported for all BMI categories. The number of patients who achieved good or excellent clinical outcomes was similar across all BMI groups. However, this study had a mean follow-up of 25.5 months, and only three patients were morbidly obese (BMI≥35). In the only study to evaluate a large patient cohort, Winslow et al.[4] evaluated 505 patients, of which 76 were morbidly obese (BMI≥35). Mean follow-up was 35 months. The study found that symptom relief and complication rates were similar across all BMI categories. In 2001, we also reported the effect of BMI on outcome following laparoscopic fundoplication in a cohort of 194 patients.[5] Fifty-two of these patients were obese (BMI 30–34), and 14 were morbidly obese (BMI≥ 35). In this report, we also found no differences in outcome for obese vs non-obese patients undergoing laparoscopic antireflux surgery, at mean 3.2 years follow-up.

Strengths of our current study are the inclusion of a large number (170) of obese or morbidly obese patients, and a long length of follow-up (mean 7.5 years), although we were not able to include an objective measure of reflux control such as pH monitoring or endoscopy in this study. However, our previous studies have shown a good correlation between the clinical outcome measures which we also used in this study and pH monitoring and endoscopy-based assessment.[7,8] Furthermore, from the patient's perspective, their satisfaction with the outcome of surgery is arguably a better measure of clinical success than data from pH monitoring, as this does not always correlate with symptoms of GORD.[14] For these reasons, the standardized clinical scoring system we used is likely to

Table 12 Yes/No Outcomes Versus BMI in Female Patients

	Normal weight	Overweight	Obese/morbidly obese	*P* (chi)
"Made correct decision to have operation"	34 (72%)	56 (85%)	76 (89%)	0.04
Abdominal bloating	25 (53%)	38 (58%)	51 (65%)	0.440
Able to relieve bloating	33 (75%)	36 (61%)	49 (60%)	0.226
Able to belch	34 (72%)	52 (80%)	63 (80%)	0.557

have adequately assessed the clinical outcome, and other studies have shown that reflux symptoms are reliable and valid measures for assessing reflux symptom severity and responses to treatment.[15] A potential weakness of our study is that only 481 out of 1,925 patients entered into our database had sufficient preoperative information available to enable their BMI to be calculated. This was because height was only determined systematically for patients enrolled in a randomized controlled trial (REF). Hence, selection bias is unlikely to have influenced the outcomes reported in this study.

Our study concentrated on symptom control following surgery for reflux. It did not address the issue of weight loss as a treatment for reflux or the option of weight reduction surgery in obese patients with symptomatic reflux. Our data supports the contention that if obese patients request treatment for gastro-esophageal reflux, they can be offered a laparoscopic fundoplication, and the outcome is likely to be similar to that of patients who are in the normal weight range at the time of surgery. However, if such a patient also requests surgical management for their obesity, then Roux-en-Y gastric bypass procedure could be the procedure of choice. Bypass provides excellent long-term control of reflux symptoms, with the additional benefit of weight loss.[16] On the other hand, laparoscopic adjustable gastric banding has also been proposed as a means of reflux control in obese patients.[17,18] However, the results of such surgery appear to be less reliable. Klaus et al.[19] has reported the outcome for 164 patients with reflux symptoms who were managed by a laparoscopic gastric banding procedure. At mean 33 months follow-up, 52 (31.7%) of their patients had persistent or aggravated reflux symptoms, a result which is certainly inferior to that achieved by fundoplication.

In conclusion, we have demonstrated that BMI does not influence the clinical outcome following laparoscopic antireflux surgery. If a patient presents complaining only of reflux symptoms, such surgery can be offered, and a high success rate should be anticipated.

Acknowledgement The authors are grateful for the assistance of Ms Lorraine Sheehan-Hennessy, Ms Marian Martin, Ms Tanya Irvine, Ms Nicola Ascott, and Ms Janet Pinno for their assistance with data collection and management.

References

1. Perez AR, Moncure AC, Rattner DW. Obesity adversely affects the outcome of antireflux operations. Surg Endosc 2001;15:986–989. doi:10.1007/s004640000392.
2. Morgenthal CB, Lin E, Shane MD, Hunter JG, Daniel Smith C. Who will fail laparoscopic Nissen fundoplication? Preoperative prediction of long-term outcomes. Surg Endosc 2007;21:1978–1984. doi:10.1007/s00464-007-9490-7.
3. D'Alessio MJ, Arnaoutakis D, Giarelli N, Villadolid DV, Rosemurgy AS. Obesity is not a contraindication to laparoscopic Nissen fundoplication. J Gastrointest Surg 2005;9:949–954. doi:10.1016/j.gassur.2005.04.019.
4. Winslow ER, Frisella MM, Soper NJ, Klingensmith ME. Obesity does not adversely affect the outcome of laparoscopic antireflux surgery (LARS). Surg Endosc 2003;17:2003–2011. doi:10.1007/s00464-003-8118-9.
5. Fraser J, Watson DI, O'Boyle CJ, Jamieson GG. Obesity and its effect on outcome of laparoscopic Nissen fundoplication. Dis Esophagus 2001;14:50–53. doi:10.1111/j.1442-2050.2001.00157.x.
6. Watson DI, Jamieson GG, Devitt PG, Kennedy JA, Ellis T, Ackroyd R, et al. A prospective randomized trial of laparoscopic Nissen fundoplication with anterior vs posterior hiatal repair. Arch Surg 2001;136:745–751. doi:10.1001/archsurg.136.7.745.
7. Watson DI, Jamieson GG, Pike GK, Davies N, Richardson M, Devitt PG. Prospective randomized double blind trial between laparoscopic Nissen fundoplication and anterior partial fundoplication. Br J Surg 1999;86:123–130. doi:10.1046/j.1365-2168.1999.00969.x.
8. Watson DI, Pike GK, Baigrie RJ, Mathew G, Devitt PG, Britten-Jones R, et al. Prospective double blind randomized trial of laparoscopic Nissen fundoplication with division and without division of short gastric vessels. Ann Surg 1997;226:642–652. doi:10.1097/00000658-199711000-00009.
9. Jamieson GG, Watson DI, Britten-Jones R, Mitchell PC, Anvari M. Laparoscopic Nissen fundoplication. Ann Surg 1994;220:137–145. doi:10.1097/00000658-199408000-00004.
10. Watson DI, Liu JF, Devitt PG, Game PA, Jamieson GG. Outcome of laparoscopic anterior 180-degree partial fundoplication for gastroesophageal reflux disease. J Gastrointest Surg 2000;4:486–492. doi:10.1016/S1091-255X(00)80091-8.
11. Watson DI, Jamieson GG, Mitchell PC, Devitt PG, Britten-Jones R. Stenosis of the esophageal hiatus following laparoscopic fundoplication. Arch Surg 1995;130:1014–1016.
12. Watson DI, Jamieson GG, Devitt PG, Mitchell PC, Game PA. Paraoesophageal hiatus hernia: an important complication of laparoscopic Nissen fundoplication. Br J Surg 1995;82:521–523. doi:10.1002/bjs.1800820428.
13. Ackroyd R, Watson DI, Game PA. Fizzy drinks following laparoscopic Nissen fundoplication: a cautionary tale of explosive consequences. ANZ J Surg 1999;69:887–888. doi:10.1046/j.1440-1622.1999.01729.x.
14. Johnsson F, Joelsson B, Gudmundsson K, Greiff L. Symptoms and endoscopic findings in the diagnosis of gastroesophageal reflux disease. Scand J Gastroenterol 1987;22:714–718. doi:10.3109/00365528709011148.
15. Revicki DA, Wood M, Wiklund I, Crawley J. Reliability and validity of the gastrointestinal symptom rating scale in patients with gastroesophageal reflux disease. Qual Life Res 1997;7:75–83. doi:10.1023/A:1008841022998.
16. Nelson LG, Gonzalez R, Haines K, Gallagher SF, Murr MM. Amelioration of gastroesophageal reflux symptoms following Roux-en-Y gastric bypass for clinically significant obesity. Am Surg 2005;71:950–954.
17. Dixon JB, O'Brien PE. Gastroesophageal reflux in obesity: the effect of Lap-Band placement. Obes Surg 1999;9:527–531. doi:10.1381/096089299765552602.
18. Iovino P, Angrisani L, Tremolaterra F, Nirchio E, Ciannella M, Borrelli V, et al. Abnormal esophageal acid exposure is common in morbidly obese patients and improves after a successful Lap-Band system implantation. Surg Endosc 2002;16:1631–1635. doi:10.1007/s00464-001-90225–0.
19. Klaus A, Gruber I, Wetscher G, Nehoda H, Aigner F, Peer R, et al. Prevalent esophageal body motility disorders underlie aggravation of GERD symptoms in morbidly obese patients following adjustable gastric banding. Arch Surg 2006;141:247–251. doi:10.1001/archsurg.141.3.247.

J Gastrointest Surg (2009) 13:1071–1077
DOI 10.1007/s11605-009-0858-y

ORIGINAL ARTICLE

Accurate Preoperative Localization of Insulinomas Avoids the Need for Blind Resection and Reoperation: Analysis of a Single Institution Experience with 17 Surgically Treated Tumors over 19 Years

Brian K. P. Goh · London L. P. J. Ooi · Peng-Chung Cheow · Yu-Meng Tan · Hock-Soo Ong · Yaw-Fui A. Chung · Pierce K. H. Chow · Wai-Keong Wong · Khee-Chee Soo

Received: 2 February 2009 / Accepted: 26 February 2009 / Published online: 17 March 2009

Abstract

Introduction Presently, the need for and choice of preoperative localization tests for insulinomas remain controversial. We report the results from a single institution experience whereby the management policy adopted was that of accurate preoperative localization before surgical exploration.

Materials and Methods From 1990 to 2008, 17 patients with a clinical and biochemical diagnosis of an insulinoma who underwent surgery were retrospectively reviewed. The diagnosis of all insulinomas were confirmed pathologically.

Results All tumors were localized preoperatively and an average of 2.2 preoperative localization studies including 1.4 noninvasive studies and 0.8 invasive studies were utilized per patient. Invasive localization modalities were more sensitive (92%) than noninvasive modalities in localizing insulinomas (71%). Intra-arterial calcium stimulation with hepatic venous sampling was the most sensitive invasive modality (100%), whereas magnetic resonance imaging was the most sensitive noninvasive modality (63%). Fifteen of 17 tumors (88%) were localized intraoperatively via inspection/palpation and/or intraoperative ultrasonography. Both insulinomas which were not localized intraoperatively were localized correctly to the distal pancreas via preoperative transhepatic portal venous sampling. None of the patients required a blind resection or surgical reexploration for failed localization. All 17 patients underwent complete surgical resection which included eight enucleations and nine distal pancreatectomies with a cure rate of 94% (16/17) at a median follow-up of 35 (range, 1–217) months. The postoperative morbidity and long-term outcome of enucleation was similar to distal pancreatectomy despite a higher rate of microscopic margin involvement.

Conclusion Accurate preoperative localization of insulinomas is useful as it eliminates the need for blind distal pancreatectomy and avoids reoperation. Complete surgical resection is the treatment of choice, and whenever possible, a pancreas-sparing approach such as enucleation should be adopted.

B. K. P. Goh (✉) · L. L. P. J. Ooi · P.-C. Cheow · Y.-M. Tan · H.-S. Ong · Y.-F. A. Chung · P. K. H. Chow · W.-K. Wong · K.-C. Soo
Department of Surgery, Singapore General Hospital,
Outram Road,
Singapore 169608, Singapore
e-mail: bsgkp@hotmail.com

L. L. P. J. Ooi · P.-C. Cheow · Y.-M. Tan · H.-S. Ong · Y.-F. A. Chung · P. K. H. Chow · W.-K. Wong · K.-C. Soo
Department of Surgical Oncology, National Cancer Centre,
11 Hospital Drive,
Singapore 169610, Singapore

L. L. P. J. Ooi · P. K. H. Chow · K.-C. Soo
Duke-NUS Graduate Medical School,
Singapore, Singapore

Keywords Insulinoma · Localization · Resection · Pancreas · Treatment

Introduction

Insulinomas are by far the most common functioning pancreatic endocrine neoplasms. However, these are rare tumors with a reported incidence of four cases per million person-years in the USA[1] and 0.8–0.9 cases per million person-years in China.[2] Insulinomas are almost always intrapancreatic,[3] and these usually present as solitary, small (<2 cm), and benign neoplasms.[4]

Presently, the need for and choice of preoperative localization tests for insulinomas remain controversial.[4] In the past, the diagnosis of Whipple triad usually meant that a patient was led directly to surgery.[4] However, at present, most surgeons prefer that some form of preoperative localization after a diagnosis of an insulinoma is established before a patient is brought to the operating room. Numerous preoperative localization modalities are currently available to the surgeon and these range from noninvasive imaging such as abdominal ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) to invasive modalities such as angiogram, transhepatic portal venous sampling (THPVS), intra-arterial calcium stimulation with hepatic venous sampling (ASVS), and endoscopic ultrasonography (EUS). Despite this wide array of localization modalities available, some investigators still prefer to minimize the number of preoperative investigations, as surgical exploration with palpation and intraoperative ultrasonography (IOUS) by experienced surgeons has consistently been shown to have an impressive overall sensitivity of 95% to 100%.[4,5]

In this study, we report the experience of a single institution with these rare tumors whereby the management policy adopted was that of accurate preoperative localization before surgical exploration. Particular attention was paid to the use of preoperative localization studies and outcome after surgical treatment of insulinomas.

Materials and Methods

A retrospective review of all patients who underwent surgery for an insulinoma at the Department of Surgery, Singapore General Hospital between 1990 and 2008 was conducted. The Singapore General Hospital is the largest tertiary level and public hospital in Singapore with approximately 1,500 beds, and it has performed more than 500 major pancreatic resections over the past 10 years.

All patients presented with typical symptoms of hypoglycaemia after fasting or exertion which resolved with glucose ingestion. The diagnosis was confirmed biochemically via a 72-h fasting glucose test and/or low blood glucose with corresponding high insulin and C peptide levels. All diagnosis of insulinomas were confirmed histologically.

At our institution, every effort was made to localize insulinomas preoperatively via noninvasive and/or invasive modalities. In some instances, confirmatory invasive localization tests were used even when noninvasive tests were positive. Differences in preoperative localization tests were compared between two time periods: 1990–1998 and 1999–2008. During the first time period, the invasive preoperative localization modality adopted at our institution was THPVS, whereas since 1999, intra-arterial calcium stimulation with hepatic venous sampling ASVS had replaced THPVS. The International Study Group on Pancreatic Fistula (ISGPF) definition of a pancreatic fistula was adopted in this study.[6]

All statistical analyses were conducted using the computer program Statistical Package for Social Sciences for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). Results were presented as median (range). Statistical analyses were performed using Mann–Whitney *U* and chi-squared tests as appropriate. Survival curves for relapse-free survival were calculated using the Kaplan–Meier method. All times were computed from the time of surgery and the endpoint was time to first recurrence or death. Data were censored at the time of last follow-up. All tests were two-sided and a *P* value of less than 0.05 was considered statistically significant.

Results

Clinicopathological Features

Seventeen patients with a diagnosis of insulinoma were identified during the study period. Their clinicopathological features are summarized in Table 1. Immunohistochemistry demonstrated positive staining to insulin in all patients. All patients had solitary tumors, with the exception of one patient with a known history of multiple endocrine neoplasms type 1 (who was found on histological exam to harbor six endocrine tumors in the tail of pancreas). Another patient had a malignant insulinoma based on the World Health Organization classification system.[7] The tumor was 11 cm in diameter and demonstrated lymph node metastases.

Localization of Insulinomas

All tumors were localized preoperatively in this study and none of the patients underwent blind surgical exploration. Over the study period, various modalities were used to localize insulinomas and these were compared over two time periods (Table 2). An average of 2.2 preoperative localization studies including 1.4 noninvasive studies and 0.8 invasive studies were utilized per patient. Overall, preoperative invasive localization modalities were more sensitive (92%) than noninvasive modalities in localizing insulinomas (71%). There was no difference in the sensitivity between any of the noninvasive or invasive imaging modalities in the localization of insulinomas between the two time periods. In seven patients, despite positive localization via noninvasive tests, confirmatory invasive localization tests were performed.

Table 1 Clinicopathological Features of the 17 Patients with Insulinomas

Parameter	
Median age (years)	50 (27–81)
Sex, M	7 (41%)
Symptom duration (months)	3 (1–36)
Site	
Head	6
Uncinate	1
Body	1
Tail	6
Body/tail	3
Median size (mm)	15 (10–110)
WHO classification	
Benign	12 (71%)
Uncertain	4 (24%)
Malignant	1 (6%)

WHO World Health Organization

ASVS was the most sensitive invasive modality, whereas MRI was the most sensitive noninvasive modality in the preoperative detection of insulinomas. None of the patients experienced significant complications as a result of the use of invasive localization tests. Fifteen of 17 tumors (88%) could be localized intraoperatively via inspection/palpation and/or IOUS. Both insulinomas which could not be localized intraoperatively were localized correctly to the distal pancreas via preoperative THPVS. None of the patients required a blind resection or surgical reexploration for failed localization.

Surgery

All 17 patients underwent complete surgical resection of the tumors. All surgical procedures were performed open and these included eight enucleations and nine distal pancreatectomies. The spleen was preserved with three distal pancreatectomies. Enucleations were performed for six tumors in the head, one in the uncinate, and one in the body/tail. The median operation time was 123 (range, 60–185) min. Seven patients (41%) experienced postoperative complications, including one death (6%). The mortality occurred in a patient who developed postoperative deep vein thrombosis complicated by fatal pulmonary embolism. Overall, there were six pancreatic fistulas (35%) according to the ISGPF definition, of which five were grade A and one was grade C. The median postoperative stay was 9 (range, 4–19) days.

The comparison between the outcomes of enucleation versus distal pancreatectomy is summarized in Table 3. Patients who underwent enucleation were more likely to have tumors in the proximal pancreas and microscopic tumor involvement of the margin. The tumors also tended to be smaller, but this was not statistically significant.

Follow-up

The median follow-up period was 35 (range, 1–217) months, and four patients were lost during the course of follow-up. Sixteen of 17 (94%) patients were cured of disease and were alive and disease-free during the follow-up period. The patient with malignant insulinoma developed recurrence after 31 months and died of disease after 55 months. Overall, the actuarial mean recurrence-free survival was 198 (95% C.I., 164–233) months, and the actuarial mean disease-specific survival was 194 (95% C.I., 152–236) months. The three patients who had a R1 resection after enucleation were alive and disease-free at a median follow-up of 72 (range, 10–132) months.

Table 2 Accuracy of Localization Investigations and Comparison Between Two Time Periods

Modality	Overall (n=17)	1990–98 (n=8)	1999–2008 (n=9)	P value
Preoperative localization				
Noninvasive imaging	12/17 (71%)	5/8 (63%)	7/9 (78%)	
US	0/1	0/1	0	NA
CT	9/16 (56%)	4/8 (50%)	5/8 (63%)	0.614
MRI	5/8 (63%)	1/2 (50%)	4/6 (67%)	0.673
Invasive imaging	12/13 (92%)	7/7 (100%)	5/6 (83%)	.261
EUS	1/1	0	1	NA
Angiography	6/12 (50%)	4/7 (57%)	2/5 (40%)[a]	0.558
THPVS	5/6 (83%)	5/6 (83%)	0	NA
ASVS	5/5 (100%)	0	5/5 (100%)	NA
Intraoperative localization				
Intraoperative	15/17 (88%)	6/8 (75%)	9/9 (100%)	0.110
Inspection and palpation	13/17 (77%)	6/8 (75%)	7/9 (78%)	0.893
IOUS	6/7 (86%)	2/3 (67%)	4/4 (100%)	0.212

US ultrasonography, *CT* computed tomography, *MRI* magnetic resonance imaging, *EUS* endoscopic ultrasound, *THPVS* transhepatic portal venous sampling, *ASVS* intra-arterial calcium stimulation with hepatic venous sampling, *IOUS* intraoperative ultrasonography

[a] Angiography was performed as part of the ASVS

Table 3 Comparison Between Enucleation and Distal Pancreatectomy

	Enucleation (n=8)	Distal pancreatectomy (n=9)	P value
ASA score			0.453
II	6 (75%)	8 (89%)	
III	2 (25%)	1 (11%)	
Site of tumor			<0.001
Proximal	7(88%)	0	
Distal	1 (13%)	9 (100%)	
Median tumor size (mm)	15 (15–30)	12 (10–110)	0.060
Median operation time (min)	150 (60–180)	110 (95–185)	0.524
R1 resection	3 (38%)	0	0.043
Morbidity	2 (25%)	5 (56%)	0.201
Pancreatic fistula	2 (25%)	4 (44%)	0.402
Operative death	1 (12.5%)	0	0.274
Postoperative stay (days)	9 (5–16)	9 (4–19)	0.847
Median follow-up (months)	55 (1–148)	26 (3–217)	0.564
Recurrence	0	1 (11.1%)	0.331
Actuarial mean recurrence-free survival (months)	NA[a]	171 (92–249)	0.221

[a] Cannot be computed as all data were censored

Discussion

The first successful surgical resection of an insulinoma was performed in Toronto in 1927 by Roscoe Graham.[8] Subsequently, several surgical series have been reported in the literature which frequently studied small numbers of patients or were multi-institutional.[5,8] Presently, the management of insulinomas especially the use of preoperative localization studies and surgical technique has not been clearly defined.[8]

The diagnosis of insulinoma has been reported to be frequently delayed and the median duration of symptoms to diagnosis has been reported to be approximately 18 months.[1,8] In our experience, the median symptom duration was comparatively shorter at 3 months. This difference may be attributed to the fact that Singapore is a small city-state whereby tertiary level care is easily available within close vicinity to the vast majority of its residents.

The use of preoperative localization studies for insulinomas presently remains controversial.[9] Many authors cite the low preoperative detection rates which are further compounded by high costs compared to the high intraoperative detection rates reported via inspection/palpation and IOUS as reasons for minimizing preoperative localization studies.[8,10,11] However, preoperative detection rates reported in the literature vary greatly depending on the time period and type of study used.[8] In general, the sensitivity of noninvasive imaging has been reported to be low. US, CT, and MRI have reported detection rates ranging from 9% to 63%,[12] 11% to 80%,[4] and 43% to 70%,[8,10] respectively. Nonetheless, advancements in the technology of scanners have resulted in a marked improvement in the sensitivity of present-day noninvasive imaging tests compared to those available two to three decades ago.[8,13] This was nicely demonstrated in a recent study which reported an improvement in the sensitivity of noninvasive imaging from 29% in the period between 1983 and 1993 to 80% in the period between 1994 and 2007.[8] However, in our present study, there was no difference between the detection rates of noninvasive imaging between both time periods, which was similar to the findings from the recent National Institute of Health (NIH) experience.[14] A possible explanation for this difference is that the study period of our study (1990–2008) and that of the NIH (1989–2008) was more recent and there has been little improvement in the accuracy of noninvasive localization of insulinoma in more recent times.

Invasive localization modalities have frequently been shown to be superior to noninvasive localization studies in detecting insulinomas.[3,4] Arteriography was once considered the "gold standard" modality but has been reported to demonstrate a wide range of detection rates from 29% to 100% depending on the experience of the operator and center.[3,4,13,15] The detection rate with angiography was 50% in the present study, which is consistent with that reported in the literature.[3] In recent times, other invasive tests such as THPVS, ASVS, and, even more recently, EUS have been added to the armamentarium of clinicians managing insulinomas. These have been shown to have superior detection rates compared to arteriography. THPVS has a reported sensitivity of 25–100%.[5,9,10] However, the use of this modality has been superceded by ASVS with its reported localization rate of 67–100%.[4,10,16,17] The superior localization rate of ASVS has been attributed to the greater

consistency of pancreatic arterial supply compared to its venous drainage.[4] Moreover, ASVS is less invasive than THPVS, as it does not require a transhepatic route and is less technically demanding.[16]

At our institution, ASVS has replaced THPVS for the above reasons since 1999. We have very limited experience with EUS in the detection of insulinomas as this technology was only introduced within the last 10 years, and coincidentally, most of our recent tumors could be detected via cross-sectional imaging and hence did not require EUS. However, we anticipate that EUS would be the preferred localization test in the future if the insulinoma is not detected via noninvasive imaging. EUS is currently the localization test of choice at most Western centers[8,18] with its reported detection rate of 57–92%.[8,10,18,19] Although it is less sensitive than ASVS, it is regarded as being less invasive. It is also important to bear in mind that EUS is less successful in detecting tumors in the tail of pancreas, with a localization rate of only 37% compared to 83% in the head in one study.[19] Nonetheless, the sensitivity of EUS is excellent especially when used in combination with CT or MRI, whereby it has been reported to approach 100%.[8]

Intraoperative localization with the aid of IOUS has been reported to have a high success rate in the detection of insulinomas.[9,10,20] It remains the most cost-effective localization modality and compares favorably with other preoperative localization tests.[4,21] A multi-institutional survey of 375 patients in 22 centers reported a 95% success rate with intraoperative localization.[5] Similarly, large single institution experiences also report intraoperative localization success rates of approximately 90%.[8,11] Several authors have cited these high intraoperative detection rates as a reason for forgoing preoperative localization studies especially when based on cost-effectiveness.[4,13]

Based on our experience, insulinomas could be localized intraoperatively in 15 of 17 (88%) patients. Although surgical exploration of insulinomas without prior preoperative localization undoubtedly remains a reasonable option especially in resource-constraint regions,[13] we do not practice this approach as there are several advantages associated with an accurate preoperative localization. Firstly, accurate preoperative localization will assist in obtaining appropriate preoperative consent and improves patient confidence,[10,16] which is increasingly important in an era whereby the medical knowledge of the general public is becoming increasingly sophisticated. Secondly, in the absence of preoperative localization, a major dilemma arises at the time of surgery when intraoperative localization fails. Presently, blind distal pancreatic resection is no longer indicated and should be abolished because of its high failure rate.[3,8] Faced with this scenario, most investigators at present would advocate aborting the surgery, reassessment via the performance of invasive localization tests such as THPVS or ASVS, and, subsequently, surgical reexploration.[3] We, on the other hand, like several others,[8,18] prefer to accurately localize insulinomas before embarking on surgical exploration so as to avoid a second surgery. Reoperation has been reported to be associated with a 50% increase in postoperative morbidity compared to the initial surgery.[18,22]

The advantage of our approach is illustrated in two of our patients who had tumors correctly localized to the distal pancreas via THPVS but could not be detected intraoperatively. These two patients would have required a second surgery if our approach was not adopted. Finally, foregoing preoperative localization may also lead to an extended operative time and the need of a radiologist or trained surgeon to accurately interpret the results of IOUS.[18] It is also important to add that accurate intraoperative localization is highly dependent on the experience of the surgeon, and as one previous author so quaintly stated, "patients should be directed to a referral center with experienced surgeons for exploration with minimal localization studies instead of performing extensive localization studies aiming at successful surgery by inexperienced surgeons".[4] Although most investigators including us would agree entirely with this statement, in real life, due to the rarity of this disease, many centers including tertiary care centers from smaller nations such as ours will invariably have a limited management experience with this disease, and the "extensive" use of preoperative localization studies may be useful to improve outcome. Undoubtedly, our approach may not be the most cost-effective, as it leads to an increase in the number of "unnecessary" tests. However, this may be a small price to pay for the patient in avoiding the need for a reexploration. Moreover, due to the rarity of this disease, it is unlikely that this increased cost will place a huge strain to our hospital resources, although we did not perform a cost analysis study. Nonetheless, it should be emphasized that our results and approach should not be extrapolated to centers which encounter these tumors on a more frequent basis. In a study of 65 patients with insulinomas from the Mayo Clinic conducted in 1992, 20 patients had 38 negative preoperative studies at a cost of US $24,000, and all 20 subsequently had their tumors successfully removed at surgery.[10,20] However, in a more recent study from the Mayo Clinic of 237 patients treated between 1987 and 2007,[23] it was noted that that was an increasing trend towards the use of preoperative localization tests, including the use of invasive studies to avoid blind pancreatic exploration. The investigators reported that from 2002 to 2007, all 69 insulinomas treated were successfully localized preoperatively and 26 (38%) had invasive localization studies.[23]

Surgical resection is the treatment of choice for insulinomas and offers the only chance for cure.[3] The overall cure rates reported in the literature after surgery vary

from 75% to 98%, and success is dependent on the stage of presentation and completeness of resection.[3] Presently, the surgical approach to insulinomas remains debated, although most investigators would advocate a pancreas-sparing approach.[5,8] We have similarly adopted a pancreas-sparing surgical policy whereby eight tumors were resected via enucleation and nine via distal pancreatectomy, of which three were spleen-preserving. All seven insulinomas in the proximal pancreas were successfully enucleated and none required a pancreaticoduodenectomy. Although some authors have raised concerns about the higher fistula rates associated with enucleation of up to 57%,[8] we did not experience any increase in the morbidity or pancreatic fistula rate with enucleation. Comparison between enucleation and distal pancreatectomy revealed no statistical difference in the postoperative morbidity and fistula rate (25% and 25% vs 56% and 44%, respectively). In our experience, enucleation can be performed safely with the concomitant use of IOUS to avoid damage to the main pancreatic duct.

In this study, we found enucleation to be associated with a higher risk of a microscopic positive margin compared with a formal resection (38% vs 0%, P=0.043). However, an R1 resection was not associated with an increase in recurrence or diminished recurrence-free survival. All three patients with an R1 resection after enucleation were alive and disease-free at a median follow-up of 72 (range, 10–132) months. This finding was similar to the recent study at the Massachusetts General Hospital whereby seven of 31 patients with enucleation had a positive margin but none had any recurrence on long-term follow-up.[8] The present study is only the second to date to examine the implication of a positive margin after enucleation of insulinomas.[8] The findings of both our study and that at the Massachusetts General Hospital are, however, not surprising as insulinomas are frequently benign and encapsulated. Laparoscopic surgery including enucleation is increasingly being used to treat insulinomas and may become the surgical approach of choice in the future.[2,13,24,25] However, thus far, we have no experience with this approach for the management of insulinomas.

In conclusion, accurate localization of insulinomas prior to surgical exploration is useful as it eliminates the need for blind distal pancreatectomy and avoids reoperation. This may be especially important in centers which do not have an extensive experience with this disease. Compete surgical resection is the treatment of choice, and whenever possible, a pancreas-sparing approach such as enucleation should be adopted.

References

1. Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma-incidence, recurrence, and long-term survival of patients: a 60-year study. Mayo Clin Proc 1991;66:711–719.
2. Liu H, Peng C, Zhang S, Wu Y, Fang H, Sheng H, Peng S. Strategy for the surgical management of insulinomas: analysis of 52 cases. Dig Surg 2007;24:463–470. doi:10.1159/000111822.
3. Tucker ON, Crotty PL, Conlon KC. The management of insulinoma. Br J Surg 2006;93:264–275. doi:10.1002/bjs.5280.
4. Lo CY, Lam KY, Kung AW, Lam KS, Tung PH, Fan ST. Pancreatic insulinomas: a 15-year experience. Arch Surg 1997; 132:926–930.
5. Rothmund M, Angelini L, Brunt LM, Farndon JR, Geelhoed G, Grama D, Herfarth C, Kaplan EL, Largiader F, Morino E, et al. Surgery for benign insulinoma: an international review. World J Surg 1990;14:393–398. doi:10.1007/BF016 58536.
6. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8–13. doi:10.1016/j.surg.2005.05.001.
7. Heitz PU, Komminoth P, Perren A, et al. WHO histological classification of tumours of the endocrine pancreas. In DeLellis RA, Lloyd RV, Heitz PU, Eng C, eds. Pathology and Genetic Tumours of Endocrine Organs, 1st ed. Lyon, France: IARC, 2004, pp 177–182.
8. Nikfarjam M, Warshaw AL, Axelrod L, Deshpande V, Thayer SP, Ferrone CR, Castillo CF. Improved contemporary surgical management of insulinomas. A 25-year experience at the Massachusetts General Hospital. Ann Surg 2008;247:165–172.
9. Daggett PR, Goodburn EA, Kurtz AB, Le Quense LP, Morris DV, Nabarro JD. Is preoperative localization of insulinoma necessary. Lancet 1981;1:483–486. doi:10.1016/S0140-6736(81)91859-6.
10. Ravi K, Britton BJ. Surgical approach to insulinomas: are preoperative localization tests necessary. Ann R Coll Surg Engl 2007;89:212–217. doi:10.1308/003588407X179008.
11. Boukhman MP, Karam JM, Shaver J, Siperstein AE, DeLorimier AA, Clark OH. Localization of insulinomas. Arch Surg 1999;134:818–823. doi:10.1001/archsurg.134.8.818.
12. Pasieka JL, McLeod MK, Thompson NW, Burney RE. Surgical approach to insulinomas. Assessing the need for preoperative localization. Arch Surg 1992;127:442–447.
13. Paul TV, Jacob JJ, Vasan SK, Thomas N, Rajarathnam S, Selvan B, Paul MJ, Abraham D, Nair A, Seshadri MS. Management of insulinomas: analysis from a tertiary care referral center in India. World J Surg 2008;32:576–582. doi:10.1007/s00268-007-9390-y.
14. Guettier JM, Kam A, Chang R, Skarulis MC, Cochran C, Alexander HR, Libutti SK, Pingpank JF, Gorden P. Localization of insulinomas to regions of the pancreas by intra-arterial calcium stimulation: the NIH experience. J Clin Endocrinol Metab 2009 (in press).
15. Geoghegan JG, Jackson JE, Lewis MP, Owen ER, Bloom SR, Lynn JA, Williamson RC. Localization and surgical management of insulinoma. Br J Surg 1994;81:1025–1028. doi:10.1002/bjs.1800810733.
16. Hiramoto JS, Feldstein VA, LaBerge JM, Norton JA. Intraoperative ultrasound and preoperative localization detects all occult insulinomas. Arch Surg 2001;136:1020–1026. doi:10.1001/archsurg.136.9.1020.
17. Lo CY, Chan FL, Tam SC, Cheng PW, Fan ST, Lam KS. Value of intra-arterial calcium stimulated venous sampling for regionalization of pancreatic insulinomas. Surgery 2000;128:903–909. doi:10.1067/msy.2000.109729.
18. Richards ML, Gauger PG, Thompson NW, Kloos RG, Giordano TJ. Pitfalls in the surgical treatment of insulinoma. Surgery 2002;132:1040–1049. doi:10.1067/msy.2002.128610.
19. Schumacher B, Lubke HJ, Frieling T, Strohmeyer G, Starke AA. Prospective study on the detection of insulinomas by endoscopic ultrasonography. Endoscopy 1996;28:273–276. doi:10.1055/s-2007-1005452.
20. Van Heerden JA, Grant CS, Czako CS, Czako PF, Service FJ, Charboneau JW. Occult functioning insulinomas: which localizing

studies are indicated? Surgery. 1992;112:1010–1014. doi:10.1007/s00268-004-7645-4.
21. Proye CA, Lokey JS. Current concepts in functioning endocrine tumors of the pancreas. World J Surg 2004;28:1231–1238. doi:10.1007/s00268-004-7645-4.
22. Simon D, Starke A, Goretzi PE, Roeher HD. Reoperative surgery for organic hyperinsulinism: indications and operative strategy. World J Surg 1998;22:666–671. doi:10.1007/s002689900450.
23. Placzkowski KA, Vella A, Thompson GB, Grant CS, Reading CC, Charboneau JW, Andrews JC, Lloyd RC, Service FJ. Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987–2007. J Clin Endocrinol Metab 2009. doi:10.1210/jc.2008-2031.
24. Berends FJ, Cuesta MA, Kazemier G, van Eijck CH, de Herder WW, van Muiswinkel JM, Bruining HA, Bonjer HJ. Laparoscopic detection and resection of insulinomas. Surgery 2000;128:386–391. doi:10.1067/msy.2000.107413.
25. Fernandez-Cruz L, Cesar-Borges G. Laparoscopic strategies for resection of insulinomas. J Gastrointest Surg 2006;10:752–760. doi:10.1016/j.gassur.2005.08.012.

J Gastrointest Surg (2009) 13:1078–1083
DOI 10.1007/s11605-009-0854-2

ORIGINAL ARTICLE

Surgical Strategy for Hepatocellular Carcinoma Patients with Portal Vein Tumor Thrombus Based on Prognostic Factors

Kazuhiro Kondo · Kazuo Chijiiwa · Masahiro Kai · Kazuhiro Otani · Koki Nagaike · Jiro Ohuchida · Masahide Hiyoshi · Motoaki Nagano

Received: 5 January 2009 / Accepted: 26 February 2009 / Published online: 19 March 2009

Abstract
Rationale Surgical strategy for patients with hepatocellular carcinoma and portal vein tumor thrombus (PVTT) remains to be established.
Methods From 1990 to 2008, 48 hepatocellular carcinoma patients with PVTT detected by preoperative imaging underwent hepatic resection, and their clinical data were retrospectively analyzed. Possible prognostic factors for survival were analyzed with postoperative survival curves, and significant factors were determined by univariate and multivariate analysis. The frequency of postoperative severe complications was investigated for each prognostic factor.
Results Significant prognostic factors included patient age <60 years, serum total bilirubin (T-Bil) >0.8 mg/dl, serum aspartate aminotransferase >30 IU/L, serum alkaline phosphatase (ALP) >300 IU/L, tumor size >4 cm, PVTT in the main trunk (Vp4), and a surgical margin <1 mm by univariate analysis, and independent prognostic factors were serum T-Bil, ALP, and Vp4. No patient with Vp4 survived for more than 400 days after surgery, and frequency of postoperative severe complications in these Vp4 patients was significantly higher than in other Vp1–3 patients.
Conclusion Hepatic resection as a first-choice treatment should be carefully selected in patients with Vp4 unless emergent removal of the PVTT is required.

Keywords Hepatocellular carcinoma · Surgical strategy · Portal vein tumor thrombus

Introduction

Hepatocellular carcinoma (HCC) is a major life-threatening cancer with a dismal prognosis despite the various existing treatments, including hepatic resection, liver transplantation, transcatheter arterial chemoembolization (TACE), and ablation therapy.[1] HCC tends to invade the portal vein and cause portal vein tumor thrombus (PVTT). HCC patients with PVTT have an extremely poor prognosis. Even in the patients who undergo hepatic resection as the only potentially curative treatment for HCC with PVTT, the postoperative 5-year survival rate is only 10–30% in recent reports having an adequate volume of patients.[2] Moreover, in HCC patients with PVTT, the volume of resected liver tends to be large, resulting in a high frequency of postoperative complications.[2] Both patients and their surgeons may avoid surgery because of the poor prognosis and the high surgical risk. However, some patients survive for a long time after surgery alone or after surgery combined with pre- and/or postoperative adjuvant therapy.[2–4] Therefore, it is essential to determine adequate treatments for HCC patients with PVTT preoperatively.

The most effective treatment strategy for HCC with PVTT remains to be established.[2] The aims of the present retrospective study were to investigate postoperative prognostic factors with special reference to the level of PVTT and frequency of postoperative severe complication and to propose a surgical treatment strategy for these patients.

K. Kondo · K. Chijiiwa (✉) · M. Kai · K. Otani · K. Nagaike · J. Ohuchida · M. Hiyoshi · M. Nagano
Department of Surgical Oncology and Regulation of Organ Function, Miyazaki University School of Medicine,
5200 Kihara,
Kiyotake, Miyazaki 889-1692, Japan
e-mail: Kazuochi@med.miyazaki-u.ac.jp

Patients and Methods

From January 1990 to August 2008, 352 surgeries (322 were first surgeries and 30 were not) were performed on HCC patients in our institution. In all patients, preoperative ultrasonography (US), computed tomography (CT), angiography, and CT during angiography were performed. From evaluation of these images by more than one experienced radiologist (for CT and angiography) or surgeon (for US), PVTT was detected in 53 patients. Of these, PVTT was confirmed macroscopically and microscopically in 50 patients after operation. Two patients with operation-related death were excluded, and the remaining 48 patients were the subjects of this investigation.

The decision to perform liver surgery was based mainly on volume of the future remnant liver as determined by CT volumetry[5] and on removable liver volume based on indocyanine green retention rate at 15 min (ICGR15) as calculated by the method of Takasaki et al.[6] Routine biochemical liver function tests including serum total bilirubin (T-Bil), albumin (ALB), and prothrombin time (PT), Child-Pugh grade,[7] degree of liver damage,[8] or results of ^{99}m-technetium galactosyl-human serum albumin scintigraphy[9] were also used in the decision.[10] Surgery was performed in patients who were determined to have removable PVTT and to obtain the survival benefit of surgery.

The level of the PVTT (Vp) detected in preoperative imaging was classified into four categories: Vp1, PVTT in distal to second-order portal branches; Vp2, PVTT in second-order branches; Vp3, PVTT in first-order branches; and Vp4, PVTT in the main trunk.[8] In the patients with PVTT growing into the main trunk of the portal vein (Vp4), the surgical technique was as follows: After careful isolation of the portal vein in the hepatic hilum, the trunk was clamped at the side of the superior mesenteric vein and the side of the contralateral lobe. The main portal trunk was incised to remove the PVTT, or the origin of the main portal branch of the tumor-bearing lobe was dissected to pull out the PVTT, and the stump was closed by running suture so as not to create a stenosis at the site.[3] During this procedure, the clamp on the contralateral portal branch was released for a moment to wash out the cancer cells in the peripheral intrahepatic portal vein by backflow.

The extent of hepatic resection performed in the patients was HrS (resection of one subsegment) in four patients, Hr1 (resection of one segment) in 10 patients, Hr2 (resection of two segments) in 27 patients, and Hr3 (resection of three segments) in four patients. After 2005, five patients in this study group underwent postoperative adjuvant chemotherapy of one-shot intra-arterial injection of cisplatin.

After surgery, patients were followed in the outpatient clinic with checks of blood chemistry including alpha-fetoprotein (AFP) and/or protein induced by vitamin K absence or antagonist II every month and with US or CT imaging every 2 or 3 months. Patients with cancer recurrence were readmitted, and TACE or transcatheter arterial infusion chemotherapy was performed according to their condition. Median follow-up time was 343.5 days.

Possible preoperative prognostic factors that would aid in determining a surgical strategy investigated in this study were patient background, including age, sex, and performance status[11]; liver function, as determined by hepatitis B surface antigen, hepatitis C antibody, ALB, T-Bil, aspartate aminotransferase (AST), alanine aminotransferase, alkaline phosphatase (ALP), PT, ICGR15, and platelet count; tumor characteristics, including multiplicity, tumor size, serum AFP, and Vp; and treatment, including preoperative TACE (within 3 months before surgery), operation time, operative blood loss, and width of the surgical margin (SM). For these factors, significant differences in postoperative survival rate were determined by univariate analysis of survival curves calculated by the Kaplan–Meier method. If more than two factors in each category were shown to be significant, multivariate analysis by Cox proportional hazard model was used to detect independent prognostic factors. In the patients with significantly poor prognostic factors, the frequency of postoperative severe complications of Clavien grade III or IV[12,13] was compared to that in patients without these factors.

For statistical analysis, postoperative survival curves calculated by the Kaplan–Meier method and logrank test were used for univariate analysis of prognostic factors, the Cox proportional hazard model was used for multivariate analysis of prognostic factors, and the Chi squared test was used to assess the relation between each prognostic factor and the frequency of postoperative severe complications. A value of $p<0.05$ was considered significant. All analyses were performed with StatView statistical software (version 5.0; SAS Institute, Cary, NC, USA).

Results

Thirty-six (75%) of the 48 patients with PVTT died during the follow-up period. Causes of death were recurrence in the remnant liver ($n=27$, 67.5%), distant metastasis ($n=6$, 15.0%), deterioration of liver function ($n=2$, 5.0%), and other cause (suicide) ($n=1$, 2.5%). In the univariate analysis of prognostic factors, only age <60 in the patient background category; T-Bil >0.8 mg/dl, AST >30 IU/L, and ALP >300 IU/L in the liver function category; tumor size >4.0 cm and Vp4 in the tumor characteristics category; and only SM <1 mm in the treatment category were significant prognostic factors (Table 1). In the liver function category, multivariate analysis revealed only T-Bil >0.8 mg/dl and ALP >300 IU/L to be significant independent factors. In the tumor characteristics category, multivariate

Table 1 Differences in Postoperative Survival Rates by Prognostic Factor as Calculated by Logrank Test and Kaplan–Meier Method

Possible prognostic factors (patient numbers)	Median survival time (days)	*p* Values
Patient profiles		
Age <60/≥60 (17/31)	206/489	*0.0378*
Sex M/F (34/14)	318/712	0.1177
Performance status 0/1/2 (15/25/8)	400/314/423	0.6411
Liver functions		
HBsAg +/− (18/30)	211/445	0.0722
HCVAb +/− (18/30)	496/252	0.2786
ALB <3.5/≥3.5 g/dl (12/36)	280/371	0.3777
T-Bil >0.8/≤0.8 mg/dl (18/30)	177/783	*0.0008*
AST >30/≤30 IU/L (43/5)	321/1,163	*0.0205*
ALT >60/≤60 IU/L (11/37)	343/344	0.5486
ALP >300/≤300 IU/L (29/19)	297/761	*0.0114*
PT <100/≥100% (34/14)	287/1,129	0.0560
ICGR15>10/≤10% (32/16)	372/324	0.5159
Plt <15/≥15×10^4/mm^3 (26/22)	267/446	0.4042
Tumor characteristics		
Tumor number single/multiple (18/20)	542/273	0.2041
Tumor size >4/≤4 cm (39/9)	334/489	*0.0382*
AFP >2×10^4/≤2×10^4 ng/ml (10/38)	222/371	0.0631
Vp 1–3/4 (43/5)	398/248	*0.0284*
Treatments		
Preoperative TACE +/− (9/39)	343/344	0.1287
Operation time >6h/≤6 h (30/18)	371/329	0.4047
Blood loss >3,000/≤3,000 ml (9/39)	256/400	0.1440
SM <1/≥1 mm (20/28)	227/497	*0.0458*

p Values<0.05 are italicized.

HBsAg hepatitis B surface antigen, *HCVAb* hepatitis C antibody, *ALB* albumin, *T-Bil* total bilirubin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *PT* prothrombin time, *ICGR15* indocyanine green retention rate at 15 min, *Plt* platelet count, *Vp1–3* PVTT in distal to first branch, *Vp4* PVTT in the main trunk, *TACE* transcatheter arterial chemoembolization, *SM* width of surgical margin

analysis revealed Vp4 to be an independent significant factor (Table 2).

Postoperative survival curves for each prognostic factor are shown in Figs. 1 and 2. Significant differences in survival rate were observed between the patients with and without these factors. The postoperative survival rates among patients with Vp1 (n=6), Vp2 (n=13), or Vp3 (n=24) were identical, whereas the survival rate of the patients with Vp4 (n=5) was quite different (Fig. 2). The causes of death in patients with Vp4 were HCC recurrence in the remnant liver in four patients and lung metastasis of HCC in one patient.

Table 2 Multivariate Analysis of the Prognostic Factors of Liver Function and Tumor Characteristics by Cox Proportional Hazard Model

Prognostic factors	Risk ratio	*p* value	95% CI
Liver functions			
T-Bil >0.8/≤0.8 mg/dl	0.329	*0.0027*	0.159–0.681
AST >30/≤30 IU/L	0.151	0.0664	0.020–1.137
ALP >300/≤300 IU/L	0.321	*0.0041*	0.147–0.697
Tumor characteristics			
Size >4/≤4 cm	0.308	0.0524	0.094–1.012
Vp 1–3/4	0.354	*0.0400*	0.131–0.954

p Values<0.05 are italicized.

CI confidence interval, *T-Bil* total bilirubin, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase, *Vp1–3* PVTT in distal to first branch, *Vp4* PVTT in the main trunk

Twenty three of 48 patients with PVTT (47.9%) suffered postoperative complications with a severity of grade I in 11 patients, grade II in seven patients, grade IIIa in three patients, and grade IVa in two patients. The relation between the significant prognostic factors and severe (grade III or IV) postoperative complications was significant only in patients with Vp4 in that 60% of these patients suffered severe postoperative complications (Table 3). The complications were grade IIIa in two patients (intraabdominal abscess and bile leakage) and grade IVa in one patient (liver failure).

Discussion

In HCC patients with PVTT detected in preoperative imaging, it is quite important to determine a treatment

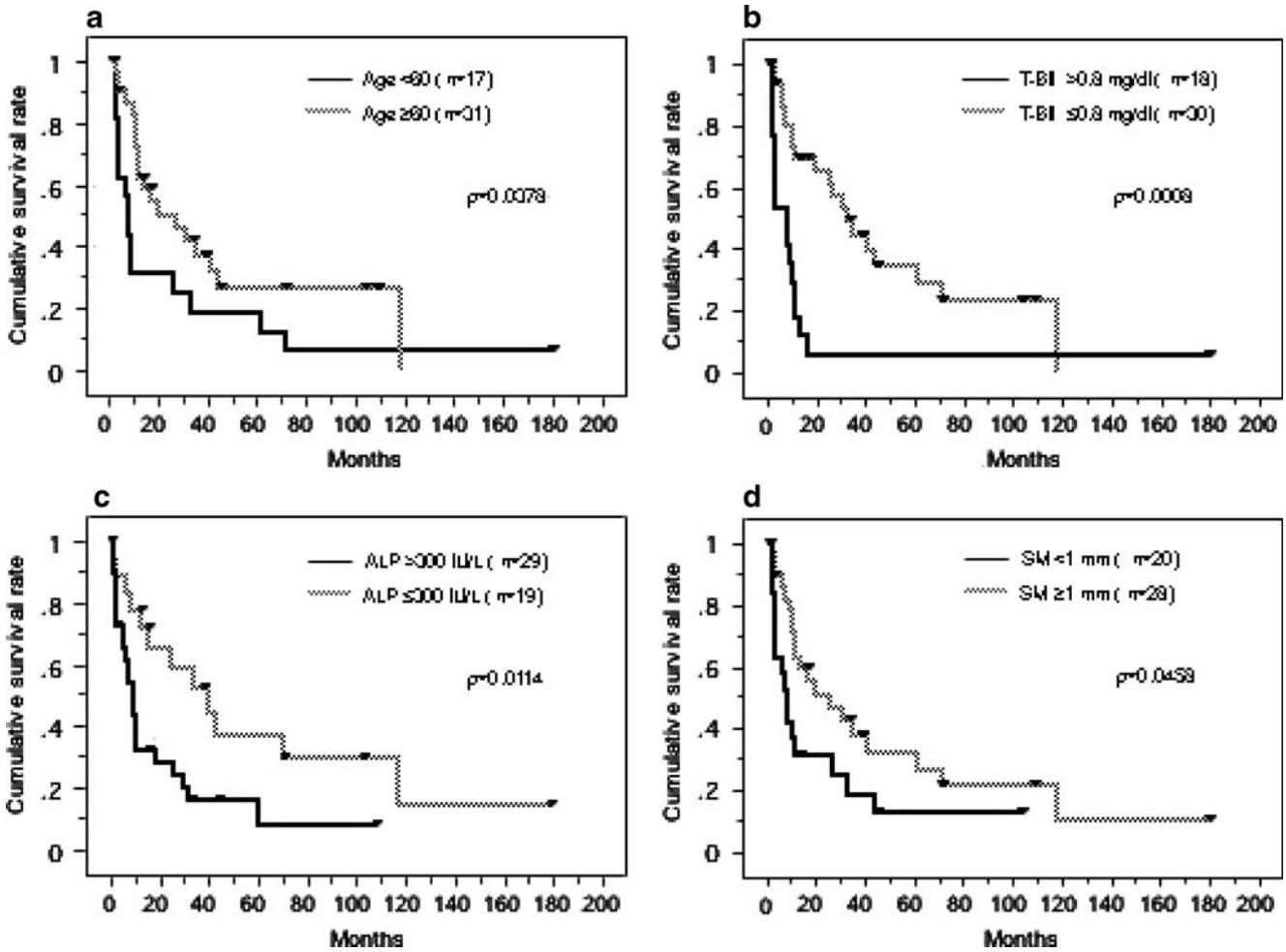

Figure 1 Overall postoperative survival rates of patients >60 and ≤60 years of age (**a**), patients with serum total bilirubin (*T-Bil*) >0.8 mg/dl and ≤0.8 mg/dl (**b**), patients with serum alkaline phosphatase (*ALP*) >300 IU/L and ≤300 IU/L (**c**), width of surgical margin (*SM*) <1 mm and ≥1 mm (**d**). Significant differences in survival rates were observed.

strategy. A previous study found that a substantial number of patients had an extremely poor prognosis (e.g., several months), whereas some patients survived for several years or more.[2] In some reports, preoperative chemotherapy and postoperative adjuvant chemotherapy have been advocated as effective in HCC patients with PVTT.[2–4] Although high-risk surgery can be attempted on patients who are expected to have long survival, patients who are not expected to survive long can hardly accept a high-risk surgery that is frequently accompanied by severe complications. Postoperative severe complications may also prevent the application of challenging adjuvant chemotherapy.[4,14,15]

Age <60 was the only significant prognostic factor in the patient background category in this study. Age was not found to be a prognostic factor in previous studies performed on surgically treated HCC patients with PVTT.[15,16] However, our data may correspond with the generally accepted theory of rapid progress of the cancer in young people.[17] Nevertheless, young patients need to be treated to gain longer survival. Therefore, we believe these patients should be treated with a radical surgical approach and, if possible, adequate preoperative or postoperative adjuvant chemotherapy. Nagano et al.[18] have recently reported postoperative chemotherapy with 5-FU/IFN combination therapy that showed a marvelous effect for selected patients with PVTT. The reported 1-, 2-, and 3-year survival rates were 40%, 28.5%, and 21.4%, respectively, in the HCC patients with Vp4 who received adjuvant chemotherapy after palliative hepatic resection. This combination therapy with at least two cycles (one cycle with 4 weeks) includes continuous arterial infusion of 5-FU (300 mg m^{-2} day^{-1}, for the initial 2 weeks) and subcutaneous injection of α-IFN (5×10^6 U, three times/week for 4 weeks). Using similar protocol for HCC patients with Vp3, the overall survival rates at 1 and 3 years were reported to be 100% and 74%, respectively.[19]

Among measurements of liver function, the significant independent prognostic factors were T-Bil and ALP levels

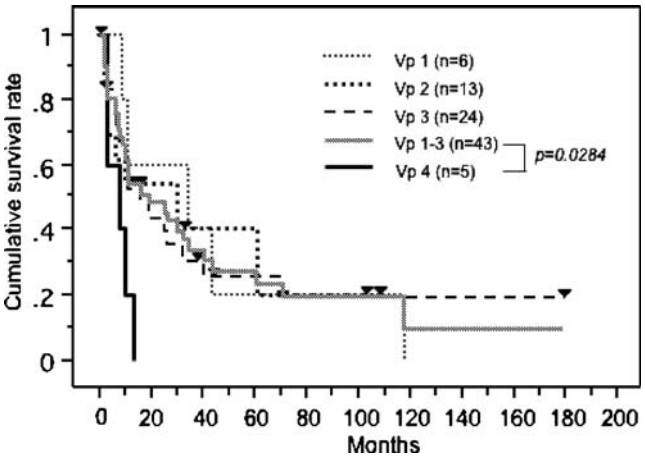

Figure 2 Overall postoperative survival rates of patients with Vp1 (PVTT in distal to second-order branches), Vp2 (PVTT in second-order branches), Vp3 (PVTT in first-order branches), and Vp4 (PVTT in the main trunk). The survival rate of the patients with Vp4 was quite different from those with other Vp levels, whereas the survival rates among patients with Vp1, Vp2, or Vp3 were identical. There was a significant difference in survival rates between patients with Vp4 and the group of patients with Vp1, Vp2, or Vp3. All patients with Vp4 died within 400 days after surgery.

in our study. These liver function measurements were not revealed as prognostic factors in previous reports of HCC patients with tumor thrombus in the second branch, first branch, or trunk of the portal vein.[15,16] However, they may indicate not only impaired liver function but also the malignant potential of HCC in that they may imply massive compression of, or invasion into, the biliary tract, as recently reported.[20] In patients with a high T-Bil level, aggressive surgery[21] and adjuvant chemotherapy around the time of surgery[3,4,14] tend to be avoided for fear of postoperative liver failure. Therefore, careful determination of surgical indications is necessary in PVTT patients with high T-Bil and ALP levels.

The postoperative prognosis of patients with Vp4 was extremely poor in our study, and all patients died from recurrent HCC within 400 days after surgery. However, some patients with Vp1, 2, or 3 obtained long survival. Thus, it appears that patients with PVTT that does not reach the main trunk should undergo surgery. Patients with PVTT in the main portal trunk may experience sudden death due to rupture of esophagogastric varices or acute liver failure, and in such cases, the thrombus should be surgically removed.[21] However, the frequency of postoperative severe complications in Vp4 patients was very high in our study, and the surgery itself and subsequent postoperative complications may deprive the patients of the opportunity for other treatment options.[2,22,23] One of the two patients with surgery-related death who was excluded from this study was a Vp4 patient (data not shown). We therefore propose that, as the first choice of treatment, surgery should not be performed on patients with Vp4 unless it is an emergent case with impending rupture of esophagogastric varices due to portal hypertension or acute liver failure caused by PVTT. However, there were only five patients with Vp4 in our study. Therefore, further investigations examining both postoperative complications and survival rates in sufficient numbers of patients with Vp4 are required.

Nonsurgical treatment options that are effective for PVTT have also been reported recently.[2,23] In the present study, because the postoperative survival rate was better and the rate of postoperative severe complications was lower in the patients with PVTT that does not reach the main portal trunk (Vp1, 2, and 3), we recommend a strategy of reducing the PVTT in the main trunk through conservative treatment followed by surgery (salvage surgery).

SM was the only prognostic treatment factor analyzed in this study. In surgery against HCC, some reports mentioned that the SM does not affect postoperative survival if the tumor is not exposed.[24,25] However, HCC with PVTT tends to show infiltrative growth, and a sufficient SM may be required to reduce the residual tumor cells and to prolong survival time. In a previous report of 381 cases of HCC with macroscopic PVTT, a SM <5 mm was revealed to be a

Table 3 Prognostic Factors and Frequency of Severe Postoperative Complication (Clavien Grade III–IV)

Prognostic factors	Number of patients with severe complication (%)	*p* Value
Age <60 (*n*=17)	3 (7.6%)	
≥60 (*n*=31)	2 (6.5%)	0.2246
T-Bil >0.8 mg/dl (*n*=18)	2 (11.1%)	
≤0.8 mg/dl (*n*=30)	3 (10.0%)	0.9029
ALP >300 IU/L (*n*=29)	5 (17.2%)	
≤300 IU/L (*n*=19)	0 (0.0%)	0.0558
Vp 4 (*n*=5)	3 (60.0%)	
1–3 (*n*=43)	2 (4.7%)	*0.0001*
SM <1 mm (*n*=20)	4 (20.0%)	
≥1 mm (*n*=28)	1 (3.6%)	0.0662

p Values<0.05 are italicized.

T-Bil total bilirubin, *ALP* alkaline phosphatase, *Vp1–3* PVTT in distal to first branch, *Vp4* PVTT in the main trunk, *SM* width of surgical margin

significant prognostic factor.[15] Thus, hepatectomy with an adequate SM should be considered in the surgery for HCC with PVTT.

Conclusion

Hepatic resection should be performed with the understanding that a poor prognosis may result in HCC patients with PVTT in whom age is <60 years, serum T-Bil is >0.8 mg/dl, and serum ALP is >300 IU/L. A sufficient SM should be maintained in the surgery. Because of the extremely poor prognosis and high rate of severe postoperative complications in HCC patients with Vp4, surgery should be carefully selected as the first choice of treatment unless the patient requires emergent removal of the PVTT.

References

1. Llovet JM. Updated treatment approach to hepatocellular carcinoma. J Gastroenterol 2005;40:225–235. doi:10.1007/s00535-005-1566-3.
2. Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. World J Gastroenterol 2006;12:7561–7567.
3. Minagawa M, Makuuchi M, Takayama T, Ohtomo K. Selection criteria for hepatectomy in patients with hepatocellular carcinoma and portal vein tumor thrombus. Ann Surg 2001;233:379–384. doi:10.1097/00000658-200103000-00012.
4. Fukuda S, Okuda K, Imamura M, Imamura I, Eriguchi N, Aoyagi S. Surgical resection combined with chemotherapy for advanced hepatocellular carcinoma with tumor thrombus: report of 19 cases. Surgery 2002;131:300–310. doi:10.1067/msy.2002.120668.
5. Okamoto E, Kyo A, Yamanaka N, Tanaka N, Kuwata K. Prediction of the safe limits of hepatectomy by combined volumetric and functional measurements in patients with impaired hepatic function. Surgery 1984;95:586–592.
6. Takasaki T, Kobayashi S, Suzuki S, Muto H, Marada M, Yamana Y, Nagaoka T. Predetermining postoperative hepatic function for hepatectomies. Int Surg 1980;65:309–313.
7. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–649. doi:10.1002/bjs.1800600817.
8. Liver Cancer Study Group of Japan. General rules for the clinical and pathological study of primary liver cancer. 2nd English ed. Tokyo: Kanehara, 2003.
9. Kwon AH, Matsui Y, Ha-Kawa SK, Kamiyama Y. Functional hepatic volume measured by technetium-99 m-galactosyl-human serum albumin liver scintigraphy: comparison between hepatocyte volume and liver volume by computed tomography. Am J Gastroenterol 2001;96:541–546. doi:10.1111/j.1572-0241.2001.03556.x.
10. Kondo K, Chijiiwa K, Funagayama M, Kai M, Otani K, Ohuchida J. Hepatic resection is justified for elderly patients with hepatocellular carcinoma. World J Surg 2008;32:2223–2229. doi:10.1007/s00268-008-9688-4.
11. Sorensen JB, Klee M, Palshof T, Hansen HH. Performance status assessment in cancer patients. An inter-observer variability study. Br J Cancer 1993;67:773–775.
12. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. Surgery 1992;111:518–526.
13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–213. doi:10.1097/01.sla.0000133083.54934.ae.
14. Liang LJ, Hu WJ, Yin XY, Zhou Q, Peng BG, Li DM, Lu MD. Adjuvant intraportal venous chemotherapy for patients with hepatocellular carcinoma and portal vein tumor thrombi following hepatectomy plus portal thrombectomy. World J Surg 2008;32:627–631. doi:10.1007/s00268-007-9364-0.
15. Zhou J, Tang ZY, Wu ZQ, Zhou XD, Ma ZC, Tan CJ, Shi YH, Yu Y, Qiu SJ, Fan J. Factors influencing survival in hepatocellular carcinoma patients with macroscopic portal vein tumor thrombosis after surgery, with special reference to time dependency: a single-center experience of 381 cases. Hepatogastroenterology 2006;53:275–280.
16. Ikai I, Hatano E, Hasegawa S, Fujii H, Taura K, Uyama N, Shimahara Y. Prognostic index for patients with hepatocellular carcinoma combined with tumor thrombosis in the major portal vein. J Am Coll Surg 2006;202:431–438. doi:10.1016/j.jamcollsurg.2005.11.012.
17. Ershler WB. Why tumors grow more slowly in old people. J Natl Cancer Inst 1986;77:837–839.
18. Nagano H, Miyamoto A, Wada H, Ota H, Marubashi S, Takeda Y, Dono K, Umeshita K, Sakon M, Monden M. Interferon-alpha and 5-fluorouracil combination therapy after palliative hepatic resection in patients with advanced hepatocellular carcinoma, portal venous tumor thrombus in the major trunk, and multiple nodules. Cancer 2007;110:2493–2501. doi:10.1002/cncr.23033.
19. Nagano H, Sakon M, Eguchi H, Kondo M, Yamamoto T, Ota H, Nakamura M, Wada H, Damdinsuren B, Marubashi S, Miyamoto A, Takeda Y, Dono K, Umeshita K, Nakamori S, Monden M. Hepatic resection followed by IFN-alpha and 5-FU for advanced hepatocellular carcinoma with tumor thrombus in the major portal branch. Hepatogastroenterology 2007;54:172–179.
20. Ikenaga N, Chijiiwa K, Otani K, Ohuchida J, Uchiyama S, Kondo K. Clinicopathologic characteristics of hepatocellular carcinoma with bile duct invasion. J Gastrointest Surg 2009;13:492–497.
21. Kumada K, Ozawa K, Okamoto R, Takayasu T, Yamaguchi M, Yamamoto Y, Higashiyama H, Morikawa S, Sasaki H, Shimahara Y, Yamaoka Y, Takeuchi E. Hepatic resection for advanced hepatocellular carcinoma with removal of portal vein tumor thrombi. Surgery 1990;108:821–827.
22. Ishikawa T, Imai M, Kamimura H, Tsuchiya A, Togashi T, Watanabe K, Seki K, Ohta H, Yoshida T, Kamimura T. Improved survival for hepatocellular carcinoma with portal vein tumor thrombosis treated by intra-arterial chemotherapy combining etoposide, carboplatin, epirubicin and pharmacokinetic modulating chemotherapy by 5-FU and enteric-coated tegafur/uracil: a pilot study. World J Gastroenterol 2007;13:5465–5470.
23. Kamiyama T, Nakanishi K, Yokoo H, Tahara M, Nakagawa T, Kamachi H, Taguchi H, Shirato H, Matsushita M, Todo S. Efficacy of preoperative radiotherapy to portal vein tumor thrombus in the main trunk or first branch in patients with hepatocellular carcinoma. Int J Clin Oncol 2007;12:363–368. doi:10.1007/s10147-007-0701-y.
24. Ochiai T, Takayama T, Inoue K, Yamamoto J, Shimada K, Kosuge T, Yamazaki S, Makuuchi M. Hepatic resection with and without surgical margins for hepatocellular carcinoma in patients with impaired liver function. Hepatogastroenterology 1999;46:1885–1889.
25. Hashimoto T, Minagawa M, Aoki T, Hasegawa K, Sano K, Imamura H, Sugawara Y, Makuuchi M, Kokudo N. Caval invasion by liver tumor is limited. J Am Coll Surg 2008;207:383–392. doi:10.1016/j.jamcollsurg.2008.02.017.

J Gastrointest Surg (2009) 13:1084–1093
DOI 10.1007/s11605-009-0841-7

ORIGINAL ARTICLE

Hepaticojejunostomy vs. End-to-end Biliary Reconstructions in the Treatment of Iatrogenic Bile Duct Injuries

Beata Jabłońska · Paweł Lampe · Marek Olakowski · Zygmunt Górka · Andrzej Lekstan · Tomasz Gruszka

Received: 23 December 2008 / Accepted: 18 February 2009 / Published online: 6 March 2009

Abstract
Background Retrospective comparison of short- and long-term results and quality of life in patients treated for iatrogenic bile duct injuries (IBDI) with Roux-Y hepaticojejunostomy (HJ) or end-to-end ductal anastomosis (EE).
Methods Between January 1990 and March 2005, 94 patients underwent reconstructive surgery for IBDI: 49, Roux-Y HJ, and 45, EE.
Results Early postoperative complications were observed in 12 (24.5%) patients undergoing HJ and three (6.7%) undergoing EE (p=0.0239). Reoperations in the early postoperative period were performed in four (8%) patients after HJ and in zero patients after EE. Following HJ, one (2%) hospital death occurred due to acute circulatory insufficiency. Long-term results were evaluated in 69 (72%) patients. Postoperative mean weight gain was significantly higher after EE than HJ (p=0.0191). Recurrent stricture was observed in two (5.3%) patients after HJ and three (9.6%) after EE (p=0.6509). Terblanche long-term results were comparable in both groups (p=0.3173). Good Karnofsky quality of life was comparable in both groups (p=0.8377).
Conclusions More early complications occurred after HJ than after EE. Long-term results were comparable after both reconstructive methods. After EE, patients achieved a higher weight gain than after HJ. Quality of life in both groups was comparable.

Keywords Bile duct injury · Hepaticojejunostomy · End-to-end anastomosis

Introduction

Treatment of iatrogenic bile duct injuries (IBDI) remains an important problem in gastrointestinal surgery. Most frequently, these develop during cholecystectomy. Recently, the number of patients with IBDI has increased twofold, which has been associated with the widespread of laparoscopic cholecystectomy.[1] Unrecognized or improperly treated biliary injuries can lead to serious complications such as biliary cirrhosis, hepatic failure, and death.[2,3] Therefore, effective treatment of IBDI is very important. Endoscopic techniques are recommended as initial treatment of IBDI.[4–6] When these techniques are not effective, surgical management is considered. The goal of surgical treatment is to reconstruct the proper bile flow to the alimentary tract. In order to achieve this goal, many techniques are used.[7–13]

There are contradictory reports on the effectiveness of bile duct reconstruction methods in the literature. Roux-Y hepaticojejunostomy (HJ) is the most frequently recommended type of reconstruction.[8–12] End-to-end ductal anastomosis (EE) is used very seldom in the surgical treatment of IBDI. However, this type of reconstruction is performed during hepatic transplantation with good results.[14–16] Some investigators recommend EE because it is more physiological.[16] Reconstruction of bile ducts following iatrogenic injuries is associated with a high risk of stricture recurrence within the anastomosis.[3,11,17] The incidence of recurrent

B. Jabłońska (✉) · P. Lampe · M. Olakowski · Z. Górka · A. Lekstan · T. Gruszka
Department of Digestive Tract Surgery,
University Hospital of the Medical University of Silesia,
Medyków 14 St,
40-752 Katowice, Poland
e-mail: bjablonska@poczta.onet.pl

strictures may depend on the type of reconstruction. Therefore, following these operations, patients require permanent, careful postoperative observation.

The aim of this study was to conduct a retrospective analysis of short- and long-term treatment results and the consequent quality of life in patients with IBDI after two methods of reconstruction; Roux-Y HJ and EE.

Material and Methods

Data Collection

Between January 1990 and March 2005, 138 patients with IBDI received surgery in the Department of Digestive Tract Surgery. Forty-nine (35.5%) Roux-Y HJ, 45 (32.6%) EE, 27 (19.5%) hepaticoduodenostomies with jejunal interposition, six (4.3%) bile duct plastic reconstructions, and 11 (7.9%) other types of reconstruction were performed. Patients with IBDI caused by open and laparoscopic cholecystectomy, choledochotomy, and partial gastric resection were included in this study. Patients with bile duct stricture due to a malignant neoplasm and benign bile duct stricture due to choledocholithiasis, cholangitis, chronic pancreatitis, and tumors of the pancreatic-duodenal area were excluded. The radiological examinations [ultrasonography of the abdominal cavity, cholangiography, endoscopic retrograde cholangiopancreatography (ERCP), computed tomography, and magnetic resonance-cholangiography] were performed in patients before their operation.

Patients' medical records were retrospectively reviewed. Retrospective analysis of the following factors was performed: patients' demographic characteristics, weight and body mass index, kind of initial trauma, duration between the initial trauma and repair procedure, duration of hospitalization, clinical presentation, laboratory investigations before and after surgical procedure (serum bilirubin, alkaline phosphatase, gamma-glutamyltranspeptidase, alanine and aspartate aminotransferases, blood counts, creatinine, and coagulation parameters), American Society of Anesthesiologists (ASA) classification, duration of the operation, postoperative bile duct drainage, early postoperative complications, and reoperations.

The level of IBDI was classified according to the Bismuth classification.[18] Follow-up data were obtained through patient-control visits and by telephone surveys. We had sent letters to all operated patients by postal surveys. A couple of letters were not delivered and turned back because of a change of the address of the recipient. All patients who had answered the letters were invited to the hospital for control visit. Long-term results were estimated on the grounds of medical review, physical examination, and accessory investigations. All patients were asked about their general health status, presence of clinical symptoms (fever, chills, jaundice, abdominal pain), and weight loss. Laboratory investigations (serum bilirubin, alkaline phosphatase, gamma-glutamyltranspeptidase, alanine and aspartate aminotransferases) were performed. The ultrasonography of the abdominal cavity in order to estimate intra- and extrahepatic bile ducts with measurement of the common bile duct (CBD) or common hepatic duct (CHD) diameter was performed. Clinical long-term results were classified with the following clinical grading according to Terblanche.[11] Quality of life was classified according to the Karnofsky Performance Scale.[19]

Information about long-term results was collected from 91 (66%) patients. Because of the number of patients with follow-up data, the exact comparative statistical analysis of two groups, Roux-Y HJ (group 1) and EE (group 2), was performed.

The EE was performed when it was possible to dissect and approximate both the proximal and distal ductal ends without tension. The sutured ends were healthy and without inflammation and ischemia. The diameter of both anastomosed ends was comparable. The anastomosis was not carried out in bile ducts that were too thin (less than 4 mm in diameter). The approximation of both ends was possible because of a wide Kocher maneuver (mobilization of the pancreatic head with the descending, horizontal, and ascending part of the duodenum out of the peritoneum). The maximal length-loss of the bile duct was 4 cm. Both reconstructions were performed when no active inflammation process was present.

The bile ducts were exposed by a laparotomy through the midline. In group 1, the proximal CHD was identified and prepared. The distal CBD was sutured. A Roux-Y jejunal limb, about 40–50 cm long, was prepared for biliary-enteric anastomosis. End-to-side or EE HJ was performed in a single layer using interrupted absorbable polydioxanone (PDS 4–0 or 5–0) sutures. In group 2, extensive mobilization of the duodenum with the pancreatic head through the Kocher maneuver, excision of the bile duct stricture, and refreshment of the proximal and distal stumps were performed. Anastomosis was performed in a single layer with interrupted absorbable PDS 4–0 or 5–0 sutures (Figs. 1, 2).

In most patients of both groups, anastomosis was secured by biliary drainage (external T tube or Rodney–Smith drainage). In some patients of the EE group, an internal Y tube was conducted into the duodenum by the papilla of Vater. The perianastomotic area was drained with closed-suction drains in both groups.

Statistical Analysis

Comparison between groups was performed using Student's *t* test, chi-square test, Fisher's exact test, Mann–Whitney U

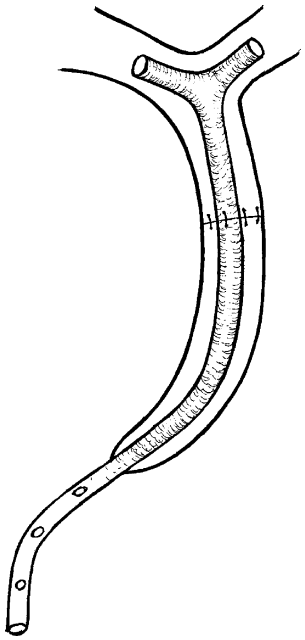

Figure 1 Illustration of the internal drainage of bile ducts in EE.

test, and Wilcoxon test. A Shapiro–Wilk test was used to test for normality of the distribution. Results are reported as the mean ± standard deviation. A p value of <0.05 was considered statistically significant.

Results

An analysis of 94 patients (26 men and 68 women) was performed. There were 49 patients (14 men and 35 women) who had HJ (group 1) and 45 patients (12 men and 33 women) who had EE (group 2). Patient characteristics, initial trauma, previous repair, and presentation are presented in Table 1. Injury classification, ASA classification, type of biliary drainage, duration of hospitalization, and duration of the operation are presented in Table 2. The age, gender, and body mass index were comparable in both groups. The mean total duration of hospitalization and duration of hospitalization from repair to discharge were not significantly longer in patients with HJ than in patients with EE. The mean duration of the operation was comparable in both groups.

The duration and kinds of clinical symptoms were comparable in both groups. Jaundice was the most common clinical symptom in both groups. Other clinical symptoms were abdominal pain, pruritus, fever, cholangitis, cholestasis, biliary fistula, nausea, and vomiting. The duration between the initial trauma and the repair was comparable in both groups. Cholecystectomy was the most frequent cause of biliary injury in both groups.

Both groups included patients who had already undergone a previous repair at an outside hospital before referral. The number of patients who had undergone previous repair was comparable in both groups (p=0.205). The duration between the previous repair and the referral one was comparable in both groups. Before referral, endoscopic biliary stenting was performed in 10 (20.4%) patients in group 1 and in 10 (22.2%) patients in group 2. Before referral, operative biliary drainage was performed in two (4%) patients in group 1 and in two (4.4%) patients in group 2. The duration between biliary drainage and surgical referral repair was comparable in both groups. Bile duct stricture was the most frequent injury in both groups.

The IBDI types in group 1 included bile duct strictures due to an ischemia during open cholecystectomy and clipping during laparoscopic cholecystectomy in 42 (85.7%) patients, bile duct strictures with biliary fistula in four (8.16%) patients, transection in one (2%) patient, excision in one (2%) patient, and ligation of the bile duct in one (2%) patient. In group 2, the IBDI types included bile duct strictures in 38 (84.4%) patients and bile duct strictures accompanied by biliary fistula in seven (15.6%) patients. The level of injury classified according to the Bismuth scale was comparable in both groups (p=0.1094). According to the ASA classification, the majority of the patients in both groups were classified as ASA 1 or 2 (p= 0.5984). Biliary drainage was required in 38 (77.55%) patients undergoing HJ and in 40 (88.89%) patients undergoing EE.

Early Outcome

Early postoperative complications occurred in 12 (24.5%) patients in group 1 and in three (6.7%) in group 2. The number of early postoperative complications was significantly higher in patients undergoing HJ than in patients undergoing EE (p=0.0239). The most frequent early

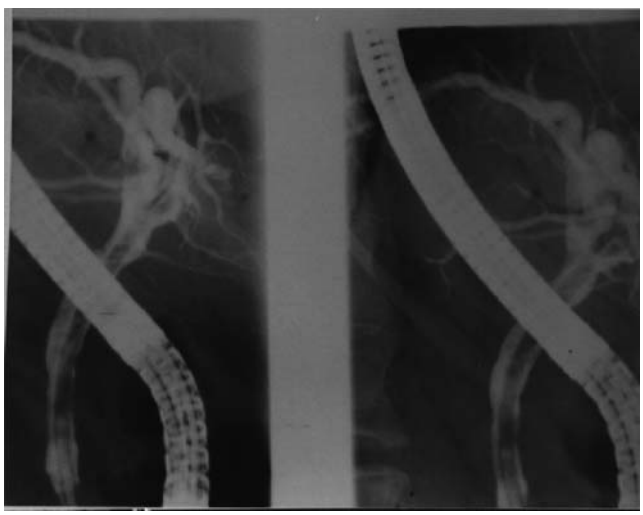

Figure 2 ERCP showing EE secured with Y internal drainage.

Table 1 Patient Characteristics, Initial Trauma, Previous Repair, and Presentation

	HJ	EE	*p*
Patient characteristics			
Age (y)	52.35±15.41 (18–85)	52.84±14.55 (18–82)	0.8727[a]
Female/male	35:14	33:12	0.9804[b]
BMI [kg/m^2]	24.39±3.51 (17.5–33.3)	24.18±2.97 (17.8–32.0)	0.7586[a]
Initial trauma			
Open Chole.	37 (75.5%)	37 (82.2%)	
Lap. Chole.	12 (24.5%)	7 (15.5%)	
Choledochotomy	18 (36.7%)	18 (4.0%)	
Others	0 (0.00%)	1 (2.2%)	
Previous repair	19 (38.7%)	11 (24.4%)	0.2050[b]
Choledochoduodenostomy	6 (12.2%)	6 (13.3%)	
Hepaticojejunostomy	13 (26.5%)	5 (11.1%)	
Presentation			
Icterus	31 (63.27%)	30 (66.67%)	0.8974[b]
Cholangitis	25 (51.02%)	21 (46.67%)	0.8295[b]
Abdominal pain	23 (46.94%)	22 (48.89%)	0.9859[b]
Fever	14 (28.57%)	13 (28.89%)	0.8460[b]
Nausea, vomiting	9 (18.37%)	2 (4.44%)	0.0756[b]
Pruritus	7 (14.29%)	3 (6.67%)	0.3886[b]
Biliary fistula	4 (8.16%)	7 (15.56%)	0.4279[b]
Cholestasis	2 (4.08%)	5 (11.11%)	0.3662[b]
Time from injury to referral (m)	67.00±96.65 (0.3–443.1)	77.41±81.46 (0.3–321.7)	0.1487[c]
Time from previous repair to referral (m)	77.18±94.76 (1.4–301.4)	10.09±7.26 (5.9–18.5)	0.0733[c]
Presentation duration (m)	20.86±33.22 (0.3–144.0)	36.66±66.17 (0.5–332.0)	0.1085[c]
Duration of biliary drainage before referral (d)	183.33±391.75 (11.0–1,225.0)	59.57±45.20 (16.0–149.0)	0.7106[c]
Biliary prothesis time	219.86±444.49 (11.0–1,225.0)	71.20±48.65 (35.0–149.0)	
T drainage time	55.50±17.68 (43.0–68.0)	30.50±20.51 (16.0–45.0)	

HJ hepaticojejunostomy, *EE* end-to-end anastomosis, *y* years, *m* months, *d* days, *BMI* body mass index, *Chole* cholecystectomy, *Lap* laparoscopic

[a] Student's *t* test

[b] Chi-square test

[c] Mann–Whitney U test

complication was wound infection, which was observed significantly more frequently in group 1 (p=0.0317). Early complications and laboratory results are presented in Table 3. In the early postoperative period, reoperations were performed in four (8%) patients with HJ: one was due to biliary-enteric anastomosis dehiscence (on postoperative day 4), one was due to subphrenic abscess (on postoperative day 30), one was due to subphrenic collection (biloma) (on postoperative day 7), and one was due to eventration (on postoperative day 10). Early reoperations were not performed in patients undergoing EE. In patients undergoing HJ, there was one (2%) hospital death because of acute circulatory insufficiency. Cholestasis and liver function parameters were significantly decreased after surgical repair in both groups. There was no difference between hemoglobin level, white blood cell count, serum creatinine, albumin, or prothrombin index before and after surgery in either group.

Long-term Results

Long-term results were analyzed in 69 (72%) patients, including 38 (77.5%) in group 1 and 31 (69%) in group 2 (Table 4). Obtaining follow-up information from 28% of the patients was not possible because communication with them was lost. Patients who were operated on in our department came from all over the country. The mean duration of follow-up was 61.9±58.87 months (range 2.17–199.87) in group 1 and 103±51.23 months (range 2.87–200.17) in group 2. Mean follow-up was significantly longer in group 2, which was associated with the higher number of EE in the earlier years analyzed and the higher

Table 2 Injury Classification, ASA Classification, Type of Biliary Drainage, Duration of Hospitalization, and Duration of Operation

	HJ	EE	*p*
Level of injury			0.1094[a]
Bismuth 1	21 (42.86%)	31 (68.89%)	
Bismuth 2	16 (32.65%)	10 (22.22%)	
Bismuth 3	7 (14.29%)	3 (6.67%)	
Bismuth 4	4 (8.16%)	1 (2.22%)	
Bismuth 5	1 (2.04%)	0 (0.00%)	
ASA classification			0.5984[a]
ASA 1	19 (38.78%)	21 (46.67%)	
ASA 2	23 (46.94%)	18 (40.00%)	
ASA 3	7 (14.29%)	5 (11.11%)	
ASA 4	0 (0.00%)	1 (2.22%)	
Type of biliary drainage			
External T tube	19 (38.78%)	13 (28.89%)	
Internal Y tube	0 (0.00%)	26 (57.78%)	
Rodney–Smith	12 (24.49%)	1 (2.22%)	
Others	7 (14.29%)	0 (0.00%)	
No drainage	11 (22.45%)	5 (11.11%)	
Total hospitalization time (d)	33.83±21.95 (11–135)	26.36±11.67 (10–63)	0.1198[b]
Hospitalization time from repair to discharge (d)	20.43±13.20 (6.0–57.0)	15.51±8.25 (6.0–47.0)	0.1198[b]
Operation duration (h)	4.93±1.98 (2.5–10)	4.11±1.20 (2–7.5)	0.1279[b]

HJ hepaticojejunostomy, *EE* end-to-end anastomosis, *ASA* American Society of Anesthesiologists, *m* months, *d* days

[a] Chi-square test

[b] Mann–Whitney U test

number of HJ in the later years analyzed. The postoperative mean weight gain was significantly higher in patients undergoing EE ($p=0.0191$). Recurrent stricture after the repair requiring surgical or endoscopic treatment was observed in two (5.3%) patients in group 1 and three (9.6%) patients in group 2 ($p=0.6509$). The mean interval between reconstruction and later repair procedures due to recurring biliary stricture was 987.5±520.5 days (2.7 years) in group 1 and 1,399.33±1,041.71 days (3.83 years) in group 2. In patients with HJ, recurrent strictures were treated surgically, with EE (1,518 days after primary repair), and surgical instrumental revision of bile ducts was conducted with biliary stenting using a T tube (467 days after primary repair). In patients with EE, Roux-Y HJ (2,771 days after primary repair), surgical dilatation of the bile duct (1,179 days after primary repair), and endoscopic dilatation by ERCP (248 days after primary repair) were performed. Three patients with EE received additional surgery because of duodenal diverticulum (duodenotomy, 359 days after primary repair), cholangitis (instrumental bile duct revision, 538 days after primary repair), and removal of a drain from the bile duct (choledochotomy, 508 days after primary repair).

General health status, clinical presentation, and CBD or CHD diameter in abdominal ultrasonography were comparable in both groups. Follow-up laboratory results are presented in Table 4. Long-term results classified according to Terblanche were comparable in both groups ($p<0.3173$). The majority of patients were classified as grade I according to Terblanche. Quality of life according to the Karnofsky scale was good and comparable in both groups ($p=0.8377$).

Discussion

IBDIs are still a serious consequence of gastrointestinal surgery. Therefore, effective and safe bile duct reconstruction is very important for patients. In the present study, early postoperative complications were observed in 24.5% of patients in group 1 who received HJ and 6.7% of patients in group 2 who received EE. The most frequent early complication was wound infection, which was observed in 16.3% of patients in group 1 and 2.2% of patients in group 2. A 2% early postoperative mortality rate and an 8% early reoperation rate were observed in group 1, whereas there were no mortalities or early reoperations in group 2. Our results are comparable with others found in the literature.[6,7,10,20–23]

In the groups analyzed, early postoperative morbidity was significantly higher in patients undergoing HJ. The

Table 3 Early Postoperative Complications and Laboratory Results Before and After Repair

	HJ	EE	Laboratory results		*p*
			Before repair	After repair (1week)	
Early complications	12 (24.5%)	3 (6.7%)			0.0239[a]
Abscess	3 (6.12%)	0 (0.00%)			0.2433[a]
Bile leakage	1 (2.04%)	0 (0.00%)			
Cholangitis	2 (4.08%)	0 (0.00%)			
Biloma	4 (8.16%)	3 (6.67%)			0.6455[a]
Peritonitis	1 (2.04%)	0 (0.00%)			
Wound infection	8 (16.33%)	1 (2.22%)			0.0317[a]
Eventration	1 (2.04%)	0 (0.00%)			
Pneumonia	3 (6.12%)	2 (4.44%)			0.9334[a]
Circulatory insufficiency	1 (2.04%)	0 (0.00%)			
In-hospital reoperations	4 (8.00%)	0 (0.00%)			
In-hospital mortality	1 (2.04%)	0 (0.00%)			
Laboratory results					
Bilirubin (mg/dl)					
HJ			3.30±4.63 (0.4–17.7)	2.85±3.30 (0.4–11.2)	0.0134[b]
EE			2.52±3.93 (0.5–20.5)	1.26±1.08 (0.5–4.6)	0.0041[b]
ALT (U/l)					
HJ			137.3±127.53 (9–588)	42.9±27.30 (13–129)	<0.001[b]
EE			103.5±125.18 (16–470)	76.5±62.33 (9–208)	0.0221[b]
AST (U/l)					
HJ			118.5±96.49 (15–340)	46.4±64.24 (16–227)	<0.001[b]
EE			97.9±130.56 (17–388)	52.5±31.82 (30–75)	0.0021[b]
ALP (U/l)					
HJ			394.6±299.7 (40–1,334)	291.3±204.5 (71–867)	0.0233[b]
EE			411.8±333.9 (87–962)	305.3±182.7 (120–597)	0.0152[b]
GGT (U/l)					
HJ			344.5±303.3 (14–1,366)	275.5±217.6 (9–683)	0.0132[b]
EE			500.6±482.6 (66–1,400)	383.7±296.4 (101–911)	0.0019[b]
Hemoglobin (g/dl)					
HJ			12.18±1.46 (9.4–15.4)	9.98±1.32 (8.1–13.2)	0.4465[b]
EE			11.78±1.41 (7.8–14.0)	10.29±1.58 (7.7–13.1)	0.8491[b]
WBC (count/mm^3)					
HJ			8.18±4.46 (3.2–21.2)	8.30±2.73 (3.3–14.4)	0.8765[b]
EE			7.65±3.67 (3.1–19.6)	8.09±2.49 (5.1–15.5)	0.7732[b]
Prothrombin index (%)					
HJ			88.8±15.02 (45.0–112.9)	84.5±15.58 (50.0–108.5)	0.8112[b]
EE			95.8±8.73 (78.0–115.3)	92.5±11.73 (70.0–100.0)	0.7748[b]
Creatinine (g/dl)					
HJ			0.83±0.21 (0.5–1.6)	0.78±0.24 (0.5–1.5)	0.9092[b]
EE			0.91±0.34 (0.3–2.2)	0.87±0.33 (0.6–1.9)	0.8712[b]

HJ hepaticojejunostomy, *EE* end-to-end anastomosis, *ALT* alanine transaminase, *AST* aspartate transaminase, *ALP* alkaline phosphatase, *GGT* gamma-glutamyltranspeptidase, *WBC* white blood cells

[a] Fisher exact test

[b] Wilcoxon test

Table 4 Long-term Results

	HJ	EE	*p*
General health status			0.2174[a]
Good	34 (89.47%)	29 (93.55%)	
Fair	3 (7.89%)	0 (0.00%)	
Poor	1 (2.63%)	2 (6.45%)	
BMI in FU (kg/m^2)	68.98±17.00 (42–106)	74.82±8.70 (62–95)	0.0653[b]
BMI difference between before repair/FU values	−4.08±9.08 (−19.0–15.0)	11.13±8.00 (−27.0–0.0)	0.0191[b]
Clinical symptoms			
Fever	10 (26.32%)	6 (19.35%)	0.5742[c]
Chills	9 (23.68%)%	4 (12.90%)	0.3568[c]
Icterus	3 (7.89%)	0 (0.00%)	0.2468[c]
Abdominal pain	4 (10.53%)	1 (3.23%)	0.3697[c]
Laboratory results			
Bilirubin (mg/dl)	0.68±0.26 (0.3–1.5)	0.73±0.30 (0.1–1.1)	0.1742[b]
ALT (U/l)	32.18±17.26 (12.0–74.0)	23.36±11.08 (13.0–53.0)	0.1232[b]
AST (U/l)	32.21±12.87 (15.0–63.0)	24.11±7.85 (10.0–39.0)	0.0799[b]
ALP (U/l)	255.86±355.14 (64.0–1,310.0)	84.59±41.65 (43.7–206.0)	0.0065[b]
GGT (U/l)	123.48±106.65 (13.0–370.5)	39.09±26.49 (11.0–97.0)	0.0195[b]
CBD/CHD diameter (mm)	7.40±3.12 (3.0–13.0)	7.18±2.01 (5.0–13.0)	0.8928[b]
Biliary anastomosis stricture	2 (5.26%)	3 (9.68%)	0.6509[b]
Terblanche clinical grading			<0.3173[a]
I—excellent result	22 (57.89%)	22 (70.97%)	
II—good result	8 (21.05%)	2 (6.45%)	
III—fair result	6 (15.79%)	4 (12.90%)	
IV—poor result	2 (5.26%)	3 (9.68%)	
Karnofsky scale			0.8377[a]
100	14 (36.84%)	12 (38.71%)	
90	8 (21.05%)	7 (22.58%)	
80	8 (21.05%)	7 (22.58%)	
70	5 (13.16%)	2 (6.45%)	
60	2 (5.26%)	3 (9.68%)	
50	0 (0.00%)	0 (0.00%)	
40	1 (2.63%)	0 (0.00%)	
30	0 (0.00%)	0 (0.00%)	
20	0 (0.00%)	0 (0.00%)	
10	0 (0.00%)	0 (0.00%)	

HJ hepaticojejunostomy, *EE* end-to-end anastomosis, *BMI* body mass index, *FU* follow-up, *ALT* alanine transaminase, *AST* aspartate transaminase, *ALP* alkaline phosphatase, *GGT* gamma-glutamyltranspeptidase, *WBC* white blood cells, *CBD* common bile duct, *CHD* common hepatic duct

[a] Chi-square test

[b] Mann–Whitney U test

[c] Fisher exact test

higher number of early postoperative complications may be due to the more complex procedure associated with HJ, which requires cutting open the alimentary tract and performing a greater number of anastomoses (biliary-enteric and entero-enteric). These procedures are associated with a higher risk of early postoperative complications. Opening of the alimentary tract is not necessary during EE. Therefore, the duration of the surgical procedure is shorter and the number of early complications is lower. The surgical procedure is limited to the bile ducts, which is associated with earlier recovery and fewer early complications. Our results show that EE is a safer surgical procedure and associated with a lower risk of complications in the early postoperative period. Total duration of hospitalization

(33.31 vs. 26.07 days, respectively) and duration of hospitalization after repair procedure (20.43 vs. 15.51 days, respectively) were not significantly longer in patients undergoing HJ vs. EE. Although the difference was not statistically significant, it supports the theory that HJ is a more complex procedure in comparison with EE.

Biliary drainage was performed in most patients in both analyzed groups. It was not performed in 22.4% of patients in group 1 and 11.2% in group 2. Biliary-enteric anastomosis was most frequently secured by external T tube (38.7%), and EE was most commonly splinted by internal Y tube (57.7%). The internal drainage was removed endoscopically. Drainage tubes were most frequently removed 3 months after the repair procedure.

The use of and duration of biliary drainage is controversial. The advantage of biliary drainage is to limit the inflammation and fibrosis that occur after the surgical procedure. Therefore, some investigators believe that the presence of the biliary tube prevents anastomosis stricture.[22] The disadvantage of biliary drainage is that it causes a higher risk of postoperative complications.[24] Mercado et al.[24] recommend using transanastomotic stents when there is a thin bile duct less than 4 mm in diameter and when there is inflammation within the ductal anastomosed edges that makes proper healing of the anastomosis questionable. The time duration of drainage is also controversial. According to most studies, the optimal length of time for biliary drainage is about 3 months. Longer durations of biliary drainage do not provide a greater advantage.[8] The internal biliary drainage that was performed in the analyzed group was very safe and effective, was not associated with an increased risk of postoperative complications, and induced proper healing of the anastomosis.

Long-term results are essential in the surgical treatment of IBDI. An absence of biliary anastomosis stricture is proof of successful surgical management. In specialist centers, a successful outcome after surgical bile duct repair is observed in 70–90% of patients.[3,5,12] According to the literature, two-thirds (65%) of recurrent biliary strictures develop within 2–3 years after the reconstructive procedure, 80% within 5 years, and 90% within 7 years. Recurrent strictures 10 years after the reconstruction have been reported.[3,6,25] Satisfactory length of follow-up, which is necessary in order to assess the long-term results of the repair procedure, is 2 to 5 years.[6,8] Some authors even recommend 10 or 20 years of observation.[9,11] The mean length of follow-up in most series is several years (from several months to many years).[26–29] In the present study, the mean follow-up was 61.9 months following HJ, and 103.18 months following EE. Excellent and good long-term results (grades I and II according to Terblanche) were achieved in 78.94% of patients undergoing HJ and in 77.42% of patients undergoing EE. The results in both analyzed groups were comparable and compatible with a high quality of life in both groups.

Most authors prefer Roux-Y HJ due to the lower number of postoperative anastomosis strictures. According to Terblanche et al.,[11] biliary-enteric anastomosis is effective in 90% of cases. According to Rossi and Tsao,[30] long-term results of EE are worse due to the higher stricture rate of 40–50%. However, after HJ method of reconstruction, bile flow into the alimentary tract is not physiological because the duodenum and upper part of the jejunum are excluded from bile passage. As a result of duodenal exclusion from bile passage, physiological conditions within the proximal gastrointestinal tract are changed. An altered bile pathway causes disturbances in the release of gastrointestinal hormones.[31]

There is a hypothesis that, in patients with HJ, the bile bypass induces gastric hypersecretion, leading to a pH change secondary to altered bile synthesis and release of gastrin. Duodenal ulcers are more frequently reported in the postoperative period following HJ, which may be caused by a loss of the neutralizing effect of the bile, including bicarbonates and the secondary gastric hypersecretion.[32] Increased gastrin and glucagon-like immunoreactivity plasma levels and decreased triglycerides, gastric inhibitory polypeptide, and plasma insulin levels were observed in patients following HJ.[33] An altered pathway of bile flow is also a cause of disturbance in fat metabolism.[32,33] The total surface of absorption is also decreased due to the exclusion of the duodenum and the upper jejunum from the passage of food. Also, in our study, significant weight gain was observed in patients undergoing EE. This type of reconstruction establishes physiological bile flow into the duodenum through the intact papilla of Vater. In some patients, extensive mobilization of the duodenum with the pancreatic head by the Kocher maneuver allows to perform tension-free anastomosis after the extensive length-loss of the bile duct. Excision of the bile duct stricture, dissection and refreshing of the proximal and distal stumps as far as the tissues are healthy and without inflammation, and the use of nontraumatic, monofilament-interrupted sutures 5–0 allows the achievement of good long-term results. The method of security with an internal Y tube conducting the hepatic ducts from the right and left into the duodenum through EE and the papilla of Vater also allows for the proper healing of the anastomosis. In our department, this reconstruction was performed when the bile duct loss was from 0.5 to 4 cm. It allowed the achievement of very good long-term results with effectiveness comparable with HJ. Establishing a physiological bile pathway allows proper digestion and absorption. Also, control endoscopic examination in these patients is possible. Therefore, some authors first recommend EE as the most physiological choice, if possible.[14]

Gazzaniga et al.[34] performed EE in the immediate repair procedures only when the injury did not exceed one-third of the duct circumference and was not located more than 2 cm below the ductal confluence, or when injury was detected during the primary operation. Reuver et al.[35] recommend EE in preoperative-detected injuries when there was no extensive tissue loss. Kohneh et al.[36] achieved a higher effectiveness with EE (100%) than with HJ (71.4%) when used during early repair procedures (less than 30 days following the initial trauma).

This study emphasizes that it is possible to achieve very good long-term results and high quality of life using both HJ and the EE. The lower number of early postoperative complications after EE is also favorable. We recommend this type of reconstruction in the treatment of IBDI when it is possible to perform it. We recommend this repair for patients when it is possible to dissect and approximate both the proximal and distal ductal ends without tension. In our material, the maximal length-loss of the bile duct was 4 cm. The sutured ends had to be healthy and without inflammation and ischemia. The diameter of both anastomosed ends was comparable. If there was a difference between the diameters of the anastomosed ends, the thinner end was incised longitudinally in the anterior surface in order to extend it. EE repair was not carried out in bile ducts that were too thin (diameter less than 4 mm). In our opinion, a patient on whom we perform first or exceptionally second bile duct repair is a candidate for EE. HJ was performed in patients who did not follow the criteria mentioned above.

References

1. Archer SB, Brown DW, Smith CD, Branum GD, Hunter JG. Bile duct injury during laparoscopic cholecystectomy. Results of a national survey. Ann Surg 2001;234:549–559. doi:10.1097/00000658-200110000-00014.
2. Negi SS, Sakhuja P, Malhotra V, Chaudhary A. Factors predicting advanced hepatic fibrosis in patients with postcholecystectomy bile duct strictures. Arch Surg 2004;139:299–303. doi:10.1001/archsurg.139.3.299.
3. Pellegrini CA, Thomas MJ, Way LW. Recurrent biliary stricture: patterns of recurrence and outcome of surgical therapy. Am J Surg 1984;147:175–180. doi:10.1016/0002-9610(84)90054-0.
4. Tocchi A, Mazzoni G, Liotta G, Lepre L, Miccini M, De Masi E, Lamazza MA, Fiori E. Management of benign biliary strictures. Arch Surg 2000;135:153–157. doi:10.1001/archsurg.135.2.153.
5. Davids P, Tanka A, Rauws E, van Gulik TM, van Leeuwen DJ, de Wit LT, Verbeek PC, Huibregtse K, van der Heyde MN, Tytgat GN. Benign biliary strictures. Surgery or endoscopy? Ann Surg 1993;217:237–243. doi:10.1097/00000658-199303000-00004.
6. Hall JG, Pappas TN. Current management of biliary strictures. J Gastrointest Surg 2004;8:1098–1110. doi:10.1016/j.gassur.2004.04.011.
7. Sicklick JK, Camp MS, Lillemoe KD, Melton GB, Yeo CJ, Campbell KA, Talamini MA, Pitt HA, Coleman J, Sauter PA, Cameron JL. Surgical management of bile duct injuries sustained during laparoscopic cholecystectomy. Perioperative results in 200 patients. Ann Surg 2005;241:786–795. doi:10.1097/01.sla.0000161029.27410.71.
8. Lillemoe KD, Melton GB, Cameron JL, Pitt HA, Campbell KA, Talamini MA, Sauter PA, Coleman J, Yeo CJ. Postoperative bile duct strictures: management and outcome in the 1990s. Ann Surg 2000;232:430–441. doi:10.1097/00000658-200009000-00015.
9. Tocchi A, Costa G, Lepre L, Liotta G, Mazzoni G, Sita A. The long-term outcome of hepaticojejunostomy in the treatment of benign bile duct strictures. Ann Surg 1996;224:162–167. doi:10.1097/00000658-199608000-00008.
10. Ahrendt S, Pitt H. Surgical therapy of iatrogenic lesions of biliary tract. World J Surg 2001;25:1360–1365. doi:10.1007/s00268-001-0124-2.
11. Terblanche J, Worthley C, Krige J. High or low hepaticojejunostomy for bile duct strictures? Surgery 1990;108:828–834.
12. Chaudhary A, Chandra A, Negi SS, Sachdev A. Reoperative surgery for postcholecystectomy bile duct injuries. Dig Surg 2002;19:22–27. doi:10.1159/000052001.
13. Blumgart LH. Hilar and intrahepatic biliary enteric anastomosis. Surg Clin North Am 1994;74:731–740.
14. Yamamoto S, Sato Y, Oya H, Nakatsuka H, Kobayashi T, Hara Y, Waguri N, Suda T, Aoyagi Y, Hatakeyama K. Risk factors and prevention of biliary anastomotic complications in adult living donor liver transplantation. World J Gastroenterol 2007;13:4236–4241.
15. Ishiko T, Egawa H, Kasahara M, Nakamura T, Oike F, Kaihara S, Kiuchi T, Uemoto S, Inomata Y, Tanaka K. Duct-to-duct biliary reconstruction in living donor liver transplantation utilizing right lobe graft. Ann Surg 2002;2:235–240. doi:10.1097/00000658-200208000-00012.
16. Górka Z, Ziaja K, Wojtyczka A, Kabat J, Nowak J. End-to-end anastomosis as a method of choice In surgical treatment of selected cases of biliary handicap. Pol J Surg 1992;64:977–979.
17. Bismuth H, Franco D. Long term results of Roux-en-Y hepatico-jejunostomy. Surg Gynecol Obstet 1978;146:161–167.
18. Bismuth H, Majno PE. Biliary strictures: classification based on the principles of surgical treatment. World J Surg 2001;25:1241–1244. doi:10.1007/s00268-001-0102-8.
19. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The use of nitrogen mustards in the palliative treatment of carcinoma. Cancer 1948;1:634–656. doi:10.1002/1097-0142(194811)1:4<634::AID-CNCR2820010410>3.0.CO;2-L.
20. Sikora SS, Pottakkat B, Srikanth G, Kumar A, Saxena R, Kapoor VK. Postcholecystectomy benign biliary strictures—long-term results. Dig Surg 2006;23:304–312. doi:10.1159/000097894.
21. McDonald ML, Farnell MB, Nagorney DM, Ilstrup DM, Kutch JM. Benign biliary strictures: repair and outcome with contemporary approach. Surgery 1995;118:582–591. doi:10.1016/S0039-6060(05)80022-4.
22. Schmidt SC, Langrehr JM, Hintze RE, Neuhaus P. Long-term results and risk factors influencing outcome of major bile duct injuries following cholecystectomy. Br J Surg 2005;92:76–82. doi:10.1002/bjs.4775.
23. Robinson TN, Stiegmann GV, Durham JD, Johnson SI, Wachs ME, Serra AD, Kumpe DA. Management of major bile duct injury associated with laparoscopic cholecystectomy. Surg Endosc 2001;15:1381–1385.
24. Mercado MA, Chan C, Orozco H, Cano-Gutiérrez G, Chaparro JM, Galindo E, Vilatobá M, Samaniego-Arvizu G. To stent or not to stent bilioenteric anastomosis after iatrogenic injury: a Dilemma not answered? Surgery 2002;137:60–63.
25. Pitt HA, Miyamoto T, Parapatis SK, Tompkins RK, Longmire WP Jr. Factors influencing outcome in patients with postoperative

biliary strictures. Am J Surg 1982;144:14–21. doi:10.1016/0002-9610(82)90595-5.
26. Kozicki I, Bielecki K. Hepaticojejunostomy in benign biliary stricture—influence of careful postoperative observations on long-term results. Dig Surg 1997;14:527–533. doi:10.1159/000172604.
27. Connor S, Garden OJ. Bile duct injury in the era of laparoscopic cholecystectomy. Br J Surg 2006;93:158–168. doi:10.1002/bjs.5266.
28. Kozicki I, Bielecki K, Kowalski A, Krolicki L. Repeated reconstruction for recurrent benign bile duct stricture. Br J Surg 1994;81:677–679. doi:10.1002/bjs.1800810515.
29. Lillemoe KD, Martin SA, Cameron JL, Yeo CJ, Talamini MA, Kaushal S, Coleman J, Venbrux AC, Savader SJ, Osterman FA, Pitt HA. Major bile duct injuries during laparoscopic cholecystectomy. Follow-up after combined surgical and radiologic management. Ann Surg 1997;225:459–471. doi:10.1097/00000658-199705000-00003.
30. Rossi RL, Tsao JI. Biliary reconstruction. Surg Clin North Am 1994;74:825–841.
31. Rudnicki M, McFadden DW, Sheriff S, Ischer JE. Roux-en-Y jejunal Bypass abolishes postprandial neuropeptide Y release. J Surg Res 1992;53:7–11. doi:10.1016/0022-4804(92)90004-J.
32. Nielsen MK, Jensen SL, Malstrom J, Niwlsen OV. Gastryn and gastric acid secretion in hepaticojejunostomy Roux-en-Y. Surg Gynecol Obstet 1980;150:61–64.
33. Imamura M, Takahashi M, Sasaki I, Yamauchi H, Sato T. Effects of the pathway of bile flow on the digestion of FAT and the release of gastrointestinal hormones. Am J Gastroenterol 1988;83:386–392.
34. Gazzaniga GM, Filauro M, Mori L. Surgical treatment of iatrogenic lesions of the proximal common bile duct. World J Surg 2001;25:1254–1259. doi:10.1007/s00268-001-0105-5.
35. Reuver PR, Bush ORC, Rauws EA, Lameris JS, van Gulik TM, Gouma DJ. Long-term results of a primary end-to-end anastomosis in peroperative detected bile duct injury. J Gastrointest Surg 2007;11:296–302. doi:10.1007/s11605-007-0087-1.
36. Kohneh SN, Lasnier C, Paineau J. Bile duct injuries at laparoscopic cholecystectomy: early repair results. Ann Chir 2005;130:218–223. doi:10.1016/j.anchir.2004.12.016.

J Gastrointest Surg (2009) 13:1094–1098
DOI 10.1007/s11605-009-0828-4

ORIGINAL ARTICLE

A Single-Institution Experience with Eight CD117-Positive Primary Extragastrointestinal Stromal Tumors: Critical Appraisal and a Comparison with Their Gastrointestinal Counterparts

Brian K. P. Goh · Pierce K. H. Chow · Sittampalam M. Kesavan · Wai-Ming Yap · Yaw-Fui A. Chung · Wai-Keong Wong

Received: 28 December 2008 / Accepted: 28 January 2009 / Published online: 24 February 2009

Abstract
Introduction Gastrointestinal stromal tumors (GISTs) arising from outside the gut wall also termed extragastrointestinal stromal tumors (EGISTs) are reported to be rare. Presently, their pathogenesis remains controversial, and recently, it has been proposed that EGISTs may be the result of extensive extramural growth of GISTs which lose contact with the gut wall. This study presents a single-institution experience with eight EGISTs and compares their clinicopathological features with mural GISTs in order to determine further insight to their possible origin.
Methods Between 1997 and 2008, 156 patients with pathologically proven CD117-positive primary GISTs were retrospectively reviewed. Eight tumors were identified as EGISTs, 104 were gastric GISTs, and 44 were small-bowel GISTs. Mural GISTs were classified as extramural or intra/transmural according to their gross pattern of growth.
Results There were five male and three female patients with a median age of 58 years (range, 42–81 years). All patients were symptomatic, and the tumors were located in the greater omentum (n=2), lesser sac (n=2), lesser omentum, retroperitoneum, small-bowel mesentery, and pancreas. The median tumor size was 140 mm (range, 55 to 220 mm). Seven of eight EGISTs were found to be in close association to the adjacent gut wall. Pathological examination demonstrated that two tumors demonstrated focal involvement of the muscularis propria of the adjacent gut wall. Four tumors demonstrated tumor abutting or adherent to the serosa but no muscle involvement and one tumor was separated from the serosa. Comparison between the clinicopathological features of EGISTs with extramural GISTs and intra/transmural GISTs demonstrated that EGISTs were significantly larger [140 range (55–220) mm vs 80 (5–260) mm vs 50 (15–190) mm, P=0.049, P<0.001 respectively].
Conclusion The occurrence of true EGISTs is rare. Most cases demonstrate some form of communication or contact with the gut wall, and EGISTs are significantly larger than extramural or intra/transmural GIST. These observations suggest that most, if not all, cases of EGISTs are likely to represent mural GISTs with extensive extramural growth with eventual loss of contact with the muscle layer of the gut.

B. K. P. Goh · P. K. H. Chow (✉) · Y.-F. A. Chung · W.-K. Wong
Department of Surgery, Singapore General Hospital,
Singapore, Singapore
e-mail: gsupc@singnet.com.sg

B. K. P. Goh
e-mail: bsgkp@hotmail.com

P. K. H. Chow
Duke-NUS Graduate Medical School,
Singapore, Singapore

S. M. Kesavan · W.-M. Yap
Department of Pathology, Singapore General Hospital,
Singapore, Singapore

Keywords Gastrointestinal stromal tumor · GIST · Extragastrointestinal stromal tumor · EGIST · Omentum · Mesentery

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract.[1] These may arise from any part of the gastrointestinal tract whereby the stomach and small intestine are by far the most

common sites.[2] Recently, mesenchymal tumors arising from extragastrointestinal sites such as the retroperitoneum, omentum, and mesentery with similar clinicopathological and molecular genetic profiles[3] similar to GISTs have been reported in the literature.[4–6] These have been termed extragastrointestinal stromal tumors (EGISTs). Isolated cases of EGISTs have also been reported at unusual sites such as the gallbladder,[7,8] liver,[9] and pancreas.[10]

CD117 (the protein product of the c-kit protooncogene) is a transmembrane receptor expressed in many cells including hematopoietic stem cells, mast cells, and germ cells.[11] It is also found in interstitial cells of Cajal (ICCs) which are pacemaker cells located in the muscular layers of the gastrointestinal tract. Based on present understanding, GISTs are widely believed to arise from ICCs as they share many characteristics with these cells including the strong expression of CD117 and CD34 and that they arise from the muscular layer of the gastrointestinal tract.[12,13]

The existence of primary EGISTs has led some investigators to question this hypothesis. This is because although ICCs have been reported to occur in the pancreas,[14] thus far it has not been convincingly demonstrated to arise at other sites outside the gastrointestinal tract.[3,11] These investigators have instead proposed that GISTs and EGISTs may arise from a common precursor cell of ICC and smooth muscle which may account for their growth from and outside the gastrointestinal tract. On the other hand, other investigators have proposed a simpler explanation accounting for the occurrence of EGISTs suggesting that these are in actual fact mural GISTS with extensive extramural growth resulting in eventual loss of their connection with the gut wall.[3]

Presently, despite numerous studies reporting on GISTs arising from the gastrointestinal tract, there have been limited studies specifically addressing EGISTs with the exception of small case reports.[1,3,6,11] To the best of our knowledge, to date only six series on EGISTs[1–3,6,11,15] have been reported in the English literature of which five[1–3,6,11] were multi-institution pathological studies. Hence, these studies were frequently limited by the lack of information available on clinical and in particular intraoperative findings. The aim of the present study is to report on a single-institution experience with EGISTs to determine its incidence and to compare its clinicopathological features with typical GISTs in order to provide further insight into their possible origin. Similar to the proposal of Agaimy and Wunsch,[3] we hypothesize that true EGISTs are very rare, and their occurrence is likely a result of extensive extramural growth of mural GISTs.

Methods

Between 1997 and 2008, all patients who underwent surgery at the Department of Surgery, Singapore General Hospital for a primary intra-abdominal or retroperitoneal mesenchymal tumor were identified from a prospectively maintained surgical database. All patient data were subsequently obtained retrospectively from the clinical, radiological, and pathological records. This study was approved by the Singapore General Hospital Institutional Review Board. Pathological specimens of tumors resected before 2002 (when CD117 staining was not routinely performed) were retrieved and were reviewed by either one of two pathologists who have a special interest in GIST as described in our previous study.[16] Immunohistochemistry with CD117, CD34, desmin, smooth muscle actin, and S100 were performed on these specimens to enable accurate diagnosis. Tumors arising from the colon were excluded, and overall, 156 CD117-positive primary tumors were classified as GISTs according to current standard criteria.[17] Of these, eight (5.1%) tumors were reported to have arisen primarily from outside the gastrointestinal tract. These tumors were diagnosed as EGISTs and the focus of the present study.

The mural GISTs were classified as extramural if these bulged outward from the stomach without mucosal involvement, transmural if these bulged outward but had mucosal involvement, and intramural if these bulged inward.[18] Subsequently, we compared the clinicopathological characteristics of EGIST with extramural and intra/transmural GISTs. All statistical analyses were conducted using the computer program Statistical Package for Social Sciences for Windows, version 10.0 (SPSS, Chicago, IL, USA). Univariate analyses were performed using Mann–Whitney U tests and chi-square tests as appropriate. Actuarial survival was calculated using the Kaplan–Meier method. All tests were two-sided, and $P<0.05$ was considered statistically significant.

Results

Of the 156 CD117-positive GISTs, 8 were reported as EGISTs, 104 were gastric GISTs, and 44 were small-bowel GISTs. Mural GISTs were classified as extramural in 52 or intramural in 49 and transmural in 47. The clinicopathological features of the eight patients with EGISTs are summarized in Tables 1, 2, and 3. All patients were symptomatic, and the tumors were located in the greater omentum ($n=2$), lesser sac ($n=2$), lesser omentum, retroperitoneum, small bowel mesentery, and pancreas.

Seven of eight EGISTs were found to be in close association to the adjacent gut wall. Pathological examination revealed that two tumors (patients 1 and 5) demonstrated focal involvement of the muscularis propria of the adjacent gut wall. Four tumors (patients 2, 4, 6, and 7) demonstrated tumor abutting or adherent to the serosa but no muscle involvement. One tumor (patient 8) was separated from the

Table 1 Clinicopathological Features of the Eight Patients with Apparent EGISTs

Case	Age/ sex	Size (mm)	Predominant site and attachments at surgery	Pathological correlation	Presentation	Surgery
1	57/F	220	Retroperitoneum attached to bladder and SI	Focal invasion into muscularis propria of SI	Abdominal discomfort and mass, 1 m	En bloc resection with cuff of bladder and SI resection
2	47/M	140	SI mesentery attached to LI mesentery	Adherent to serosa of SI but no involvement of muscle layer	Abdominal pain, mass, loss of weight and anemia, 3 m	En bloc resection with SI resection and right hemicolectomy
3	58/F	55	Lesser omentum	No bowel involvement	Abdominal discomfort and loss of weight, 1 m	Resection of lesser omentum
4	58/M	90	Pancreas attached to duodenum	Tumor within pancreas involving duodenal subserosal fat but no involvement of muscle layer	Incidental	Pancreaticoduodenectomy
5	60/F	140	Lesser sac attached to stomach, pancreas and transverse colon mesentery	Tumor abutting pancreas with focal involvement of gastric muscularis propria	Abdominal pain	En bloc resection with subtotal gastrectomy, subtotal pancreatectomy, splenectomy and segmental colectomy
6	69/M	215	Greater omentum	Tumor in greater omentum adherent to gastric serosa	Abdominal mass	Omentectomy and wedge resection of stomach (synchronous 15 mm gastric GIST)
7	81/M	220	Greater omentum attached to stomach and transverse colon	Tumor adherent to serosa of stomach and colon but not muscle layer	Abdominal discomfort	Omentectomy, distal gastrectomy and transverse colectomy
8	41/M	110	Lesser sac attached to stomach	Tumor separate from gastric serosa	Abdominal discomfort	Wedge resection of stomach

M male, *F* female, *m* months, *SI* small intestine

gastric serosa. Immunohistochemistry revealed that CD117 was positive in eight, CD34 in six, smooth muscle actin in two, S100 in one, and desmin in none of the patients. The eight patients had a median follow-up time of 20 (range 1–120) months. The actuarial mean recurrence-free survival was 98 (95% confidence interval, 60–136) months.

Comparison between the clinicopathological features of EGISTs (Table 3) with intra/transmural GISTs demonstrated that EGISTs were significantly larger and more likely to demonstrate tumor necrosis. EGISTs were also significantly larger (albeit less markedly) than extramural GISTs.

Discussion

Recently, Agaimy and Wunsch[3] reported that most cases of supposed EGISTs were most likely mural GISTs with extensive extramural growth resulting in minimal or loss of communication with muscularis propria of the gut wall. These communications may have been missed or lost during surgical or postoperative manipulation. They further proposed that true EGISTs were likely to be GISTs which grew extramurally and eventually lost their connection with the muscular layer of the gastrointestinal tract after attaining

Table 2 Pathological Features and Outcome of Eight Patients with EGISTs

Case	Cell type	Mitotic count, per 50 hpf	NIH risk criteria	Follow-up	Outcome
1	Spindle	>10	High	42 m	Alive with disease
2	Mixed	>10	High	27 m	Disease-free
3	Spindle	<5	Intermediate	6 m	Disease-free
4	Spindle	>10	High	58 m	Disease-free
5	Spindle	<5	High	12 m	Disease-free
6	Mixed	5–10	High	3 m	Disease-free
7	Spindle	>10	High	2 w	Postoperative mortality
8	Spindle	0	High	120 m	Disease-free

m months, *w* weeks, *hpf* high power field

Table 3 Comparison Between the Clinicopathological Features of Eight EGISTs vs 52 Extramural and 96 Intra/Transmural GISTs

	EGIST	Extramural	Intra/transmural	*P* value[a]	*P* value[b]
Number	8	52	96		
Median age (years)	58 (42–81)	61 (32–92)	62 (32–85)	0.656	0.600
Sex, male	5 (63%)	30 (58%)	55 (57%)	0.797	0.775
Symptom	8 (100%)	37 (71%)	81 (84%)	0.079	0.227
Size≥100 mm	6 (75%)	21 (40%)	15 (16%)	0.067	**<0.001**
Median size (mm)	140 (55–220)	80 (5–260)	50 (15–190)	**0.049**	**<0.001**
Mitotic count (≥5/50 hpf)	5 (63%)	23 (44%)	40 (42%)	0.335	0.253
NIH prognostic index				0.408	0.057
Very low	0	2 (4%)	2 (2%)		
Low	0	8 (15%)	31 (32%)		
Intermediate	1 (13%)	12 (23%)	26 (27%)		
High	7 (88%)	30 (58%)	37 (39%)		
Necrosis	6 (75%)	28 (54%)	36 (38%)	0.243	**0.038**
Pleomorphism	3 (38%)	16 (31%)	21 (22%)	0.703	0.314
Cell type				0.422	0.529
Spindle	6 (75%)	41 (79%)	76 (79%)		
Mixed	2 (25%)	6 (12%)	7 (7%)		
Epitheloid	0	5 (10%)	13 (14%)		

hpf high power field

[a] Comparison between EGISTs and extramural GISTs

[b] Comparison between EGISTs and intra/transmural GISTs

a large size. In their study of 14 apparent EGISTs, eight were reclassified as mural GISTs as these demonstrated some focal contact to the bowel wall, and two were found to be recurrent metastastic GISTs. Only three of the 14 apparent EGISTs or 1.5% of their cohort of 200 GISTs did not demonstrate any form of contact with the gut wall.

In the present study, we too found that six of eight cases of EGISTs demonstrated some form of communication or contact with the gut wall. Four tumors were demonstrated pathologically to be abutting or adherent to the serosal layer without communication with the muscle layer. In two patients, careful pathological examination demonstrated a focal communication to the small bowel and gastric muscularis propria, respectively. Comparison between the clinicopathological features of EGISTs and mural GISTs demonstrated that both were essentially similar. The only difference detected was that EGISTs were significantly much larger and demonstrated an increased frequency of tumor necrosis (which is likely the result of their larger size) compared to transmural or intramural GISTs. EGISTs also tended to be larger (albeit less marked) than extramural GISTs.

These observations as a whole seem to support the hypothesis of Agaimy and Wunsch[3] that most if not all reported EGISTs were likely to be mural GISTs with extensive extramural growth. As most of the previous studies of EGISTs[1,2,6,11] reported in the literature were pathological series with cases from multiple institutions without good correlation with clinical and operative findings, important information regarding focal communication with the gastrointestinal tract were very likely to be not readily available.. Hence, it is very likely that many of these cases of reported EGISTs may have demonstrated some form of communication with the gastrointestinal tract which was not detected at pathological examination. Furthermore, some of these may have even represented cases of peritoneal metastases (omental and mesenteric) metastases.[3]

The tumors in our study seem to be in various stages in their evolution towards forming EGISTs. GISTs with extensive extramural growth progressively lose most of their contact with the muscularis propria and, when resected at this stage, demonstrate only a small focal communication with the muscle layer (patients 1 and 5). Further growth results in total loss of communication with the muscle layer with only involvement of the subserosa (patient 4) and eventually only serosa which may be seen pathologically as tumor adherent to or abutting the serosa (patients 1, 2, 6, and 7). Finally, all contact with the gut wall may be lost (patients 3 and 8).

However, despite our observations, one may argue that larger size and adherence to the gut cannot be used to solely support the hypothesis by Agaimy and Wunsch.[3] The larger tumor size observed in EGIST compared to intramural and transmural GISTs may be attributed primarily to their extramural location. Patients with EGISTs like extramural GISTs tend to present late when the tumors have grown to a considerable size with clinical features such as abdominal discomfort, distension, and mass. On the other hand, intramural and transmural GIST tend to present earlier with occult or gross gastrointestinal bleed. Adherence or even invasion to the adjacent gut wall is also not uncommonly

seen with other large intra-abdominal tumors such as retroperitoneal sarcomas and does not necessarily imply that these tumors originated from the gut wall. Nonetheless, the larger size of EGIST compared to even extramural GISTs in our study suggest that the EGISTs probably arose after extensive extramural growth.

Numerous observations reported in the literature provide further evidence to support this "extensive extramural growth" hypothesis. In 2004, Yamamoto et al. reported that EGISTs share similar KIT mutations to typical GISTs which suggest that these tumors have a similar origin.[1] The results from the Armed Forces Institute of Pathology[11] which demonstrated that omental EGISTs share many histological similarities with gastric GISTs and have a better prognosis than mesenteric EGISTs which share the characteristics of intestinal GISTs[11] also provide further support for this hypothesis.[3] Presently, it is widely accepted that gastric GISTs in general have a better prognosis than intestinal GISTs,[16,19] and hence, it is logical to presume that omental EGISTs arise from gastric GISTs, whereas mesenteric EGISTs arise from small bowel.

In conclusion, this study illustrates that the occurrence of true EGISTs is extremely rare. Most cases demonstrate some form of communication or contact with the gut wall, and EGISTs are significantly larger than extramural or intra/transmural GIST. These observations suggest that most cases of EGISTs are likely to represent mural GISTs with extensive extramural growth eventually resulting in loss of contact with the muscle layer of the gut. Further studies are needed to determine if EGISTs represent true occurrence of mesenchymal tumors arising primarily from extragastrointestinal tract CD117-positive cells.

References

1. Yamamoto H, Oda Y, Kawaguchi K, Nakamura N, Takahira T, Tamiya S, Saito T, Oshiro Y, Ohta M, Yao T, Tsuneyoshi M. C-kit and PDGFRA mutations in extragastrointestinal stromal tumor (gastrointestinal stromal tumor of the soft tissue). Am J Surg Pathol 2004;28:479–488. doi:10.1097/00000478-200404000-00007.
2. Reith JD, Goldblum JR, Lyles RH, Weiss SW. Extragastrointestinal (soft tissue) stromal tumors: an analysis of 48 cases with emphasis on histologic predictors of outcome. Mod Pathol 2000;13:577–585. doi:10.1038/modpathol.3880099.
3. Agaimy A, Wunsch PH. Gastrointestinal stromal tumours: a regular origin in the muscularis propria, but an extremely diverse gross presentation. A review of 200 cases to critically re-evaluate the concept of so-called extra-gastrointestinal stromal tumours. Langenbecks Arch Surg 2006;391:322–329. doi:10.1007/s00423-005-0005-5.
4. Takao H, Yamahira K, Watanabe T. Gastrointestinal stromal tumor of the retroperitoneum: CT and MR findings. Eur Radiol 2004;14:1926–1929. doi:10.1007/s00330-004-2404-3.
5. Takizawa I, Morishita H, Matsuki S, Komeyama T, Emura I, Hara N. Primary gastrointestinal stromal tumor in the retroperitoneum. Int J Urol 2006;13:1245–1248. doi:10.1111/j.1442-2042.2006.01545.x.
6. Sakurai S, Hishima T, Takazawa Y, Sano T, Nakajima T, Saito K, Morinaga S, Fukayama M. Gastrointestinal stromal tumors and KIT-positive mesenchymal cells in the omentum. Pathol Int 2001;51:524–531. doi:10.1046/j.1440-1827.2001.01224.x.
7. Ortiz-Hidalgo C, de Leon Bojorge B, Albores-Saavedra J. Stromal tumor of the gallbladder with phenotype of interstitial cells of Cajal: a previously unrecognized neoplasm. Am J Surg Pathol 2000;24:1420–423. doi:10.1097/00000478-200010000-00013.
8. Park JK, Choi SH, Lee S, Min KO, Yun SS, Jeon HM. Malignant gastrointestinal stromal tumor of the gallbladder. J Korean Med Sci 2004;19:763–767.
9. Hu X, Forster J, Damjanov I. Primary malignant gastrointestinal stromal tumor of the liver. Arch Pathol Lab Med 2003;127:1606–1608.
10. Daum O, Klecka J, Ferda J, Treska V, Vanecek T, Sima R, Mukensnabl P, Michal M. Gastrointestinal stromal tumor of the pancreas: case report with documentation of KIT gene mutation. Virchows Arch 2005;446:470–472. doi:10.1007/s00428-004-1200-4.
11. Miettinen M, Monihan JM, Sarlomo-Rikala M, Kovatich AJ, Carr NJ, Emory TS, Sobin LH. Gastrointestinal stromal tumors/smooth muscle tumors (GISTs) primary in the omentum and mesentery. Clinicopathologic and immunohistochemical study of 26 cases. Am J Surg Pathol 1999;23:1109–1118. doi:10.1097/00000478-199909000-00015.
12. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT). Gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cell of Cajal. Am J Pathol 1998;152:1259–1269.
13. Sakurai S, Fukasawa T, Chong JM, et al. Embryonic form of smooth muscle myosin heavy chain (SMemb/MHC-B) in gastrointestinal stromal tumor and interstitial cells of Cajal. Am J Pathol. 1999;154:23–28.
14. Popescu LM, Hinescu ME, Ionescu N, Ciontea SM, Cretoiu D, Ardeleanu C. Interstitial cells of Cajal in pancreas. J Cell Mol Med 2005;9:169–190. doi:10.1111/j.1582-4934.2005.tb00347.x.
15. Llenas-García J, Guerra-Vales JM, Moreno A, Ibarrola C, Castelbon FJ, Fernández-Ruiz M, Meneu JC, Ballestin C, Moreno E. Primary extragastrointestinal stromal tumors in the omentum and mesentery: a clinicopathological and immunohistochemical study. Hepatogastroenterology. 2008;55(84):1002–1005.
16. Goh BK, Goh BK, Chow PK, Yap WM, Kesavan SM, Song IC, Paul PG, Ooi BS, Chung YF, Wong WK. Which is the optimal risk stratification system for surgically treated localized primary GIST? Comparison of three contemporary prognostic criteria in 171 tumors and a proposal for a modified Armed Forces Institute of Pathology risk criteria. Ann Surg Oncol 2008;15:2153–2163. doi:10.1245/s10434-008-9969-z.
17. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol 2002;33:459–465. doi:10.1053/hupa.2002.123545.
18. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach. A clinicopathologic, immunohistochemical and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol 2005;29:52–68. doi:10.1097/01.pas.0000146010.92933.de.
19. Goh BK, Chow PK, Kesavan S, Yap YM, 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.

J Gastrointest Surg (2009) 13:1099–1106
DOI 10.1007/s11605-009-0827-5

ORIGINAL ARTICLE

Early Anastomotic Repair in the Rat Intestine is Affected by Transient Preoperative Mesenteric Ischemia

L. A. E. Posma · R. P. Bleichrodt · R. M. L. M. Lomme · B. M. de Man · H. van Goor · T. Hendriks

Received: 14 January 2009 / Accepted: 28 January 2009 / Published online: 26 February 2009

Abstract
Introduction During bowel surgery, perioperative blood loss and hypotension can lead to transient intestinal ischemia. Recent preclinical studies reveal that the strength of intestinal anastomoses can be compromised after reperfusion. So far, this phenomenon has not been investigated in the very first days of healing when wound strength is lowest.
Material and Method Ischemia was induced in rats by clamping both the superior mesenteric artery and ileal branches for 30 min. Immediately after declamping, anastomoses were constructed in both terminal ileum and descending colon. The same was done in control groups after sham-ischemia. Anastomotic bursting pressure and breaking strength were measured immediately after operation (day 0) and after 1, 2, or 3 days. Anastomotic hydroxyproline content, gelatinase activity, and histology were analyzed.
Results and Discussion In ileal anastomoses, at day 1, both the breaking strength and bursting pressure were significantly ($p<0.05$) lower in the ischemic group, while at day 2, this was the case for the bursting pressure only. In the colon, the bursting pressure in the ischemic group was lower at day 1. Anastomotic hydroxyproline content remained unchanged. Increased presence of the various gelatinase activities was found in ileum only at day 0 and in colon at days 1 and 2. Histological mucosal damage was found in ischemia–reperfusion groups.
Conclusion Transient mesenteric ischemia can negatively affect anastomotic strength during the very first days of healing, even if the tissue used for anastomotic construction looks vital.

Keywords Anastomosis · Healing · Intestine · Ischemia · Reperfusion injury

Introduction

Anastomotic dehiscence remains a feared complication in gastrointestinal surgery, and diminishing its frequency, if not preventing it completely, constitutes a formidable challenge. A multitude of local factors and systemic conditions have been causally related to its occurrence,[1] and research into the underlying mechanisms is mandatory in order to provide a sound basis for optimal clinical treatment of the patients needing resection and anastomosis of the intestine.

Uninterrupted wound healing requires oxygen. Essential features of the repair sequence depend on adequate wound-tissue oxygenation.[2] In fact, impaired perfusion of the splanchnic system most likely is a substantial factor in an number of conditions that are believed to increase the risk for anastomotic dehiscence. Anastomotic leak related to ischemia is a source of significant morbidity and mortality in gastrointestinal surgery.[3] Experimental data unequivocally show persisting ischemia to impair the development of anastomotic strength.[4,5]

During bowel surgery, perioperative blood loss and hypotension can lead to transient intestinal ischemia. Events caused by reperfusion constitute an additional danger to tissues, both locally and systemic, resulting in damage that frequently exceeds the original ischemic

L. A. E. Posma · R. P. Bleichrodt · R. M. L. M. Lomme · B. M. de Man · H. van Goor · T. Hendriks (✉)
Department of Surgery,
Radboud University Nijmegen Medical Center,
PO Box 9101, 6500 HB Nijmegen, The Netherlands
e-mail: t.hendriks@chir.umcn.nl

insult.[6] Recent preclinical studies have established that the strength of intestinal anastomoses can be compromised if reperfusion after a transient period of ischemia precedes intestinal resection and anastomosis. This effect occurs both in the locally affected area[7,8] but also if the anastomosis is constructed at a distance.[9,10]

So far, this phenomenon has been investigated from 3 days after operation onwards, and experiments aimed at preventing this negative effect are mostly conducted at a single time point, often after 6 or 7 days. In a preceding comprehensive study, we have demonstrated a profound negative effect of transient mesenteric ischemia on the development of anastomotic strength from 3 days after operation onwards.[11] As yet, no data are available on the very first inflammatory phase of anastomotic healing, where wound strength is at its lowest and presumably the risk of dehiscence at its highest. This study describes the effects of ischemia–reperfusion (IR) on anastomotic strength during the early postoperative period, from immediately after construction to the third day. In this phase, wound strength depends on the suture-anchoring capacity of the existing extracellular matrix. The quality of the matrix can be affected by the presence of proteolytic enzymes, the matrix metalloproteinases (MMPs), which are essential to the repair sequence.[12] Since both MMP-2 and, especially, MMP-9 are upregulated during intestinal healing[13,14] and are believed to contribute to reperfusion injury in the gut,[15,16] their activity in anastomotic tissue has also been examined.

Material and Methods

Animals

Male Wistar rats (n=112; mean weight, 280 g; Harlan BV, Horst, The Netherlands) were allowed to become accustomed to laboratory conditions for 1 week before experimental use. They were housed two per cage under specified pathogen-free conditions with free access to water and standard rodent food (Hope Farms, Woerden, The Netherlands). The study was approved by the Animal Ethics Review Committee of the Radboud University Nijmegen.

Study Design

In experimental groups (IR, n=56, four subgroups of 14 each), animals were subject to ischemia (see below) before anastomotic construction. In control groups (C, n=56, four subgroups of 14 each), anastomosis was performed without previous ischemia. Animals were killed either immediately after anastomotic construction (day 0) or at the first, second, or third postoperative day. From each subgroup, three animals were used for histological analysis, and 11 animals were used for measuring anastomotic strength and biochemical parameters.

Operative Procedures

All rats were anesthetized by using isoflurane (Abbott Laboratories, Queensborough, UK) in a mixture of oxygen and nitrous oxide. Procedures were performed under semi-sterile conditions, using an operation microscope (Carl Zeiss, Oberkochen, Germany).

In the experimental (IR) groups, the superior mesenteric artery (SMA) was dissected free and occluded just distal to its origin with a microvascular clamp (S & T, Neuhausen am Rheinfall, Switzerland). Additionally, collateral circulation was interrupted by clamping ileal branches in the mesentery. Ischemia lasted 30 min. In the control (C) groups, the SMA and ileal branches were dissected free but not occluded. After releasing the clamps, a 2-cm resection was performed at the distal ileum, 15 cm proximal to the cecum. Continuity was restored by constructing an end-to-end anastomosis with eight single-layer, inverting, interrupted 8-0 Ethilon® (Ethicon, Norderstedt, Germany) sutures. The same procedure was carried out in the descending colon, 3 cm proximal to the peritoneal reflection. This way, anastomoses were constructed in the experimental groups in parts of the bowel that had been ischemic (ileum) or had experienced normal perfusion (descending colon). The abdomen was closed, using a continuous 3-0 Vicryl® (Ethicon, Norderstadt, Germany) suture for the musculofascial layer and staples for the skin. During operations, body temperature was kept at 38°C using a heating pad. Temperature, heart rate, and peripheral oxygen saturation were monitored. The intestines were covered with gauze pads soaked with 0.9% NaCl to minimize desiccation. To compensate for fluid loss, 10 ml of 0.9% NaCl was administered subcutaneously during the operation. Postoperative analgesia was performed with buprenorphine, 0.02 mg/kg subcutaneously, twice daily for 2 days. Animals were weighed daily and observed for signs of illness.

All operative procedures were performed by the same investigator (LAEP).

Anastomotic Strength

Animals were anesthetized and killed by intracardiac puncture. A relaparotomy was performed, and the peritoneal cavity was explored for the presence of adhesions or dehiscence. Segments of approximately 4 cm in length containing the anastomosis in the middle were carefully resected, including surrounding tissues and adhesions. In order to measure bursting pressure, the segments were

infused (2 ml/min) with normal saline containing methylene blue. The maximum pressure (mmHg) recorded immediately before sudden loss of pressure was taken as the bursting pressure. The area under the curve was considered to represent the bursting energy. The site of rupture (within or outside the anastomotic line) was also noted. Subsequently, the segments were placed in a tensiometer, and the breaking strength (in gram) was measured. This procedure, which analyses both parameters for wound strength within the same anastomotic segment, has been validated before.[17] Then the anastomotic segments were cleaned from adhering tissue and debris. A 5-mm sample containing the anastomosis in the middle was frozen in liquid nitrogen and stored at −80°C until further processing.

Biochemical Analysis

After lyophilization, tissue samples were weighed, pulverized, and lyophilized again. The hydroxyproline content, as a measure of the collagen content, was measured by high-performance liquid chromatography after hydrolysis with 6 N hydrochloric acid and derivatization with dabsyl chloride. Both hydroxyproline concentration (μg/mg tissue) and hydroxyproline content (μg/5 mm tissue) were quantitated.

Preparation of tissue extracts and procedures for quantitative gelatin zymography have been described extensively before.[18] The various gelatinase activities, representing MMP-2 and MMP-9, were quantitated on the basis of lyzed area and expressed as arbitrary units. Collagenase type 1 (from *Clostridium histolyticum*, Sigma Chemical, St Louis, MO, USA) was electrophoresed on each gel as an internal standard for in-between comparison of values obtained on different gels. The presence of true MMP activity was confirmed by adding 10 mM ethylenediaminetetraacetic acid or 1,10 phenanthroline to the buffers used after electrophoresis.

Histology

Intestinal samples of approximately 1-cm length containing the anastomosis in the middle were carefully resected en bloc, opened at the mesenteric side, and washed gently in 0.9% NaCl. They were spread out and immobilized, and the samples were immediately fixed in 4% (*v*/*v*) phosphate-buffered formaldehyde, pH 7.3. Each anastomosis was divided into two or three longitudinal strips. Specimens were dehydrated and embedded in paraffin. Sections of 4 μm in thickness were stained with hematoxylin and eosin. Sections were analyzed in a blinded fashion using a binocular light microscope. Histological parameters such as epithelial damage, necrosis, and presence of neutrophils were assessed.

Statistics

Differences over time within either C or IR groups were tested for significance using an analysis of variance (ANOVA) and, if indicated, a Tukey–Kramer post test. Differences between C and IR groups were analyzed using a one- (strength) or two-tailed (MMPs) unpaired *t* test. Use, by exception, of any other test is mentioned in the text. Differences with p value <0.05 were considered significant.

Results

General

SMA occlusion and interruption of the collateral circulation resulted in diminished pulsations in the mesentery and pale coloring of the ileum and ascending colon. These phenomena were reversed after circulation was restored by releasing the clamps. Heart rate, temperature, and peripheral oxygen saturation remained constant during the procedure.

No premature deaths occurred in the control group and four (7%, ns) in the IR group, all during the first 24 h after operation. Except for one animal that showed signs of generalized peritonitis, no obvious cause of death could be established.

All animals lost weight after operation. At day 3, the average relative weight, as a percentage of preoperative weight, was 92.5% (SD, 2.6) in the control group and 89.5% (2.9) in the IR group (p=0.059). At necropsy, no overt signs of complications were found in any of the 56 control animals. In the 52 animals from the IR groups that completed the experiment, signs of ileus and intra-abdominal abscesses were each seen in four (different) animals. Furthermore, obvious signs of anastomotic dehiscence were observed in another four animals (8%, p=0.050).

Anastomotic Strength

During measurements of anastomotic strength, the site of tissue disruption was always within the suture line. In the ileum, anastomotic strength diminishes immediately after construction (Fig. 1). Analyzing the four control groups together, this effect was significant for the bursting pressure (ANOVA, p=0.0095) and breaking strength (p<0.0001) but not for the breaking energy (p=0.0609). Within the IR groups, all parameters showed extreme significance (p<0.0001). The relative loss of strength between day 0 and 1 was invariably greater in the IR groups: The average bursting pressure was reduced by 38% in the controls and by 71% in the IR group. The same was true for the bursting energy, 36% vs 62%, and the breaking strength, 47% vs

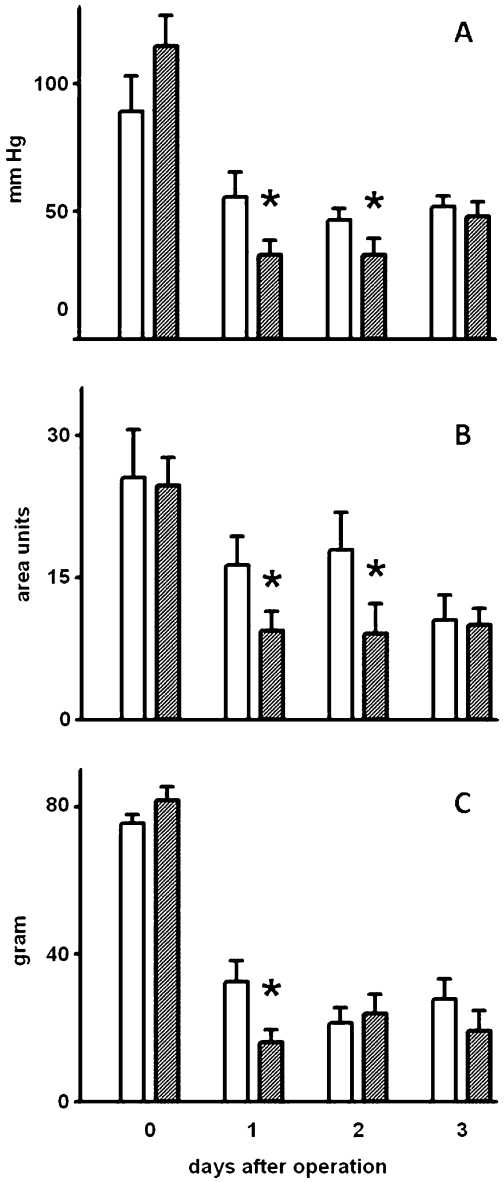

Figure 1 Anastomotic strength in the ileum. *Columns* represent mean values+SEM for control (*open bars*) and IR (*striped bars*) groups. Results are given for the bursting pressure (**a**), the bursting energy (**b**), and the breaking strength (**c**). *$p<0.050$ vs control group.

80%. As a result, anastomotic strength in the IR group was significantly ($p<0.05$) lower than in the control group 24 h after surgery. With regard to the bursting pressure, this negative effect persisted another 24 h (day 2). Although the mean breaking strength at day 3 was 30% lower in the IR group, this difference failed to reach significance ($p=0.12$).

The loss of wound strength over time, observed in the ileum, did not occur in the colon (Fig. 2). Still, a degree of reperfusion injury was also observed at this remote site since the bursting pressure in colonic anastomoses was significantly lower in the IR group than the controls at day 1 after operation. No differences were found for the breaking strength (not shown).

Biochemistry and Histology

Hydroxyproline levels, expressed as both the hydroxyproline concentration (μg/mg dry tissue) and content (μg/5-mm tissue), were analyzed as a measure for collagen content in the anastomosis. In the ileal anastomoses, no significant (ANOVA) changes with time were found in either control or IR groups (Table 1). In addition, no differences were observed at any time point between control and IR groups. The same was true for colonic anastomoses (data not shown).

Quantitative gelatin zymography allows the separate analysis of the various forms of the gelatinases present in tissue extracts (Fig. 3 a, b). The active and latent forms of both MMP-2 and MMP-9 were measured, and their total activity within the (5 mm) anastomotic segment was calculated. In the ileal anastomoses, both forms of the MMPs exhibited significant ($p<0.05$, Kruskal–Wallis) changes over time (Fig. 4). In the controls, both active and proMMP-9 were highest at day 1. This pattern was changed in the IR groups. Immediately after construction, both active and proMMP-9 activities were significantly higher in the IR group than in the controls. The same was true for proMMP-9 at day 3, but here, active MMP-9 was lowest in the IR group. MMP-2 activities were lowest at day 0, where the active form was increased in the IR group. Subsequently, both MMP-2 forms

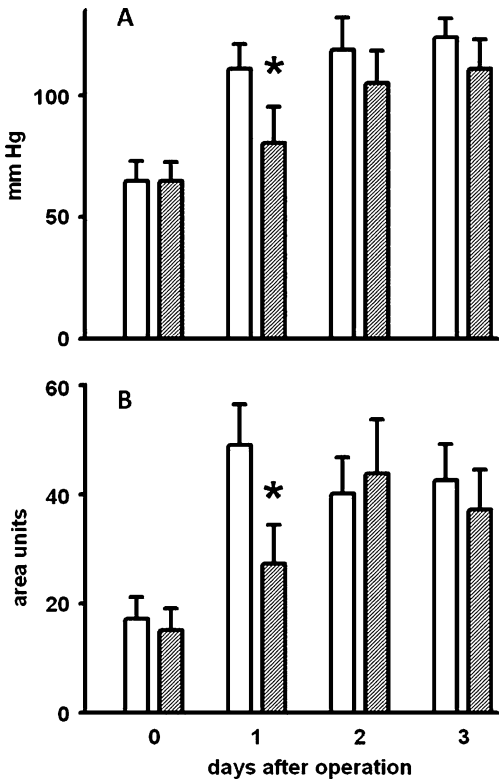

Figure 2 Anastomotic strength in the colon. *Columns* represent mean values+SEM for control (*open bars*) and IR (*striped bars*) groups. Results are given for the bursting pressure (**a**) and the bursting energy (**b**). *$p<0.050$ vs control group.

Table 1 Anastomotic hydroxyproline in the ileum

	Day 0	Day 1	Day 2	Day 3
Concentration (μg/mg)				
Controls	10.0 (2.9)	8.2 (4.1)	7.6 (2.6)	5.9 (2.4)
IR	9.1 (3.1)	9.2 (3.3)	7.1 (2.1)	7.9 (2.4)
Content (μg/5 mm)				
Controls	147 (73)	131 (54)	149 (47)	127 (36)
IR	119 (42)	129 (37)	130 (43)	191 (65)

Data represent means and (in brackets) SD. No significant differences between control and IR groups.

were higher, and a significant difference between control and IR groups was only observed for proMMP-2 at day 2. The MMP activities in colonic anastomoses are depicted in Fig. 5. For MMP-9, hardly any difference was found between control and experimental groups. Interestingly, both latent and active MMP-2 activities were significantly higher in the IR groups at days 1 and 2, while at day 3, the opposite trend was observed.

Histological analysis immediately after anastomotic construction, at day 0, revealed mucosal damage in the IR groups, with elevation of the epithelial layer from the lamina propria and denuding and loss of height of the villi. These effects of ischemia and reperfusion gradually subsided during the first 24 h. Except for these differences, microscopic architecture of the anastomoses appeared to be similar in control and IR groups.

Discussion

If an anastomosis is constructed in an intestinal segment, immediately after tissue perfusion has been restored following

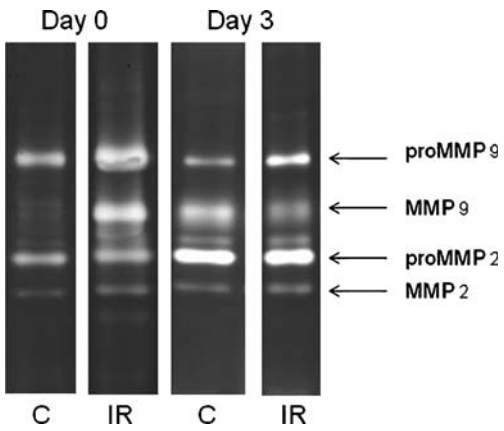

Figure 3 MMP activity in ileal anastomoses as demonstrated by gelatin zymography. Representative samples of tissue extracts as used for quantitation of the pro- and active forms of MMP-2 and MMP-9, which are separated by molecular weight on a gelatin gel. Samples from the control (*C*) and IR groups at both days 0 and 3.

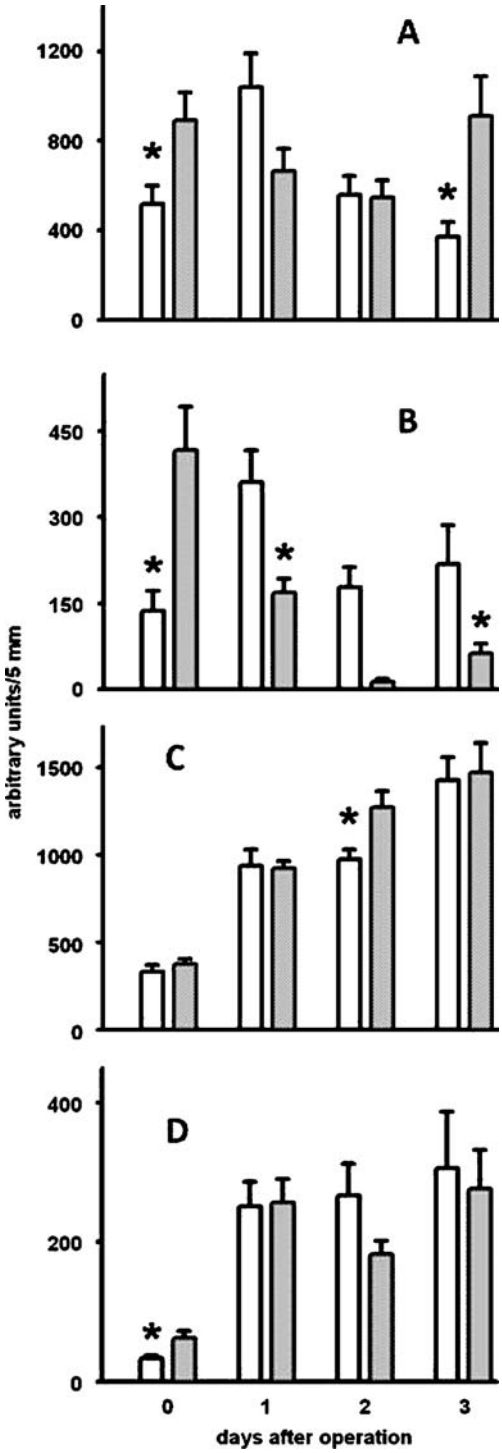

Figure 4 MMP activity in ileal anastomoses. *Columns* represent mean values+SEM for control (*open bars*) and IR (*striped bars*) groups. Data represent total activities, in arbitrary units, per 5-mm segment for proMMP-9 (**a**), MMP-9 (**b**), proMMP-2 (**c**) and MMP-2 (**d**). *$p<0.050$ for differences between control and IR group at any of the time points.

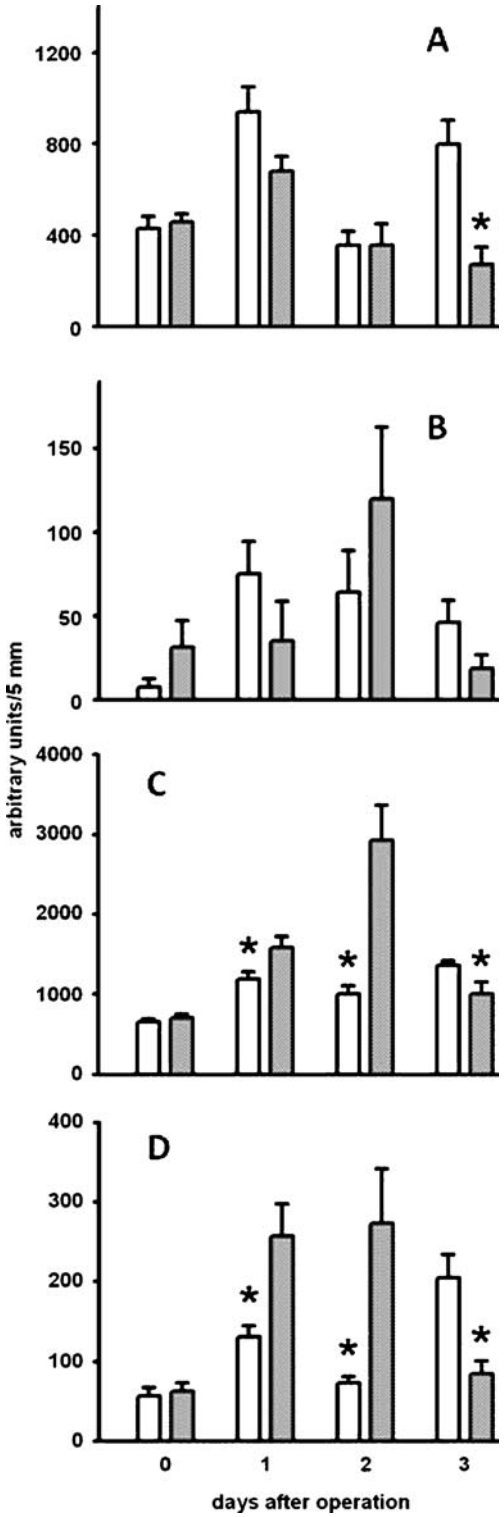

Figure 5 MMP activity in colonic anastomoses. Columns represent mean values+SEM for control (*open bars*) and IR (*striped bars*) groups. Data represent total activities, in arbitrary units, per 5-mm segment for proMMP-9 (**a**), MMP-9 (**b**), proMMP-2 (**c**), and MMP-2 (**d**). *$p<0.050$ for differences between control and IR group at any of the time points.

a period of intestinal ischemia, wound strength is compromised during the very first days after operation. The data reported now are the first on such an effect being present in the early period of anastomotic healing. Together with those from our prior study,[11] they demonstrate that IR-related injury results in loss of wound strength over the entire first postoperative week, thus affecting both the inflammatory and proliferation phases of the healing process.

Clamping and declamping of the SMA, together with its ileal branches in the mesentery, is an established method to interrupt mesenterial blood flow to the ileum and the ascending colon.[19] Although it induces deep ischemia, this procedure, even if followed by anastomotic construction, shows a 93% survival rate (in the IR group) and thus provides a good model to study effects of reperfusion injury on wound repair.

The primary outcome parameter for anastomotic healing is wound strength, which can be measured as both bursting pressure and breaking strength, even in the same animal.[17] If the tissue ruptures within the true anastomotic line, as is the case within the time period under investigation here, the former represents the ability of the wound to withstand intraluminal pressure and the latter its ability to resist forces applied longitudinally. Both type of forces are presumably at work during intestinal movement, and therefore, both parameters are very relevant, although they may behave independently.[20] Any reduction in either of the two may be taken as a sign of impaired healing. Thus, IR has a significant negative effect on anastomotic strength: if the anastomosis is constructed in ileal tissue, which actually has suffered an ischemic event, wound strength is compromised at 24 and 48 h after operation. If the anastomosis is constructed at a distance, in the descending colon, systemic effects of reperfusion result in a lower wound strength after 24 h. As a consequence, the risk of anastomotic failure is enhanced: Signs of dehiscence are repeatedly observed in the IR group and not in the controls.

If the results from the present and preceding[11] studies, covering the entire first postoperative week, are taken together, they demonstrate that mesenteric IR consistently lowers anastomotic strength from the first postoperative day onwards. The first days of healing are characterized by the inflammatory phase: From approximately 3 days after operation onwards, the proliferative phase becomes increasingly important.[1] Presumably, wound strength in the first few days depends on the existing extracellular matrix and only later on the newly deposited collagen. Thus, it could very well be that the mechanism causing loss of strength at day 2 is entirely different to the one causing the same phenomenon at day 7. Such a difference seems not unlikely because of the fact that, during the early days, the bursting pressure is clearly affected, while this is less so if anastomoses are examined from day 3 onwards.[11] Very

recently, a number of studies have reported treatments to prevent loss of anastomotic strength after reperfusion injury, almost invariably analyzed at least 6 days after operation.[2,5,10,21,22] The current results emphasize the need to also investigate the first period of healing, since different pathways may be responsible for delayed repair. Furthermore, investigators should be well advised to measure the parameter for anastomotic strength, which is most sensitive to reperfusion injury.

By anchoring the sutures, the extracellular matrix determines wound strength in the period investigated in this study, well before any deposition of newly formed collagen occurs within the wound area.[23] The hydroxyproline measurements, admittedly a relatively insensitive way to estimate the anastomotic collagen content, are not suggestive for increased matrix degradation in the IR groups. Still, local action of MMPs could result in focused and limited degradation,[24] for instance in areas next to sutures, thereby weakening the wound. Still, our data on MMP-2 and MMP-9 do not yield a consistent picture of upregulation after IR. Immediately after anastomotic construction (day 0) in the ileum, MMP-9 and active MMP-2 activities are greater in the IR groups, which is consistent with earlier findings in the rat intestine after a 90-min reperfusion.[25] However, this effect does not persist, and at later time points, active MMP-9 is even reduced in the IR groups. Remarkably, in the colonic anastomoses, MMP-2 activities after IR are enhanced at days 1 and 2 but reduced at day 3. It remains to be determined if a relatively short period of enhanced proteolytic activity can induce enough local damage of the extracellular matrix to result in a lasting period of reduced wound strength. Any definite proof of a causal role of MMPs in lowering wound strength can only come from studies using specific inhibitors.

Mesenteric ischemia is a common event in surgery. During bowel surgery, intraoperative blood loss or cardiopulmonary events may cause hypoperfusion and relative intestinal ischemia, which can lead to impaired healing.[26] In fact, IR injury of the intestine is a significant problem in a multitude of situations, such as abdominal aortic aneurysm surgery, small bowel transplantation, cardiopulmonary bypass, strangulated hernias, and neonatal necrotizing enterocolitis. It can also occur in septic and hypovolemic shock.[27]

The present data have been obtained in an animal model. As always, it remains to be proven that they are relevant to the clinical situation also. Still, together with the existing literature, they show what the implications could be of deep but transient intestinal ischemia. Even when seemingly vital tissue is used for anastomotic construction, local healing may be compromised from the very first day onwards, ultimately leading to dehiscence. Bearing this in mind, it is apparent that studies aimed at establishing actual mechanisms and finding preventive measures are needed.

References

1. Witte MB, Barbul A. Repair of full-thickness bowel injury. Crit Care Med 2003;31(Suppl 8):538–546. doi:10.1097/01.CCM.0000081436.09826.A4.
2. Enestvedt CK, Thompson SK, Chang EY, Jobe BA. Clinical review: healing in gastrointestinal anastomoses, part II. Microsurgery 2006;26:137–143. doi:10.1002/micr.20198.
3. 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 clinically relevant animal model. J Gastrointest Surg 2008;12:1762–1770. doi:10.1007/s11605–008–0635–3.
4. Topçu O, Karaday K, Kuzu MA, Ulukent S, Erkek B, Alaçayir I. Enteral and intraluminal short-chain fatty acids improves ischemic left colonic anastomotic healing in the rat. Int J Colorectal Dis 2002;17:171–176. doi:10.1007/s003840100357.
5. Parra-Membrives P, Ruiz-Luque V, Escudero-Severín C, Aguilar-Luque J, Méndez-García V. Effect of pentoxifylline on the healing of ischemic colorectal anastomoses. Dis Colon Rectum 2007;50:369–375. doi:10.1007/s10350-006-0803-z.
6. Mallick IH, Yang W, Winslet MC, Seifalian AM. Ischemia–reperfusion injury of the intestine and protective strategies against injury. Dig Dis Sci 2004;49:1359–1377. doi:10.1023/B:DDAS.0000042232.98927.91.
7. Kuzu MA, Köksoy C, Kale IT, Tanik A, Terzi C, Elhan AH. Reperfusion injury delays healing of intestinal anastomosis in a rat. Am J Surg 1998;176:348–351. doi:10.1016/S0002-9610(98)00198-6.
8. Wasserberg N, Tzakis AG, Santiago SF, Ruiz P, Salgar SK. Anastomotic healing in a small bowel transplantation model in the rat. World J Surg 2004;28:69–73. doi:10.1007/s00268-003-7028-2.
9. Kologlu M, Yorganci K, Renda N, Sayek I. Effect of local and remote ischemia–reperfusion injury on healing of colonic anastomoses. Surgery 2000;128:99–104. doi:10.1067/msy.2000.107414.
10. Teke Z, Sacar M, Yenisey C, Atalay AO, Bicakci T, Erdem E. Activated protein C prevents deleterious effects of remote reperfusion injury caused by intestinal ischemia on wound healing in the left colonic anastomoses: an experimental study in the murine model. Am J Surg 2008;196:774–787. doi:10.1016/j.amjsurg.2007.09.039.
11. Posma LA, Bleichrodt RP, van Goor H, Hendriks T. Transient profound mesenteric ischemia strongly affects the strength of intestinal anastomoses in the rat. Dis Colon Rectum 2007;50:1070–1079. doi:10.1007/s10350-006-0822-9.
12. Gill SE, Parks WC. Metalloproteinases and their inhibitors: regulators of wound healing. Int J Biochem Cell Biol 2008;40:1334–1347. doi:10.1016/j.biocel.2007.10.024.
13. Savage FJ, Lacombe DL, Boulos PB, Hembry RM. Role of matrix metalloproteinases in healing of colonic anastomosis. Dis Colon Rectum 1997;40:962–970. doi:10.1007/BF02051206.
14. de Hingh IH, Lomme RM, van Goor H, Bleichrodt RP, Hendriks T. Changes in gelatinase activity in the gastrointestinal tract after anastomotic construction in the ileum or colon. Dis Colon Rectum 2005;48:2133–2141. doi:10.1007/s10350-005-0142-5.
15. Robinson EK, Kelly DP, Mercer DW, Kozar RA. Differential effects of luminal arginine and glutamine on metalloproteinase

production in the postischemic gut. JPEN J Parenter Enteral Nutr 2008;32:433–438. doi:10.1177/0148607108319806.
16. Costantino G, Egerbacher M, Kolbe T, Karaghiosoff M, Strobl B, Vogl C, Helmreich M, Müller M. Tyk2 and signal transducer and activator of transcription 1 contribute to intestinal I/R injury. Shock 2008;29:238–244.
17. de Waard JW, Wobbes T, de Man BM, van der Linden CJ, Hendriks T. Post-operative levamisole may compromise early healing of experimental intestinal anastomoses. Br J Cancer 1995;72:456–460.
18. Siemonsma MA, de Hingh IH, de Man BM, Lomme RM, Verhofstad AA, Hendriks T. Doxycycline improves wound strength after intestinal anastomosis in the rat. Surgery 2003;133:268–276. doi:10.1067/msy.2003.27.
19. Megison SM, Horton JW, Chao H, Walker PB. A new model for intestinal ischemia in the rat. J Surg Res. 1990;49:168–173. doi:10.1016/0022-4804(90)90257-3.
20. Mansson P, Zhang XW, Jeppsson B, Thorlacius H. Anastomotic healing in the rat colon: comparison between a radiological method, breaking strength and bursting pressure. Int J Colorectal Dis 2002;17:420–425. doi:10.1007/s00384-002-0392-9.
21. Teke Z, Aytekin FO, Kabay B, Yenisey C, Aydin C, Tekin K, Sacar M, Ozden A. Pyrrolidine dithiocarbamate prevents deleterious effects of remote ischemia/reperfusion injury on healing of colonic anastomoses in rats. World J Surg 2007;31:1835–1842. doi:10.1007/s00268-007-9106-3.
22. Colak T, Turkmenoglu O, Dag A, Polat A, Comelekoglu U, Bagdatoglu O, Polat G, Kanik A, Akca T, Aydin S. The effect of remote ischemic preconditioning on healing of colonic anastomoses. J Surg Res 2007;143:200–205. doi:10.1016/j.jss.2006.10.030.
23. Verhofstad MHJ, Lange WP, van der Laak JAWM, Verhofstad AAJ, Hendriks T. Microscopic analysis of anastomotic healing in the intestine of normal and diabetic rats. Dis Colon Rectum 2001;44:423–431. doi:10.1007/BF02234744.
24. Agren MS, Andersen TL, Mirastschijski U, Syk I, Schiødt CB, Surve V, Lindebjerg J, Delaissé JM. Action of matrix metalloproteinases at restricted sites in colon anastomosis repair: an immunohistochemical and biochemical study. Surgery. 2006;140:72–82. doi:10.1016/j.surg.2005.12.013.
25. Rosario HS, Waldo SW, Becker SA, Schmid-Schonbein GW. Pancreatic trypsin increases matrix metalloproteinase-9 accumulation and activation during acute intestinal ischemia–reperfusion in the rat. Am J Pathol. 2004;164:1707–1716.
26. Matthiessen P, Hallböök O, Rutegård J, Sjödahl R. Intraoperative adverse events and outcome after anterior resection of the rectum. Br J Surg. 2004;91:1608–1612. doi:10.1002/bjs.4530.
27. Mallick IH, Yang W, Winslet MC, Seifalian AM. Ischemia–reperfusion injury of the intestine and protective strategies against injury. Dig Dis Sci. 2004;49:1359–1377. doi:10.1023/B:DDAS.0000042232.98927.91.

J Gastrointest Surg (2009) 13:1107–1110
DOI 10.1007/s11605-009-0851-5

ORIGINAL ARTICLE

Prevalence of Internal Hernias After Laparoscopic Colonic Surgery

Stefano Sereno Trabaldo · Mehran Anvari · Joel Leroy · Jacques Marescaux

Received: 17 November 2008 / Accepted: 26 February 2009 / Published online: 17 March 2009

Abstract
Introduction Laparoscopic approach for colorectal resections is gaining popularity. Internal small bowel herniation (SBH) through a mesenteric defect has been described and, although rare, is a severe complication. The aim of this study was to evaluate the incidence and outcome of internal hernias after laparoscopic colorectal resection.
Material and methods During a 5-year period, all patients who underwent laparoscopic left colon resection were included in the study. A retrospective data base query was performed searching for all patients in whom SBH required surgical reintervention.
Results A total of 436 laparoscopic left colorectal resections were performed from January 2000 to July 2006. Five male patients presented symptomatic internal hernias and required re-operation. Four had a resection for cancer and one for sigmoiditis. The mesenteric defect was not initially closed in three cases. In all cases, we found small bowel hernias through the mesocolon defect. One patient was re-operated on post-op day 2 for mesenteric ischemia and died after 24 h.
Discussion Internal hernia is a rare but fatal complication after laparoscopic colonic resection. Suspicion of this diagnosis requires emergency re-operation because symptoms are nonspecific.
Conclusion All mesenteric defects created during colorectal laparoscopy surgery should be meticulously closed.

Keywords Internal hernias · Mesenteric closure · Colorectal surgery

Introduction

Laparoscopic colorectal resections are frequently performed for benign colorectal pathology, and this approach is gaining popularity for colorectal cancer. Evidence shows equivalent short-term results between laparoscopic and conventional colorectal resection for colorectal cancer resections with the advantages of laparoscopy.[1,2]

A variety of rather unusual and potential serious complications related to colorectal resections have been extensively reported and described. This complications include incisional hernias, wound infection, intraabdominal abscess, bleeding, leaks, stenosis, recurrence, and perhaps the most common complication reported is the intestinal obstruction.[3–6]

Small bowel obstruction (SBO) after open or laparoscopic colorectal resection can occur in 2% to 3.6% in the first 3 years after surgery, but the diagnosis is difficult because it is rare, and the symptoms are insidious.[7–9] Adhesions can explain 49% to 74% of the SBO.

Internal herniation through the defect created during resection of the specimen has been described as a rare cause of SBO after open and laparoscopic gastric bypass surgery, liver and kidney transplant surgery, laparoscopic Nissen procedure and cholecystectomy.[10–17] They have an overall reported incidence of less than 1% and, if untreated, a

SAGES April 2007, Las Vegas

S. Sereno Trabaldo (✉)
Servicio de Cirugía Bariátrica y Metabólica,
Real San José Hospital,
Tarascos 3514-6, Fracc. Monraz, CP 44670,
Guadalajara, Jalisco, México
e-mail: ssereno@gmail.com

M. Anvari
Centre for Minimal Access Surgery, McMaster University,
Hamilton, ON, Canada

J. Leroy · J. Marescaux
IRCAD-EITS, University Louis Pasteur,
Strasbourg, France

mortality exceeding 50%.[18] In the field of laparoscopic colon surgery, only isolated cases of internal hernia as a cause of SBO have been reported in the literature.[19–23]

The aim of this study was to know the incidence of the internal hernias after laparoscopic colonic surgery and the outcome of these patients.

Material and Methods

All patients who underwent laparoscopic left colon resection (including partial resection, sigmoidectomy, and low anterior resections with total mesorectal excision) from the 1st of January 2000 to the 30th of June 2006 at the Chirurgie A Service at the University Louis Pasteur Civil Hospital, Strasbourg, France, were included in the study.

A retrospective data base query was performed searching for all the aforementioned patients in whom SBO was developed and needed a surgical reintervention, according to the international classification of disease that include intestinal obstruction or occlusion (Codes: K46.0, K56.6, K91.3.).

Data was collected for age, gender, first surgery original diagnosis, previous history of obstruction, ASA, BMI, type of colonic resection, freedom of the hepatic or splenic flexure, closure of mesenteric defect, resumption of oral diet, and length of hospital stay. Regarding the reintervention, data was collected for pre-re-operative symptoms (vomiting, nausea, abdominal pain), laboratory, X-ray findings, pre-re-op diagnosis, time from presentation to surgery, surgical findings, surgical technique, resumption of oral diet, post-op morbidity, length of hospital stay, and mortality.

Internal hernia was defined as a protrusion of a part of the small and/or large bowel through a normal or created mesenteric aperture within the peritoneal cavity found during surgical re-operation.

Results

In the period of time between January 2000 and July 2006, a total of 436 laparoscopic left colorectal resections were performed. Five patients (1.14%) developed symptoms of occlusion that required surgical re-intervention.

Mean age was 69 (60–78), and all cases where male. Mean body mass index (BMI) was 30.07 (26.81–32.66). Symptoms, technique for mesenteric closure, and morbidity are cited in Table 1.

Diagnosis after the first colorectal surgery was in each of the five cases, recto-sigmoidal cancer pT2N0 (second third of rectum), adenocarcinoma of the rectum pT3N1 (10 cm from AV), left colon adenocarcinoma pT3N0, sigmoid adenocarcinoma pT3N0M1-liver 5(20 cm from AV), and diverticulitis.

The type of resection in each case was: very low rectal resection + end-to-end (E-E) colorectal mechanical anastomosis + protective ileostomy, total mesorectal excision (TME) + low colorectal anastomosis with J pouch + protective ileost, extended left colectomy + E-E colorectal mechanical anastomosis + small bowel transmesenteric passage, sigmoidectomy + E-E mechanical anastomosis + Meckel diverticulum resection, and finally a sigmoidectomy + E-E colorectal mechanical anastomosis.

Findings at X-ray examination with abdominal X-ray and/or computed tomography (CT) scan were: collection in the dissected area, normal, pneumonitis, occlusion + small bowel dilation, and normal.

Time from presentation to surgery was: (1) 8 h, (2) 5 days, (3) 18 h, (4) 24 h, and (5) 8 h. Surgical procedure at reintervention was: reduction of internal hernia + closure of mesenteric defect (suture), reduction of internal hernia + closure of mesenteric defect (suture), complementary resection of 10 cm of small bowel + suture of colonic perforation + terminal ileostomy + drainage, reduction of internal hernia + closure of mesenteric defect (suture), and reduction of the hernia + Hartmann procedure + terminal colostomy.

Length of hospital stay was 15 days (8–30). The patient who developed the atelectasia stayed at the hospital for 30 days. One patient died after the second surgery wherein complete mesenteric ischemia was found. The patient developed septic shock and a pneumopathy post-inhalation.

Discussion

Internal hernias after laparoscopic surgery are clearly described and identified after cholecystectomy, nephrectomy, gastric fundoplications and gastric bypass, and the closure of all the mesenteric-created defects has been encouraged.

Rarely described in the literature, the real incidence of internal hernias after laparoscopic left colon resections is not clearly known, and there has not been enough data to promote preventive closure of the mesenteric defects as it is done in other procedures.

In the present study, we found that although the incidence of internal herniation after laparoscopic left colonic resections is low (1.14%), it is related with a high mortality rate (20%).

There are several mechanisms that can explain internal herniation after laparoscopic left colonic resection.

– Reduced adhesions: there is a reduced formation of postoperative adhesions, which can lead to free

Table 1 Symptoms of Internal Hernia, Mesenteric Closure Technique and Morbidity

Case	Symptoms	Mesenteric closure technique	Morbidity
1	Abdominal pain + shock	Ligasure™ device	Oral intake 6th day
2	Abdominal pain	Staples	None
3	Abdominal pain + penumonitis	None	Atelectasia, abdominal wall abscess
4	Dyspnea (gastric aspiration) + hemodynamic instability	None	2nd re-operation: complete mesenteric ischemia (death)
5	Pain in the left iliac fossa	None	None

movement of the small bowel inside the abdominal cavity.

- Early mobility: the patients re-start to walk earlier thus putting the mesenteries in tension after the surgical procedure.
- Axe of the mesenteries: Small bowel mesentery is anchored in the posterior abdominal wall in a sense from up to down, left to right, and posterior to anterior. This disposition creates, by gravity, a small bowel that has a natural tendency to lie downwards to the left iliac fossa. Left mesocolon is right on the way between this point and the root of the small bowel mesentery. One can easily deduce that a defect created on this site will be the perfect door for the passage of the small bowel through it (Although not the objective of this study, but we found no internal hernias among the right colon laparoscopic resections.).
- Treitz ligament: this anatomical landmark is the pivot point for the rotation of the small bowel. Located in the root of the transverse mesocolon naturally maintains the proximal jejunum close to the posterior abdominal wall. A defect in the descending colon mesentery would be close to the proximal jejunum, and this bowel can slide toward the left parieto-colic and inguinal fossa.
- Tension of the left colonic mesentery: when the splenic flexure is not dissected, the mesentery of the descending or transverse colon that is pulled down into the pelvis for the anastomosis, would have more tension compared to when it is completely free. On one hand, this tension can avoid the passage of the small bowel into it, but on the other hand, if the bowel ever passes under the mesentery, it will easily be trapped by it.
- Method used to close the mesentery: regarding laparoscopic gastric bypass, it has been described that there is a lower incidence of internal hernias when using a running suture with a nonabsorbable material. In this series, two of five patients had a complete closure of the mesentery, once using a Ligasure™ device and the second using staples.

Abdominal imaging including simple X-ray or CT scan has been described to be useful in making the diagnostic of an internal hernia.[18,22] In this series, imaging was generally not contributive in making the diagnosis. The typical CT findings of intersigmoid hernia (hidroaeric levels, U- or C-shaped cluster of small-bowel loops posterior and lateral to left-sided colon, etc.) may not be present. When imaging does not suggest occlusion, it does not exclude the presence of an internal hernia.

An internal hernia can be asymptomatic or can be the cause of complex symptomatology including abdominal discomfort, intermittent colicky pain, nausea, vomiting, and recurrent intestinal obstruction. Abdominal pain was the most common clinical sign in this study. Any abnormal abdominal pain after surgery should be suspicious for internal hernia and should be studied as one.

All the internal hernias developed early in the postoperative period. The latest was in the fifth post-op day. A suspicion of an internal hernia in the early postoperative time should alert the surgeon to re-operate the patient.

Not surprisingly, four of the five patients who developed internal hernia after left laparoscopic colon resection had cancer. During oncologic resection, the dissection goes up to the root of the colonic mesentery, and the created defect can be larger than the defect created for benign resections.

There are different particular situations that could lead to the patients of this study to develop an internal hernia. In one case, the mesentery was closed with Ligasure™. In this patient, the proteic seal was not enough to maintain the mesentery closed after the surgery, although it has been suggested to prevent internal hernias in previous reports.[23]

Another patient had a rectal and sigmoid resection for cancer, and the mesentery was closed with staples. Apparently, this method of closure can lead to disruption of the mesenteric closure even if the splenic flexure was dissected.

A patient had a left colectomy extended to the left colic angle, and the proximal colon was passed through the mesentery of the small bowel to reach the pelvis (Toupet technique). The mesenteric defect was not closed, and this led to an internal hernia.

Only one of the patients with internal hernia was operated for benign disease, but the mesentery was not closed thus leading to an internal hernia. This patient had the highest BMI of the series.

Finally, death occurred in one patient with cancer where the mesentery was not closed. This patient had the most advanced colorectal cancer of the group. A further investigation of this case helps us to understand that in the fourth post-op day, the internal hernia led to a severe bowel obstruction with consequent gastric aspiration and hemodynamic instability. Although the internal hernia was reduced and the mesenteric defect was closed, the clinical evolution of the patient worsened toward septic shock, post-inhalation pneumopathy, and mesenteric ischemia. The final result of this patient should be considered as a complication of the internal hernia.

Prevention of internal hernia formation has been proposed by a systematic closure of all the mesenteric defects after laparoscopic sigmoidectomy, using nonabsorbable material.[20] It has also been suggested to completely liberate the duodeno-jejunal angle by cutting the Treitz muscle to decrease the tendance of the proximal small bowel to pass beneath the mesocolon, but there is not enough evidence to generally recommend it.[22] Furthermore, closure of the mesenteric defects should not be done with Ligasure™ device or staples.

Conclusion

Internal hernia after laparoscopic colonic resection can be fatal, and we strongly recommend that all left-sided mesenteric defects created should be meticulously closed.

References

1. Cochrane Database Syst Rev. 2005;(3):CD003145.
2. Lacy A. Colon cancer: laparoscopic resection. Ann Oncol 2005;16 (Suppl 2):ii88–ii92. doi:10.1093/annonc/mdi733.
3. Franklin ME Jr, Rosenthal D, Abrego- Medina D, Dorman JP, Glass JL, Norem R, Diaz A. Prospective comparison of open vs. laparoscopic colon surgery for carcinoma. Five-year results. Dis Colon Rectum 1996;39(Suppl10):S35–S46. doi:10.1007/BF02053804.
4. Wexner SD, Reissman P, Pfeifer J, Bernstein M, Geron N. Laparoscopic colorectal surgery: analysis of 140 cases. Surg Endosc 1996;10(2):133–136.
5. Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004;350(20):2050–2059. doi:10.1056/NEJMoa032651.
6. 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-metastatis colon cancer: a randomized trial. Lancet 2002;359(9325):2224–2229. doi:10.1016/S0140-6736(02)09290-5.
7. Duepree HJ, Senagore A, Delaney CP, Fazio VW. Does means of access affect the incidence of small bowel obstruction and Ventral Hernia after bowel resection? laparoscopy versus laparotomy. J Am Coll Surg 2003;197(2):177–181. doi:10.1016/S1072-7515(03)00232-1.
8. Edna TH, Bjerkeset T. small bowel obstruction in patients previously operated on for colorectal cancer. Eur J Surg 1998;164:587–592. doi:10.1080/110241598750005688.
9. Ryan MD, Wattchow D, Walker M, Hakendorf P. Adhesional small bowel obstruction after colorectal surgery. ANZ J Surg 2004;74(11):1010–1012. doi:10.1111/j.1445-1433.2004.03225.x.
10. Filipi JE, Mattar SG, Bowers SP, et al. Internal hernia formation after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Am Surg 2002;68:640–643.
11. Livingston EH. Complications of bariatric surgery. Surg Clin North Am 2005;85:853–868. doi:10.1016/j.suc.2005.04.007.
12. Row D, Maddineni S, Maffucci L, Rangraj M. Late sigmoid colon internal herniation into the jejuno-jejunostomy mesenteric defect after laparoscopic Roux-en-Y gastric bypass. Obes Surg 2006;16 (2):208–210. doi:10.1381/096089206775565087.
13. Regan JP, Cho ES, Flowers JL. Small bowel obstruction after laparoscopic donor nefrectomy. Surg Endosc 2003;17:108–110. doi:10.1007/s00464-002-8600-9.
14. Letourneux H, Tasseti V, Saussine C, Jacqmin D. Internal hernia of the small intestine after laparoscopic nephrectomy. Prog Urol 2006;16(1):82–84.
15. Patterson M, Walters D, Browder W. Postroperative bowel obstruction following laparoscopic surgery. Am Surg 1993;59 (10):656–657.
16. Malas MB, Katkhouda N. Internal hernia as a complication of laparoscopic Nissen fundoplication. Surg Laparosc Endosc 2002;12:115–116. doi:10.1097/00129689-200204000-00008.
17. Perez Rouiz L, Gabarrel Oto A, Casals Garrigo R, Soda Marti R, Ziza F. Intestinal obstruction caused by internal transmesosigmoid hernia: a complication of laparoscopic surgery? Minerva Chir 1997;52(9):1109–1112.
18. Martin L, Merkle E, Thompson W. Review of internal hernias: radiographic and clinical findings. AJR Am J Roentgenol 2006;186(3):703–717. doi:10.2214/AJR.05.0644.
19. Nagata K, Tanaka J, Endo S, Tatsukawa K, Hidaka E, Kudo SE. Internal hernia through the mesenteric opening after laparoscopic-assisted transverse colectomy. Surg Laparosc Endosc Percutan Tech 2005;15(3):177–179. doi:10.1097/01.sle.0000166969.38972.fa.
20. Elio A, Veronese E, Frigo F, Residori C, Salvato S, Orcalli F. Ileal volvulus on internal hernia following left laparoscopic-assisted hemicolectomy. Surg Laparosc Endosc 1998;8(6):477–478. doi:10.1097/00019509-199812000-00016.
21. Kawamura YJ, sunami E, Masaki T, Muto T. Transmesenteric hernia after laparoscopic-assisted sigmoid colectomy. JSLS 1999;3(1):79–81.
22. Blanc P, Delacoste F, Atger J. A rare cause of intestinal obstruction after laparoscopic colectomy. Ann Chir 2003;128:619–621. doi:10.1016/j.anchir.2003.07.003.
23. Sabbagh C, Vibert E, Renou M, Yzet T, Regimbeau JM. Hernie interne après colectomie gauche laparoscopique, un moyen simple de la prévenir. J Chir (Paris) 2005;142(1):44–45.

J Gastrointest Surg (2009) 13:1111–1115
DOI 10.1007/s11605-009-0829-3

ORIGINAL ARTICLE

Fertility Preservation for Young Women with Rectal Cancer—A Combined Approach from One Referral Center

Shai E. Elizur · Togas Tulandi · Sarkis Meterissian · Jack Y. J. Huang · Dan Levin · Seang Lin Tan

Received: 24 December 2008 / Accepted: 28 January 2009 / Published online: 18 February 2009

Abstract
Background Up to 6% of women with colorectal cancer are diagnosed in the reproductive age and are at risk for premature ovarian failure and infertility due to pelvic irradiation and chemotherapy.
Study Design Between 1997 and 2007, six women with rectal carcinoma were referred to the McGill Reproductive Center (Montreal, Canada) for fertility preservation. Following resection of their primary tumor, they were scheduled to undergo pelvic irradiation.
Results Five patients underwent laparoscopic ovarian lateral transposition before radiotherapy in order to relocate their ovaries outside the radiation field. A concomitant ovarian wedge resection was performed for ovarian cryopreservation. In two of these women, before dissecting the ovarian cortical tissue for cryopreservation, all visible follicles were aspirated. The sixth patient who had had low anterior resection underwent hormonal ovarian stimulation followed by oocyte retrieval and embryo vitrification.
Conclusions Fertility preservation in women with rectal cancer is feasible. This includes laparoscopic ovarian transposition and cryopreservation of ovarian tissue, embryo, or oocyte.

Keywords Rectal cancer · Fertility preservation · Ovarian transposition

Introduction

Colorectal cancer is the third most common malignant disease and the second most frequent cause of cancer-related death in the USA. Worldwide, colorectal cancer is the fourth most commonly diagnosed malignant disease, with an estimated 1,023,000 new cases and 529,000 deaths each year.[1] Ninety percent of patients are diagnosed after the age of 55 years. However, 3–6% of patients with colorectal cancer are diagnosed in the 20- to 40-year-old age group, and nearly 48% of these patients are women. It seems that young patients present with a late-stage disease and aggressive histopathologic forms of colorectal cancer.[2] Unfortunately, only 15% of women aged 18–45 years with colorectal cancer received pretreatment fertility counseling.[3]

We present six young women with rectal cancer who underwent fertility preservation. We used a combined approach of laparoscopic lateral ovarian transposition and ovarian tissue and oocyte or embryo cryopreservation.

Material and Methods

Between 1997 and 2007, six women with rectal carcinoma were referred to the McGill Reproductive Center (Montreal, Canada), a university-based tertiary medical center, by their primary physician. They had undergone resection of the primary tumor and were scheduled to undergo further

S. E. Elizur (✉) · T. Tulandi · J. Y. J. Huang · D. Levin · S. L. Tan
Department of Obstetrics and Gynecology,
Division of Reproductive Endocrinology and Infertility,
McGill University,
Montreal, Quebec H3A 1A1, Canada
e-mail: shai.elizur@gmail.com

S. Meterissian
Department of Surgery, McGill University,
Montreal, Quebec, Canada

treatment with pelvic irradiation and 5-fluorouracil (5FU). Each patient was evaluated and consulted by a reproductive endocrinology and infertility specialist and a qualified coordinating nurse regarding the various fertility preservation options.

Five patients consented to laparoscopic ovarian transposition before radiotherapy. The sixth patient who had had low anterior resection underwent hormonal ovarian stimulation followed by oocyte retrieval and embryo vitrification.

The procedure of ovarian lateral transposition has been previously described.[4] Briefly, using a laparoscopic approach, the course of both ureters was followed, and the ovarian ligament was electrocoagulated and divided. The same procedure was performed on the mesovarium. The dissection was continued to the infundibulopelvic ligament, but the vascular pedicle inside the ligament was left intact. The ovaries were then mobilized to the level of the anterior superior iliac spine without transecting the fallopian tubes and anchored to the peritoneum with two sutures. Laparoscopic ovarian suspension was performed by one surgeon (TT).

A concomitant ovarian wedge resection was performed for ovarian cryopreservation. We excised approximately one third to half of ovary. In two cases before dissecting the ovarian cortical tissue for cryopreservation, all visible follicles were aspirated with an 18-gauge syringe needle that was attached to a 10-mL syringe.[5] The aspirates were flushed in oocyte washing medium (CooperSurgical/Sage, Trumbull, CT, USA) and searched for cumulus–oocyte complexes under the dissecting microscope. Following follicle aspiration, the ovarian cortical tissues were isolated in the oocyte washing medium, cut into 4 mm^3 ($2\times2\times1$) pieces, and searched for the presence of additional oocytes. Immature oocytes were matured in an organ tissue culture dish (60×15 mm^2; Falcon, NJ, USA) containing 1.0 mL of In vitro maturation (IVM) medium (Coopersurgical/Sage, CT, USA) supplemented with a final concentration of 75 mIU/mL of follicle-stimulating hormone and luteinizing hormone at 37°C in an atmosphere of 5% CO_2 in air with high humidity. Oocyte vitrification and ovarian tissue cryopreservation was performed as previously described.[5]

Results

We performed ovarian transposition in five women (Table 1). Two weeks following low anterior resection, case 1 was reoperated for a pelvic abscess and vaginal fistula. Due to severe pelvic adhesions, we did not offer ovarian transposition, and she was treated with hormonal ovarian stimulation followed by oocyte aspiration. Six mature oocytes were retrieved, five of them fertilized, and five embryos vitrified.

Cases 2 to 6 underwent laparoscopic ovarian transposition and ovarian cryopreservation. In cases 3 and 5, before dissecting the ovarian cortical tissue for cryopreservation, all visible follicles were aspirated. In case 3, no oocytes were aspirated, and therefore, only ovarian tissue was cryopreserved. In case 5, three germinal vesicle (GV) stage oocytes were aspirated and incubated in IVM medium. Two oocytes matured in vitro and were vitrified (Table 2).

All women completed fertility preservation treatment successfully. No complications occurred following the procedure, and all patients were able to initiate their radio/chemotherapy regimen, as scheduled. Patient 2 conceived spontaneously 2 years after her operation and delivered a healthy child.[6] Subsequently, she conceived again but had a miscarriage.

Discussion

Colorectal cancer may affect women of reproductive age. Beside surgery, these women frequently require adjuvant treatment with pelvic irradiation that is deleterious to their ovaries.

The tremendous improvement in cancer treatment the last three decades has resulted in a steady increase in the

Table 1 Characteristic of Six Women with Rectal Cancer Who Underwent Fertility Preservation

Number	Age	Stage of rectal cancer	Presence of male partner	Adjuvant treatment	Fertility preservation
1	34	T3cN1	Yes	5FU and radiotherapy	IVF and embryo vitrification
2	33	T1NxMx	Yes	5FU and radiotherapy	Lap. lat. ov. trans. and rt. ov. wedge resection for cryo
3	29	T3N1M0	No	5FU and radiotherapy	Lap. lat. ov. trans. and rt. ov. wedge resection for cryo
4	39	T2N2Mx (anal carcinoma)	Yes	5FU, mitomycin, and radiotherapy	Lap. lat. ov. trans. and rt. ov. wedge resection for cryo.
5	38	T3N0M0	Yes	5FU and radiotherapy	Lap. lat. ov. trans. and rt. ov. wedge resection for cryo. and IVM with oocytes vitrification
6	28	T3N1M0	Yes	Radiotherapy	Lap. lat. ov. trans. and rt. ov. wedge resection for cryo

Lap. lat. ov. trans. laparoscopic lateral ovarian transposition, *Rt. ov.* right ovary, *Cryo* cryopreservation

Table 2 Fertility Preservation in Six Women with Rectal Cancer

Number	Age	Ovarian transposition	Ovarian tissue cryopreservation	Embryo cryopreservation	Oocyte cryopreservation
1	34	No	No	5 embryos	No
2	33	Yes	Yes	No	No
3	29	Yes	Yes	No	No
4	39	Yes	Yes	No	No
5	38	Yes	Yes	No	2 oocytes
6	28	Yes	Yes	No	No

survival rates of these patients. It has been shown that women face chemotherapy with greater equanimity if they have had fertility preservation.[7]

Radiation therapy is an important adjuvant treatment in rectal cancer, and clearly, preoperative administration has improved rates of local control.[8] Our paper deals mainly with the preservation of fertility in women undergoing radiation therapy. Whether administered pre- or postoperatively, the considerations for preservation of female fertility are similar, although if administered preoperative, referral to an infertility clinic must be done early on.

The degree and persistence of ovarian damage following pelvic irradiation is related to the patient's age, the total dose, and the number of episodes needed to deliver the dose. Radiation is more toxic when given in a single dose compared with fractionated doses.[9] Two studies indicated that the breakpoint for radiation-induced ovarian failure is approximately 300 cGy to the ovaries. Only 11–13% experienced ovarian failure below 300 cGy versus 60–63% above that threshold value.[10] The radiation doses to the ovaries with standard pelvic irradiation for colorectal cancer (50–65 Gy) will uniformly induce ovarian failure. With shielding over the ovaries and uterus, the total ovarian dose of radiation is reduced to 8–15%; however, there may be scatter and transmission through the shield.

Therefore, laparoscopic ovarian transposition is the preferred fertility preservation option for women with colorectal cancer before pelvic irradiation. In women younger than 40 years, it is associated with preservation of ovarian function in 88.6% of the cases.[6] Before surgery, the field of radiation can be outlined by a radiation oncologist. This will give an idea of how high and lateral the ovaries should be transposed. In practice, placing the ovaries above the pelvic brim and as lateral as possible will place them outside the radiation field. The transposed ovaries should be securely sutured to the peritoneum. The inferior border of the ovary is marked with vascular hemoclips bilaterally. Ovarian transposition can be performed with preservation of the integrity of the fallopian tubes allowing a possible future spontaneous conception.[6]

Of the chemotherapeutic agents used to treat colorectal cancer patients, oxaliplatin has moderate gonadotoxic effects, while 5FU has mild or no gonadotoxic potential.[11] The chemotherapeutic agent of choice in conjunction with radiation therapy is continuous infusion 5FU.[12] It acts against epithelial malignancies arising in the gastrointestinal tract, breasts, as well as the head and neck. It has been shown not to adversely affect human reproductive function.[13] There has been only a single report in the literature of 5FU-induced infertility; so overall, it is a safe drug.[14]

Oxaliplatin, in combination with 5FU and leucovorin, is used postoperatively as adjuvant therapy for stage III and aggressive stage II disease.[8] By the time oxaliplatin is used, the patient should already have had a variety of fertility preservation options, such as ovarian transposition, oocyte cryopreservation, and/or ovarian tissue cryopreservation.

During laparoscopy, a portion of the ovary could be removed for ovarian cryopreservation. This allows the patient to maintain her options of fertility and of autografting her ovary if ovarian failure occurs.[15] Ovarian tissue cryopreservation was performed for all of our patients who underwent laparoscopic ovarian transposition without any complications or significant prolongation of operation time. The goal of cryobanking ovarian tissue is to preserve the primordial and primary follicles. They comprise 70–90% and 20–30% of ovarian follicles, respectively.[16, 17] However, secondary and antral follicles, which account for about 7% of the follicular population, do not survive the cryopreservation procedure.[18] Possible explanations for their poor tolerance to cryopreservation include their complex cellular structure, leading to incomplete cryoprotectant penetration, and their large water content, resulting in the formation of ice crystals. In addition, follicular atresia may be hastened after thawing due to ischemic damage to the ovarian vasculature.[19]

In order to cryopreserve a number of oocytes, we aspirated all visible antral follicles before preparing the ovarian tissue for cryopreservation in cases 3 and 5. In case 5, we aspirated three immature oocytes at a GV stage. Two of these oocytes matured in vitro following incubation in special IVM media and were vitrified. Immature oocyte retrieval followed by IVM has become an effective option for infertile women with polycystic ovaries or polycystic ovary syndrome, resulting in acceptable clinical pregnancy

and implantation rates per embryo transfer.[20, 21–24] More than 400 healthy infants have been born to date.[25] We recently reported that oocytes, which were matured in vitro and vitrified, resulted in a birth of a healthy offspring.[26] Our live birth rate is 20% using vitrified-thawed in vitro matured oocytes.[27] It appears that this method of fertility preservation is safe and promising.[28] In a review of 200 babies conceived following oocyte vitrification, we did not find increased risk of adverse obstetric and perinatal outcomes.[29]

By using combined fertility preservation technique of ovarian transposition, ovarian tissue cryopreservation, and in vitro maturation and vitrification of oocytes or embryos (when a male partner is available), we were able to provide women three different fertility preservation treatments using only one surgical procedure. It is believed that with irradiation doses in the range of 85 Gy with external beam plus intracavitary brachytherapy, the resultant endometrial damage may preclude successful pregnancy due to endometrial damage.[30] Contrary to this notion, one of our patients conceived and delivered a healthy female baby. At the time of this writing, she is a healthy 7-year-old girl.

Conclusions

Fertility preservation in women with rectal cancer is feasible. This includes laparoscopic ovarian transposition and cryopreservation of ovarian tissue, embryo, or oocyte.

Acknowledgment We wish to thank Dr. Gary Mok for his assistance in collecting the data.

References

1. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. N Engl J Med 2005;352:476–487. doi:10.1056/NEJMra040958.
2. O'Connell JB, Maggard MA, Liu JH, Etzioni DA, Livingston EH, Ko CY. Do young colon cancer patients have worse outcomes? World J Surg 2004;28:558–562. doi:10.1007/s00268-004-7306-7.
3. Strong M, Peche W, Scaife C. Incidence of fertility counseling of women of child-bearing age before treatment for colorectal cancer. Am J Surg 2007;194:765–767. (discussion 767–768). doi:10.1016/j.amjsurg.2007.08.031.
4. Tulandi T, Al-Took S. Laparoscopic ovarian suspension before irradiation. Fertil Steril 1998;70:381–383. doi:10.1016/S0015-0282(98)00155-1.
5. Huang JY, Tulandi T, Holzer H, Tan SL, Chian RC. Combining ovarian tissue cryobanking with retrieval of immature oocytes followed by in vitro maturation and vitrification: an additional strategy of fertility preservation. Fertil Steril 2008;89:567–572. doi:10.1016/j.fertnstert.2007.03.090.
6. Bisharah M, Tulandi T. Laparoscopic preservation of ovarian function: an underused procedure. Am J Obstet Gynecol 2003;188:367–370. doi:10.1067/mob.2003.38.
7. Partridge AH, Gelber S, Peppercorn J, et al. Web-based survey of fertility issues in young women with breast cancer. J Clin Oncol 2004;22:4174–4183. doi:10.1200/JCO.2004.01.159.
8. Gill S, Blackstock AW, Goldberg RM. Colorectal cancer. Mayo Clin Proc 2007;82:114–129.
9. Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod Update 2001;7:535–543. doi:10.1093/humupd/7.6.535.
10. Husseinzadeh N, Nahhas WA, Velkley DE, Whitney CW, Mortel R. The preservation of ovarian function in young women undergoing pelvic radiation therapy. Gynecol Oncol 1984;18:373–379. doi:10.1016/0090-8258(84)90049-0.
11. Marhhom E, Cohen I. Fertility preservation options for women with malignancies. Obstet Gynecol Surv 2007;62:58–72. doi:10.1097/01.ogx.0000251029.93792.5d.
12. Hosein PJ, Rocha-Lima CM. Role of combined-modality therapy in the management of locally advanced rectal cancer. Clin Colorectal Cancer 2008;7:369–375. doi:10.3816/CCC.2008.n.049.
13. Meistrich ML, Vassilopoulou-Sellrin R, Lipshultz LI. Gonadal Dysfunction. In DeVita VT, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology. Philadelphia: Lippincott Williams & Wilkins, 2001.
14. Azem F, Amit A, Merimsky O, Lessing JB. Successful transfer of frozen-thawed embryos obtained after subtotal colectomy for colorectal cancer and before fluorouracil-based chemotherapy. Gynecol Oncol 2004;93:263–265. doi:10.1016/j.ygyno.2003.12.030.
15. Meirow D, Levron J, Eldar-Geva T, et al. Pregnancy after transplantation of cryopreserved ovarian tissue in a patient with ovarian failure after chemotherapy. N Engl J Med 2005;353:318–321. doi:10.1056/NEJMc055237.
16. Gougeon A. Dynamics of follicular growth in the human: a model from preliminary results. Hum Reprod 1986;1:81–87.
17. Lass A, Silye R, Abrams DC, et al. Follicular density in ovarian biopsy of infertile women: a novel method to assess ovarian reserve. Hum Reprod 1997;12:1028–1031. doi:10.1093/humrep/12.5.1028.
18. Gosden RG. Gonadal tissue cryopreservation and transplantation. Reprod Biomed Online. 2002;4(Suppl 1):64–67.
19. Revel A, Schenker J. Ovarian tissue banking for cancer patients: is ovarian cortex cryopreservation presently justified? Hum Reprod 2004;19:14–19. doi:10.1093/humrep/deh002.
20. Elizur SE, Son WY, Yap R, et al. Comparison of low-dose human menopausal gonadotropin and micronized 17beta-estradiol supplementation in in vitro maturation cycles with thin endometrial lining. Fertil Steril. 2009; in press.
21. Chian RC, Lim JH, Tan SL. State of the art in in-vitro oocyte maturation. Curr Opin Obstet Gynecol 2004;16:211–219. doi:10.1097/00001703-200406000-00003.
22. Chian RC, Buckett WM, Tulandi T, Tan SL. Prospective randomized study of human chorionic gonadotrophin priming before immature oocyte retrieval from unstimulated women with polycystic ovarian syndrome. Hum Reprod 2000;15:165–170. doi:10.1093/humrep/15.1.165.
23. Chian RC, Gulekli B, Buckett WM, Tan SL. Priming with human chorionic gonadotropin before retrieval of immature oocytes in women with infertility due to the polycystic ovary syndrome. N Engl J Med 1999;341(21):1624–1626.
24. Son WY, Chung JT, Herrero B, et al. Selection of the optimal day for oocyte retrieval based on the diameter of the dominant follicle in hCG-primed in vitro maturation cycles. Hum Reprod 2008;23:2680–2685. doi:10.1093/humrep/den332.
25. Jurema MW, Nogueira D. In vitro maturation of human oocytes for assisted reproduction. Fertil Steril 2006;86:1277–1291. doi:10.1016/j.fertnstert.2006.02.126.
26. Chian RC, Gilbert L, Huang JY, et al. Live birth after vitrification of in vitro matured human oocytes. Fertil Steril 2009; in press.

27. Chian RC, Huang JY, Gilbert L, et al. Obstetric outcomes following vitrification of in vitro and in vivo matured oocytes. Fertil Steril. 2009; in press.
28. Elizur SE, Chian RC, Pineau CA, et al. Fertility preservation treatment for young women with autoimmune diseases facing treatment with gonadotoxic agents. Rheumatology 2008;47:1506–1509. doi:10.1093/rheumatology/ken293.
29. Chian RC, Huang JY, Tan SL, et al. Obstetric and perinatal outcome in 200 infants conceived from vitrified oocytes. Reprod Biomed Online 2008;16:608–610.
30. Farber LA, Ames JW, Rush S, Gal D. Laparoscopic ovarian transposition to preserve ovarian function before pelvic radiation and chemotherapy in a young patient with rectal cancer. MedGenMed 2005;7:66.

J Gastrointest Surg (2009) 13:1116–1119
DOI 10.1007/s11605-009-0826-6

ORIGINAL ARTICLE

The Use of the Loose Seton Technique as a Definitive Treatment for Recurrent and Persistent High Trans-Sphincteric Anal Fistulas: A Long-Term Outcome

Arieh Eitan · Marina Koliada · Amitai Bickel

Received: 24 January 2009 / Accepted: 28 January 2009 / Published online: 24 February 2009

Abstract
Background The loose seton technique (suggested to avoid any external anal division following seton placement, to ensure anal continence) was assessed as the ultimate approach for primary as well as recurrent and persistent anal fistula.
Study Design Between 2000 and 2006, 97 patients were operated for trans-sphincteric anal fistula, 41 patients of whom (42.3%) underwent the loose seton technique. The outcome was assessed periodically at the outpatient colorectal clinic and finally by detailed telephonic questionnaire. Mean age was 45.3 years. Thirty one operations were elective (75.6%). Fifteen (36.5%) patients had concomitant diseases, of whom three suffered from Crohn's disease. Twenty nine patients had previous anal operations.
Results The time from seton placement to its removal ranged from 3 to 7 months. At short-term follow-up, early complications were noted in five patients (bleeding in one and abscess formation in four). Late complications included liquid stool soiling in one patient (2.4%), solid soiling in two, and mucous discharge in three. Post-operative clinical assessment of incontinence according to Cleveland Clinic Incontinence Score revealed scoring ranging from 2 to 6 in those six patients. Neither gross stool nor flatus incontinence was noted. Fistula recurrence (persistence) was noted in eight (19.5%) patients and successfully treated by the same loose seton technique.
Conclusions The loose seton technique for trans-sphincteric anal fistula carries favorable results and can be safely applied while preserving the external sphincter function. We also recommend repeating the technique in case of post-operative fistula recurrence or persistence.

Keywords Perianal fistula · Loose seton technique · Anal incontinence

Introduction

The trans-sphincteric fistulae constitute about 30–40% of all perianal fistulae (according to Parks' classification). In this type, the primary tract passes through the external sphincter into the ischiorectal fossa. The fistula may be uncomplicated or associated with secondary tracts. In general, surgical treatment for fistula aims to cure the disease by abolishing and draining the primary and secondary tracts, while maintaining continence.[1–3]

The oldest strategy suggested to approach surgical repair of fistula was by using the seton, enabling preservation of the sphincter mechanism.[4] The staged fistulotomy using a seton (usually by using a polypropylene thread to encircle the external anal sphincter) is regarded as one of the techniques to deal with trans- and supra-sphincteric perianal fistulas.[1,2,5,6] The seton works by several mechanisms: (1) It assists in identifying and marking the fistula tract during excision of a trans-sphincteric fistula; (2) it helps in draining pus and controlling sepsis prior to definitive treatment; (3) it stimulates fibrosis to prevent retraction of

A. Eitan · M. Koliada
Department of Surgery, Western Galilee Hospital, Nahariya, affiliated to the Faculty of Medicine, the Technion, Israel Institute of Technology, Haifa, Israel

A. Bickel (✉)
Department of Surgery, Western Galilee Hospital, P.O. Box 21, Nahariya 22100, Israel
e-mail: amitai@netvision.net.il

the cut ends of the external sphincter, following delayed division for completion of fistulotomy; (4) the tight (cutting) seton promotes slow transaction of the external sphincter muscle.[7–9] The loose seton technique was further suggested in an attempt to avoid any external anal sphincter division following treatment of complex anal fistulae, thus ensuring anal continence.[10–13] In cases of failed treatment (recurrence or persistence of fistulae), it is a common practice to complete fistulotomy by division of the external sphincter, which might be accompanied by some degree of incontinence.[12] In our study, we used the loose seton technique repetitively for the treatment of this sub-population.

The aim of our study was to evaluate long-term outcome following the loose seton technique as the ultimate procedure for trans-sphincteric anal fistula, primary, as well as for recurrent and persistent, namely, without delayed muscle division.

Patients and Methods

During a 6-year period (January 2000 to January 2006), 97 patients were operated for trans-sphincteric anal fistula. Data was collected retrospectively. The loose seton technique was implemented in 41 (42.3%) patients. This study group included 36 male (87.8%) and five females. Mean age was 45.3 years (range 21 to 86 years). Thirty one (75.6%) operations were done on an elective basis. Concomitant diseases were inspected in 15 (36.5%) patients, including Crohn's disease in three patients. Previous anal operations had already been performed in 29 patients, including abscess drainage in 27, fistulotomy in seven, and lateral sphincterotomy in five patients. Concerning the type of treated fistulae, 38 patients suffered from high trans-sphincteric fistula and three had complex fistula related to Crohn's disease.

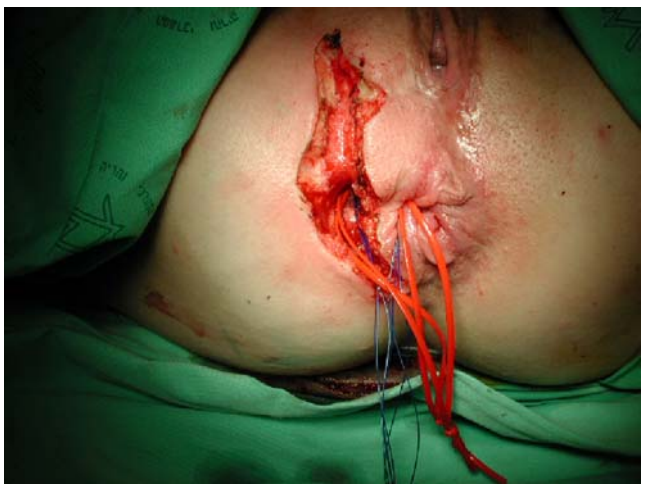

Figure 1 A loosely tied no. 1 prolene or rubber seton placed to encircle the remaining external anal sphincter and the internal sphincter.

Table 1 High Trans-Sphincteric Fistula Treated by the Loose Seton Technique

Description of data	Number (range, percentage)
Total no. of patients	97
Loose seton technique	41 (42.3%)
Mean age	45.3 (21–86)
Elective operations	31 (75.6%)
Previous anal operations	29
Type of fistula (no. of patients)	
High trans-sphincteric	38 patients
Complex	3 (Crohn's)
Follow-up duration	5.1 (2–8) years
Duration of loose seton placement	4.9 (3–7) months
Perioperative (early) complications	
Total	5 patients (12%)
Post-op. bleeding	1
Superficial abscess formation	4
Late complications	6 patients
Liquid stool soiling	1 (2.4%)
Solid stool soiling	2 (4.8%)
Mucous discharge	3 (7.3%)
Gross stool or flatus incontinence	0 (%)
Fistula persistence	8 (19.5%)

In short, the technique involved initial examination of the anal canal under anesthesia, identification and lying open of secondary extensions, excising the anal mucosa and opening of the inter-sphincteric space with an attempt to preserve the internal anal sphincter as much as possible, and eradication of affected anal glands. Finally, a loosely tied no. 1 prolene or rubber seton is placed to encircle the remaining external anal sphincter and the internal sphincter whenever possible (Fig. 1). The seton was removed after a minimal period of 3 months, leaving a tract for spontaneous healing. In some patients, the seton was removed after a longer period, mainly due to their delayed arrival for follow-up. In case of recurrence or persistency of fistule, the remaining tract was identified, undergoing debridement, and further loosely encircled by the seton without sphincter division.

During follow-up (until January 2008), the patients were admitted periodically to our colorectal outpatient clinic for physical evaluation until complete healing was observed. Clinical anal continence was assessed according to the Cleveland Clinic Incontinence Score.[14] In cases of fistula persistence, the patients were admitted for further surgical treatment. Outcome was assessed retrospectively by patients' medical charts review (based on our follow-up). Prior to final analysis of our data, a detailed telephone questionnaire was carried out to complete the long-term outcome.

Results

Mean follow-up duration was 5.1 years and ranged from 2 to 8 years (between 2 and 3 years—seven patients; 4 years—five patients; 5 years—ten patients; 6 years—12 patients; 7 years—six patients; 8 years—one patient). The mean time from seton placement to its removal was 4.87 months and ranged from 3 to 7 months (3 months—six patients; 4 and 5 months—ten patients each; 6 months—11 patients; 7 months—three patients). In one patient, we could not obtain the required data.

Early (perioperative) complications were noted in five (12%) patients; one suffered from post-operative bleeding and four had superficial abscess formation. Late (persistent) complications were found in six patients; one (2.4%) had liquid stool soiling, two (4.8%) had solid soiling, and three (7.3%) experienced mucous discharge. The preoperative fecal incontinence severity score was zero for all the study population. Post-operative fecal incontinence score were recorded to be zero for 35 patients, 2 for three patients, and 4, 5, and 6 for one patient each. Post-operative pad usage was sometimes noted in three patients. Gross stool or flatus incontinence was not recorded (Table 1). Fistula persistence (non-healing fistula) was recorded in eight (19.5%) patients.

Successful treatment (healing) of fistula persistence was achieved in all those cases by the same loose seton technique. The duration of secondary seton placement was for at least 3 months.

Discussion

In our study, we have demonstrated that, after an unsuccessful attempt to achieve a complete repair of high trans-sphincteric and complex fistula by the loose seton technique, division of the external anal sphincter is actually not obligatory in order to achieve satisfactory fistulous tract healing. Although time consuming, all eight (19.5% of the study group) patients who did not recover completely by the primary procedure healed successfully following repetitive debridement and loose seton application. The consequent obvious surgical advantage was avoidance of the interruption of the sphincter mechanism which may lead to anal incontinence.

However, this is a retrospective study, which is its main drawback.

Generally speaking, our results concerning the success rate of the loose seton technique are fair in comparison to previous studies (between 44% and 83% of short-term successful healing), as about 80% of our patients healed satisfactorily following the procedure.[5,10–15]

Our study group is rather large, and the complication rate (especially liquid and solid stool soiling) was relatively low, around 5%.

As this technique does not involve the cutting of the external anal sphincter and lying open of the fistulous tract for secondary repair, its success rate might be lower in comparison to the latter, and its efficacy of treatment may fall over a long term of follow-up.[10]

However, the completion of the division of the sphincter is common following failure of the loose seton technique (recurrence or persistence) in order to achieve successful healing. The price is a potential insult to the continence of the anal mechanism. This was successfully avoided by re-insertion of the seton, without further division of the anal sphincter. In addition, our efforts to preserve the internal anal sphincter have also contributed to the low incontinence rate. Another clear advantage of re-insertion of the loose seton in cases of fistula persistence/recurrence derives from the fact that, following a failed attempt of an initial treatment of a complex fistula by the loose seton technique, the primary fistulous tract usually becomes shorter and better defined (in comparison to the initial pre-treatment anal sepsis illness). Accordingly, this makes it more suitable for a successful eradication by secondary application of a loose seton through it, as was demonstrated in our study (eight patients). The approach of seton re-insertion in case of recurrence has already been documented for complex anal fistula in patients with Crohn's disease, though not necessarily as a completely definitive approach.[7] Considering the various surgical armamentarium to deal with difficult fistula like high trans-sphincteric or complex fistula, the loose seton approach, though necessitates a prolonged waiting period, avoids a significant rate of continence complications that is related to external sphincter division and that may be over 50%.[1–3,12,13] In conclusion, loose seton approach is efficacious as a definitive long-term treatment for primary high trans-sphincteric anal fistula, and we further advocate its beneficial use in cases of persistence or recurrence. However, we recommend a prospective and randomized study to assess our data.

References

1. Phillips RKS, Lunniss PJ. Anorectal sepsis. In Nicholls RJ, Dozois RR, eds. Surgery of the colon & rectum. New York: Churchill Livingstone, 1997, pp 255–284.
2. Scott NA, Keighley M. Anorectal fistula. In: Keighley MRB, Wiliams NS ed. Surgery of the anus, rectum and colon. W.B. Saunders, 1999, pp. 488–530.
3. van Tets WF, Kuijpers HC. Continence after anal fistulotomy. Dis Colon Rectum 1994;37:1194–1197.
4. McCourtney JS, Finlay IG. Setons in the surgical management of fistula in ano. Br J Surg 1995;82:448–452.
5. Williams JG, MacLeod CA, Rothenberger DA, Goldberg SM. Seton treatment of high anal fistulae. Br J Surg 1991;78:1159–1161.
6. Kuypers HC. Use of seton in the extrasphincteric anal fistula. Dis Colon Rectum 1984;27:109–110.

7. Takesue Y, Ohge H, Yokohama T, Murakami Y, Imamura Y, Sueda T. Long term results of seton drainage on complex anal fistulae in patients with Crohn's disease. J Gastroenterol 2002;37:912–915.
8. Theerapol A, So BYJ, Ngoi SS. Routine use of setons for the treatment of anal fistulae. Singapore Med J 2002;43:305–307.
9. Durgun V, Perek A, Kapan M, Kapan S, Perek S. Partial fistulotomy and modified cutting seton procedure in the treatment of high extrasphincteric perianal fistulae. Dig Surg 2002;19:56–58.
10. Buchanan GN, Owen HA, Torkington J, Lunniss PJ, Nicholls RJ, Cohen CRG. Long term outcome following loose-seton technique for external sphincter preservation in complex anal fistula. Br J Surg 2004;91:476–480.
11. Kennedy HL, Zegarra JP. Fistulotomy without external sphincter division for high anal fistulae. Br J Surg 1990;77:898–901.
12. Thomson JPS, Ross AHM. Can the external anal sphincter be preserved in the treatment of trans-sphincteric fistula-in-ano. Int J Colorect Dis 1989;4:247–250.
13. Lunniss PJ, Thomson JPS. The loose seton. In Phillips RKS, Lunniss PJ, eds. Anal fistula: surgical evaluation and management. London: Chapman and Hall Medical, 1996, pp 87–93.
14. Jorge JMN, Wexner SD. Etiology and management of fecal incontinence. Dis Colon Rectum 1993;36:77.
15. Hammond TM, Knowles CH, Porrett T, Lunniss PJ. The snug Seton; short and medium term results of slow fistulotomy for idiopathic anal fistula. Colorectal Dis 2006;8:328–337.

J Gastrointest Surg (2009) 13:1120–1124
DOI 10.1007/s11605-008-0585-9

HOW I DO IT

How I Do It: Laparoscopic Heller Myotomy with Toupet Fundoplication for Achalasia

Roger P. Tatum · Carlos A. Pellegrini

Received: 15 April 2008 / Accepted: 16 June 2008 / Published online: 12 July 2009

Abstract Achalasia, an esophageal motility disorder characterized by aperistalsis and failure of lower esophageal sphincter (LES) relaxation, is most effectively treated by surgical ablation of the LES. In this report, we describe our technique of laparoscopic extended Heller myotomy with Toupet partial posterior fundoplication. The technical details of this procedure include careful division of the longitudinal and circular muscle fibers of the LES anteriorly, including extension of the myotomy 3 cm distal to the esophagogastric junction onto the gastric cardia. The Toupet procedure, involving a posterior wrap of the gastric fundus which is secured to both edges of the myotomy as well as to the crura of the hiatus, is added to prevent post-myotomy gastroesophageal reflux. From a recently published report, mean dysphagia scores remained low (3 out of 10 severity on a visual analog scale) and symptoms of reflux were reported minimally in a series of 63 patients followed for a median of 45 months. This technique provides excellent and durable relief of dysphagia associated with achalasia while minimizing post-myotomy acid reflux symptoms.

Keywords Achalasia · Heller myotomy · Antireflux procedure

Introduction

Achalasia is a relatively rare but well-known esophageal motility disorder involving the failure of relaxation of the lower esophageal sphincter (LES) upon swallowing and the loss of esophageal peristalsis. While not specifically curable, treatment for achalasia is aimed at ablation of the LES in order to relieve the symptoms of dysphagia and regurgitation invariably produced by this disease. The first such therapy, described by Thomas Willis in 1674, involved rigid esophageal dilation with a sponge-tipped whalebone.[1] Surgical treatment was introduced by Ernest Heller in 1913, consisting of an anterior and posterior myotomy across the LES performed via a thoracotomy.[2] Much more recently, the laparoscopic technique has become the most widely used surgical approach to this disease, yielding excellent results which are generally superior to non-surgical therapy. The purpose of this report is to describe in detail how we perform the extended laparoscopic Heller myotomy with Toupet fundoplication for achalasia. Results from a recently published series with long-term follow-up are included to illustrate the success and durability of this particular technique.[3]

Technique

All patients are routinely evaluated with upper endoscopy, barium esophagography, and esophageal manometry to confirm the diagnosis and plan the procedure. The patient is prepared for surgery in the standard fashion, with orders to be NPO after midnight. For patients who present with a dilated esophagus, in particular those with esophageal dilatation greater than 4 cm and/or with a long or tortuous esophagus, we will discontinue solid food 4–5 days prior to the procedure and utilize a high-energy liquid diet. The idea is to clear the esophagus of solid debris as much as

R. P. Tatum (✉) · C. A. Pellegrini
Department of Surgery, University of Washington,
VA Puget Sound HCS, 1660 S. Columbian Way, s-112-gs,
Seattle, WA 98108, USA
e-mail: rtatum@u.washington.edu

possible. A first-generation cephalosporin such as cefazolin is given as antibiotic prophylaxis prior to incision. The patient is placed under general endotracheal anesthesia and then positioned in low-lithotomy; a bean-bag underneath the patient is secured to the table in order to prevent slippage when the patient is subsequently placed in a steep reverse-Trendelenberg position. Alternatively, a pair of safety belts may be mounted on each side of the operating table and used to secure the patient's thighs, in essence, forming a sling rather like a climbing harness. It is also helpful to turn the operating table at an approximately 30° angle to the long axis of the room, so that the laparoscopic tower and screen may be placed at the patient's left shoulder leaving the head of the table free for the anesthesia team and for the surgeon in the event the need arises for instrumentation (endoscopy) of the esophagus.

Pneumoperitoneum is obtained using a Veress needle technique, either in the left subcostal position or at the primary camera position, a point approximately 2 cm above and 1–2 cm to the left of the umbilicus, as desired. The remaining ports, five in all, are placed in a fashion identical to that used in a laparoscopic antireflux procedure (Fig. 1). It is our practice to use a 10-mm supraumbilical port for a 10-mm, 30° laparoscope, (a good quality 5 mm laparoscope can be used instead) 10 mm ports in the right and left subcostal positions respectively, a 10 mm right flank port, and a 5 mm left flank port. The right flank port may be omitted in patients with relatively small livers if one chooses a Nathason retractor which can be placed through a 4–5-mm epigastric opening without a port. The left lateral segment of the liver is then retracted with a paddle-style liver retractor through the right flank port (or the Nathanson through the epigastric entry site). Either retractor is secured using a table-mounted "iron intern" self-retracting device.

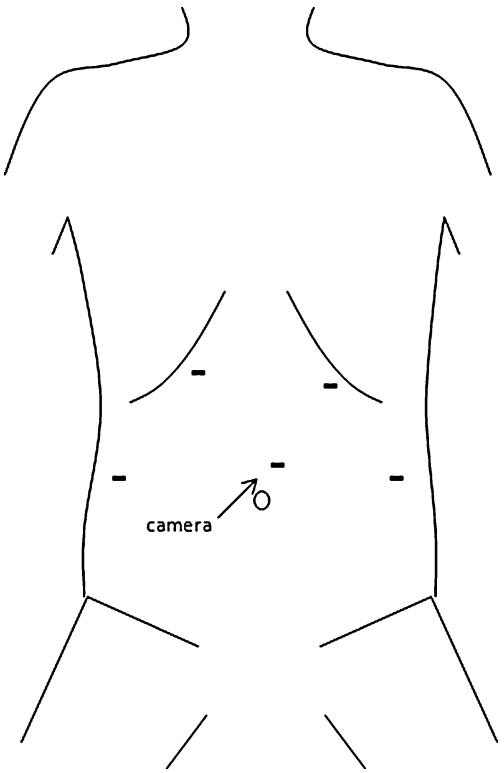

Figure 1 Port placement for laparoscopic Heller myotomy

A point is chosen along the greater curvature of the stomach approximately 1/3 of the way distal to the esophagogastric junction, and the short gastric vessels are divided using an ultrasonic coagulator proximally to mobilize the fundus, thus avoiding tension on the antireflux procedure performed subsequent to the myotomy. The hiatus is then dissected and the esophagus is exposed within the distal mediastinum. It is not necessary to dissect the esophagus circumferentially in the mediastinum, only the anterior aspect where the myotomy will be made. The dissection is carried up far enough to permit the performance of the myotomy to 8 cm proximal to the level of the esophagogastric junction. A 1/2-in. Penrose drain placed around the esophagogastric junction is helpful in providing retraction to complete this dissection, and brings the distal esophagus more easily into the operative field, thus limiting the amount of work that needs to be done above the hiatus. The anterior (left) vagus nerve is identified and carefully preserved, and the epigastric fatpad is dissected away to facilitate precise identification of the esophago-gastric junction and the distal extension of the myotomy onto the cardia. In most patients, there is no need to close the hiatus. In fact, we prefer to leave it open as we do not wish to risk compromising the lumen of the esophagus. Thus, when we anticipate performing a partial posterior fundoplication (Toupet type), we dissect both crura free from adjacent tissues but leave the hiatus open and slightly larger than when we started the operation given that we have been dissecting the esophagus up above and have produced some lateral stretching. If a large hiatus hernia is identified, present in approximately 20% of patients with achalasia, the crura may need to be closed, using interrupted sutures posterior to the esophagus. Care must be taken to avoid tightening the hiatus too much, allowing for a small window posterior to the esophagus such that when the dilator is subsequently placed the hiatus is not tightly apposed to the circumference of the esophagus.

A lighted 52-French esophageal dilator is next passed transorally by the anesthesiologist with the tip positioned well into the gastric body. This provides a platform for performance of the myotomy, and aids in identification of the submucosal layer. Notably, it is important to have an anesthesiologist who is very familiar with this surgical procedure and thus experienced and comfortable with placement of the dilator, to best avoid esophageal perforation. Otherwise, it is beneficial for a member of the surgical

team to perform this important step. A 10-mm laparoscopic Babcock clamp is used to spread the anterior esophagus and/or the stomach wall over the Babcock clamp, providing tension on the muscularis and thus facilitating division of the muscle fibers. With that platform in place, we then expose and review the anatomy, identify the location of the previously dissected anterior vagus and, precisely, the gastroesophageal junction (GEJ). We then measure 3 cm below the GEJ, and at a point close to the lesser curvature (usually 2–2.5 cm to the left of the lesser curvature), we start the myotomy over the bougie and move upwards in a straight line towards the GEJ. This is always the most difficult part of the procedure, and it is useful to do it first. It is challenging in this area to clearly identify the muscular planes and to find the mucosa, and it is helpful to divide longer areas (1 cm or so) on the serosa and initial muscular layers and then gently "find" your way through the rest of the muscularis until the mucosa is seen. The deepest part of the muscularis of the stomach in this area, the oblique fibers that are descending from the angle of His down to the lesser curvature, do not easily separate away from the mucosa and a lot of gentle work must be done as the myotomy is enlarged. We usually do the entire 3 cm to the GE junction and then gently re-do the area that has been myotomized until we have good mucosal exposure and completely separated edges. Electrocautery is used rarely and with very short bursts in the area near the mucosa. The myotomy is then continued up through the GEJ and into the body of the esophagus by gently dividing the muscular fibers with either a hook electrocautery or the ultrasonic coagulator to expose the submucosa of the esophagus. The esophageal myotomy is much simpler, as the layers are well delineated (except in patients who received botulinum toxin preoperatively) and the mucosa is thicker with a submucosal plane that allows relative ease of dissection. Both the outer longitudinal and inner circular muscle layers must be identified and divided (Fig. 2). Extension of the myotomy for a distance of 3 cm distally onto the gastric cardia and about 6–8 cm proximally on the esophagus is the goal. Most bleeding encountered during this step of the procedure can be controlled with time and/or the application of pressure using a closed blunt grasper. In our experience, bleeding subsides when it is coming from the submucosal vessels in all instances, sometimes with the application of pressure, or by holding on to the bleeding vessel gently with the grasper. We do not recommend using electrocautery on the mucosa. The vessels that tend to be more worrisome are always within the wall of the esophagus and start bleeding as the muscularis, or the adventitia is divided (the latter is more common in large esophagi and the vessels are superficial to the muscularis). These vessels can and should be controlled either with electrocautery, making sure that the electrocautery is pressed against the muscle and not in contact with the mucosa, or, should the bleeding be more substantial, with an ultrasonic coagulator, a clip (with a tiny piece of muscle attached) or a suture. If a perforation of the mucosa should occur, it is typically easily identified and can be repaired using interrupted intracorporeal stitches with fine (4–0) absorbable suture.

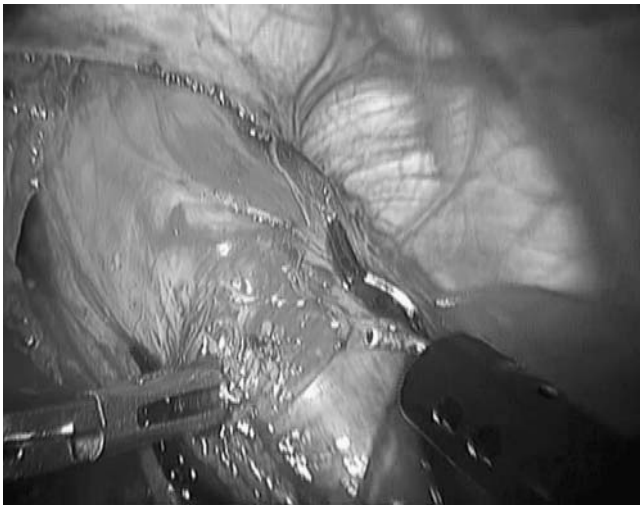

Figure 2 Division of both longitudinal and circular muscle fibers of the LES on the anterior aspect of the esophagus using a hook electrocautery device

Once the myotomy is deemed to be adequate in terms of length, it can be checked using flexible fiberoptic endoscopy, taking great care when approaching the myotomy with the endoscope. The myotomized region should easily open with air insufflation from the scope, and there should be no narrow or tight areas from the esophagus to the stomach. It is sometimes necessary to extend the myotomy at this point based on localization of a residual high-pressure zone. This technique also helps to identify any previously-unrecognized perforation.

The final step is the performance of the antireflux procedure. Our preference is for the Toupet partial posterior fundoplication. This is begun by passing the tip of the gastric fundus posterior to the esophagogastric junction, and securing it with interrupted sutures of 2–0 silk to the right crus of the diaphragm. The fundic tip is then sutured to the right edge of the myotomy, using three sutures. Similarly, the proximal aspect of the fundus is sutured to the left edge of the myotomy, and also to the left crus (Fig. 3). A Dor fundoplication is routinely chosen in patients in whom there has been a perforation of the mucosa so as to buttress the mucosal closure. The procedure is now complete, the ports are all removed, and the port sites closed.

Patients are started on a clear liquid diet after transfer from the post-anesthesia care unit, and a soft diet is begun

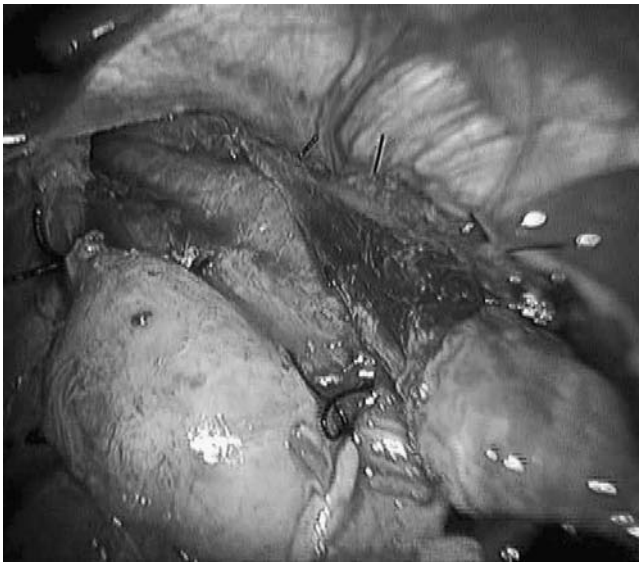

Figure 3 The completed extended myotomy with Toupet fundoplication

the following morning. Patients are typically discharged home on the first postoperative day.

Results

Between 1998 and 2003, 63 patients underwent the laparoscopic extended Heller myotomy with Toupet fundoplication as described above, and these results have been published recently.[3] Mean dysphagia frequency, assessed preoperatively by five-point questionnaire administered to all patients (0="no symptoms," 1="once per month," 2="once per week," 3="daily," and 4="multiple times per day") was 3.8±0.7. There were no significant perioperative complications, and median hospital stay was 1.8±0.6 days. With a median follow-up of 45 months, mean dysphagia frequency was significantly reduced to 1.7±1.4 and mean dysphagia severity scores were 3.1±2.6 on a 0–10 visual analog scale. Other symptoms, including heartburn, were minimal. Three patients required subsequent dilations, between 36 and 56 months after surgery, and no patient required a reoperation. A subset of 31 patients was followed up for a median of 63 months, with similar scores for postoperative dysphagia (3.7±3.0) and other symptoms.[3]

Discussion

The technique described above proves to be a very effective and durable treatment for achalasia, while minimizing the amount of esophageal acid reflux associated with division of the lower esophageal sphincter. In particular, both the length of the myotomy onto the gastric cardia and the performance and choice of an antireflux procedure are important in achieving these results.

Extended Myotomy

The debate concerning the length of the myotomy onto the gastric cardia has evolved over time, and centers around the balance between maximal relief of dysphagia and the prevention of postoperative reflux. The argument for a shorter myotomy proposes that by maintaining some of the "clasp and sling" fibers of the gastric cardia, a component of the antireflux barrier is preserved. Ellis et al., describing their technique of modified Heller myotomy via a left thoracotomy, as it was commonly performed at the time, advocated that the LES be divided only a few millimeters onto the cardia, citing an incidence of clinically significant reflux in only 3% of their patients after the procedure, with good to excellent results in 84%.[4] The first description of a minimally invasive approach to the Heller myotomy emulated this technique using a thoracoscopic approach. Notably, three of 17 patients required an early second operation for extension of the myotomy onto the cardia.[5] A subsequent comparison between 35 patients undergoing the thoracoscopic approach and 133 patients undergoing a laparoscopic Heller myotomy, in which it is easier to extend the myotomy further onto the cardia, yielded good to excellent relief of dysphagia in 85% of the thoracoscopic group compared to 93% of patients approached laparoscopically.[6] Based upon these results and subsequent observations, the laparoscopic technique was further modified at our institution to extend the myotomy a full 3 cm onto the cardia. When compared with a shorter myotomy (1.5 cm onto the cardia) and Dor fundoplication, this extended myotomy has resulted in significantly lower postoperative dysphagia scores and markedly less reintervention.[7]

Antireflux Procedure

The issue of whether or not to perform an antireflux procedure in conjunction with the Heller myotomy has been a longstanding controversy. The incidence of reflux after myotomy performed without some type of antireflux procedure is reported to be as high as 100%. Some authors have expressed concern over the creation of a barrier in the face of an aperistaltic esophagus.[8] However, in a 2004 randomized trial of Heller myotomy with or without Dor partial anterior fundoplasty, Richards et al. demonstrated equivalent postoperative dysphagia scores, while the Heller–Dor group had significantly lower mean acid exposure times compared to the Heller-alone group at 6 months follow-up with 24-h pH monitoring (0.4% vs. 4.9%, $p=0.001$). Of the 43 patients enrolled in the trial, only 9% of the Heller–Dor

group exhibited pathologic reflux, compared to 47.6% of the Heller-alone patients.[9]

In our experience, the addition of an antireflux procedure, whether Dor anterior fundoplasty or Toupet partial posterior fundoplication leads to a relatively low incidence of reflux-related complaints while providing good to excellent relief of dysphagia in the majority of patients.[3,7,10] In some patients with a very wide distal esophagus (usually seen in conjunction with a dolico-megaesophagus, redundant length and loss of the axis of the esophagus) it is not possible to perform a Toupet (or a Dor) without narrowing the size of the esophagus. In these patients, we prefer to dissect the distal esophagus and simply suture the esophageal wall to the right and left crura to try and restore its axis as much as possible. For the average patient, our preference is for the Toupet fundoplication as described above, as we feel it provides better control of reflux than the Dor fundoplasty. However, this is yet to be definitively demonstrated when it is combined with Heller myotomy. Another likely advantage of the Toupet procedure includes a "stenting" effect of the myotomy which may help to prevent scarring and reapproximation of the divided muscle edges. Some authors have also described good results with a total fundoplication performed in conjunction with Heller myotomy. For example, Rossetti et al. reported relief of dysphagia in 92% of 195 patients, with no measurable pathologic acid reflux in a subset of 75 patients who had undergone postoperative pH monitoring.[11] Nonetheless, the majority of surgeons performing Heller myotomy continue to employ a partial fundoplication procedure when an antireflux procedure is included.

Conclusion

The laparoscopic extended Heller myotomy with Toupet fundoplication is an effective and definitive procedure for the relief of dysphagia in patients with achalasia. Important technical considerations in this procedure include division of all longitudinal and circular muscle fibers in the high-pressure zone of the LES, and extension of the myotomy distally to 3 cm below the esophagogastric junction onto the cardia. The addition of the Toupet partial posterior fundoplication is relatively effective in the control of gastroesophageal reflux which is otherwise expected after ablation of the LES, and does not result in an increase in postoperative dysphagia.

References

1. Willis T. Pharmaceutice rationalis sive diatribe de medicamentorum operationibus in human corpore. London, England: Hagae Comitis, 1674.
2. Heller E. Extramukose kardioplastic beim chronischen kardiospasmus mit dilatation des oesophagus. Mitt Grenzeb Med Chir 1913;27:141–9.
3. Wright AS, Williams CW, Pellegrini CA, Oelschlager BK. Long-term outcomes confirm the superior efficacy of extended Heller myotomy with Toupet fundoplication for achalasia. Surg Endosc 2007;21(5):713–8. doi:10.1007/s00464-006-9165-9.
4. Ellis FH Jr, Gibb SP, Crozier RE. Esophagomyotomy for achalasia of the esophagus. Ann Surg 1980;192(2):157–61. doi:10.1097/00000658-198008000-00004.
5. Pellegrini C, Wetter LA, Patti M et al. Thoracoscopic esophagomyotomy. Initial experience with a new approach for the treatment of achalasia. Ann Surg 1992;216(3):291–6. discussion 296–9. doi:10.1097/00000658-199209000-00008.
6. Patti MG, Pellegrini CA, Horgan S et al. Minimally invasive surgery for achalasia: an 8-year experience with 168 patients. Ann Surg 1999;230(4):587–93. discussion 593–4. doi:10.1097/00000658-199910000-00014.
7. Oelschlager BK, Chang L, Pellegrini CA. Improved outcome after extended gastric myotomy for achalasia. Arch Surg 2003;138(5):490–5. discussion 495–7. doi:10.1001/archsurg.138.5.490.
8. Richards WO, Clements RH, Wang PC et al. Prevalence of gastroesophageal reflux after laparoscopic Heller myotomy. Surg Endosc 1999;13(10):1010–4. doi:10.1007/s004649901158.
9. Richards WO, Torquati A, Holzman MD et al. Heller myotomy versus Heller myotomy with Dor fundoplication for achalasia: a prospective randomized double-blind clinical trial. Ann Surg 2004;240:405–15. doi:10.1097/01.sla.0000136940.32255.51.
10. Tatum RP, Kahrilas PJ, Manka M, Joehl RJ. Operative manometry and endoscopy during laparoscopic Heller myotomy. An initial experience. Surg Endosc 1999;13(10):1015–20. doi:10.1007/s004649901159.
11. Rossetti G, Brusciano L, Amato G et al. A total fundoplication is not an obstacle to esophageal emptying after Heller myotomy for achalasia: results of a long-term follow up. Ann Surg 2005;241(4):614–21. doi:10.1097/01.sla.0000157271.69192.96.

J Gastrointest Surg (2009) 13:1125–1128
DOI 10.1007/s11605-008-0642-4

HOW I DO IT

Laparoscopic Transumbilical Cholecystectomy Without Visible Abdominal Scars

Ninh T. Nguyen · Kevin M. Reavis · Marcelo W. Hinojosa · Brian R. Smith · Samuel E. Wilson

Received: 20 June 2008 / Accepted: 22 July 2008 / Published online: 15 August 2009

Abstract
Introduction We present a novel surgical technique for cholecystectomy utilizing three laparoscopic ports placed through the umbilicus. This new method is natural orifice transumbilical surgery (NOTUS) and describes a laparoscopic operation that can be performed with all incisions placed within the umbilicus obviating visible abdominal scars.
Objectives To develop a novel laparoscopic surgical technique for cholecystectomy utilizing only transumbilical incisions.
Summary Background Data Natural orifice translumenal endoscopic surgery (NOTES) has become an exciting area of surgical development. Significant limitations to this surgical concept, however, are lack of surgical expertise and appropriate flexible instrumentation. An alternative and competing technology to NOTES is NOTUS.
Methods We describe a patient in whom a laparoscopic surgical technique for cholecystectomy utilized incisions all placed entirely within the umbilicus. This new technique is called NOTUS and describes a laparoscopic operation that can be performed without visible abdominal scar.
Results The operative time was 70 min. There were no intraoperative complications. The patient did well postoperatively and was discharged on the same operative day. There were no postoperative complications at 2 months follow-up.
Conclusion Cholecystectomy performed through laparoscopic incisions placed within the umbilicus was technically feasible and safe in our patient. Development of advanced flexible instrumentation and visualization platforms may facilitate this new operative approach. Further advantages of NOTUS cholecystectomy compared to conventional laparoscopic cholecystectomy will ultimately require a randomized clinical trial.

Keywords Laparoscopy · Single-site surgery · Transumbilical cholecystectomy · Single laparoscopic incision transabdominal surgery · NOTUS

Introduction

Natural orifice translumenal endoscopic surgery (NOTES) is an exciting area of surgical development. Potential benefits of NOTES include lack of an abdominal scar, reduction of postoperative pain, ability to be performed under conscious sedation, and faster recovery. However, until now, the majority of human clinical experiences with NOTES are hybrid procedures requiring access through a natural orifice (transorally or transvaginally) in combination with an umbilical or other transabdominal port for safe peritoneal entry and maintenance of pneumoperitoneum.[1–3] A true NOTES procedure without the use of any abdominal port(s) is still under investigation with many potential obstacles including safe peritoneal entry and closure of the visceral gastrotomy.

A competing surgical technology to NOTES is single-port or single-access transabdominal surgery and natural orifice transumbilical surgery (NOTUS). Single-access or single-port surgery holds the promise of advancing minimally invasive surgical techniques to the next frontier with the use of only a single laparoscopic incision or multiple

N. T. Nguyen (✉) · K. M. Reavis · M. W. Hinojosa · B. R. Smith · S. E. Wilson
Department of Surgery,
University of California Irvine Medical Center,
333 City Blvd. West, Suite 850,
Orange, CA 92868, USA
e-mail: ninhn@uci.edu

incisions that are placed within a single site such as the umbilicus to eliminate any visible abdominal scars. For example, rather than performing a laparoscopic cholecystectomy through the conventional four laparoscopic trocars, the procedure would be performed through a single port or single incision placed within the umbilicus which then will be used for extraction of the gallbladder. A potential disadvantage with the single incision technique is restriction in the degree of movement of laparoscopic instruments and camera.

We report a laparoscopic cholecystectomy procedure that was performed utilizing three laparoscopic trocars all placed within the umbilicus. By positioning these incisions separately within the umbilicus, there is a greater degree of freedom for instrument movement thus reducing the technical complexity of this operation.

Case Study and Surgical Technique

A 23-year-old woman with a body mass index of 38 kg/m^2 who had undergone a previous laparoscopic adjustable gastric banding procedure 12 months ago presented with intermittent right upper quadrant abdominal pain. Abdominal ultrasound showed a thickened gallbladder wall with multiple gallstones consistent with symptomatic chronic cholecystitis. Our conventional laparoscopic cholecystectomy operation requires placement of four abdominal trocars with a 12-mm trocar within the umbilicus and three additional abdominal ports. In this case, three laparoscopic incisions (5 mm) were made within the umbilicus. Both the operative surgeon and assistant who holds the camera stand on the patient's left side (Fig. 1). Through these incisions, pneumoperitoneum was established with a Veress needle.

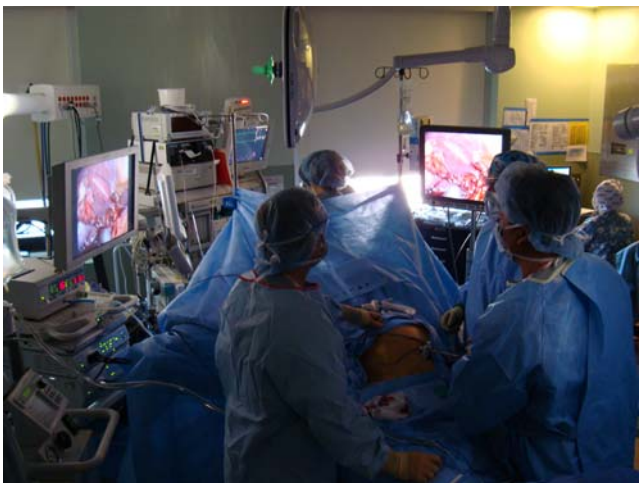

Figure 1 Operative set-up for NOTUS cholecystectomy with both the surgeon and assistant (holding the camera) standing on the patient's left side.

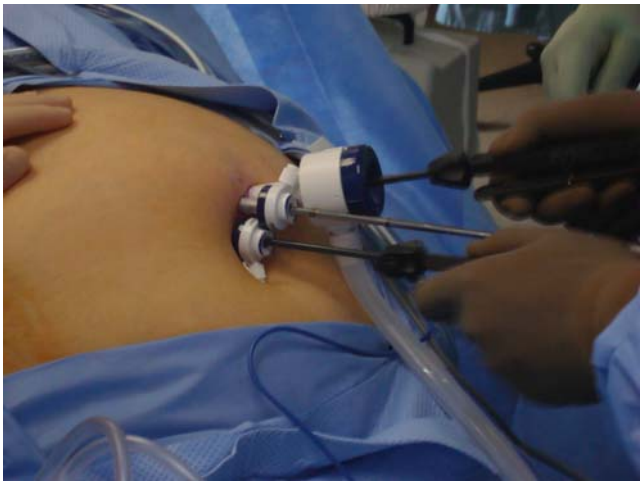

Figure 2 Transumbilical port position for NOTUS cholecystectomy with two 5-mm ports and one 12-mm port. The 5-mm flexible-tip camera is placed in-between the two working instruments.

Three 5-mm trocars were placed (Fig. 2). A 5-mm flexible-tip camera was placed for visualization. A rigid grasper was used to retract the infundibulum of the gallbladder, and rigid and flexible-tip dissectors were used to dissect out the critical structures within the triangle of Calot (Fig. 3a,b). A critical view of structures within the triangle of Calot was obtained before ligation and division of the cystic duct and artery. Once the cystic duct and artery were clearly identified as the only two structures entering the gallbladder, they were clipped proximally and distally with a rigid 5-mm multiclip applier (Fig. 4). A rigid scissor was used to divide these two structures between the clips. A flexible-tip L-hook instrument was used to dissect the gallbladder from the liver bed (Fig. 5). One of the 5-mm ports was replaced with a 12-mm port to enlarge the fascia in preparation for removal of the specimen. Upon removal of the gallbladder, all trocars were removed. Using a direct technique, the 12-mm fascial defect was closed with an interrupted suture. The operative time was 70 min. There were no operative complications. The patient recovered well postoperatively and was discharged on the same day. There were no postoperative complications.

Discussion

Laparoscopy has revolutionized the methods surgeons use in many general surgery operations. Innovations in new instrumentation and technology have recently pushed minimally invasive surgery into a new frontier of even less invasive approaches. NOTES has been an emerging area of interest for surgeons and gastroenterologists with many institutions performing research in this field. However, NOTES procedures are limited by difficulty in access, lack

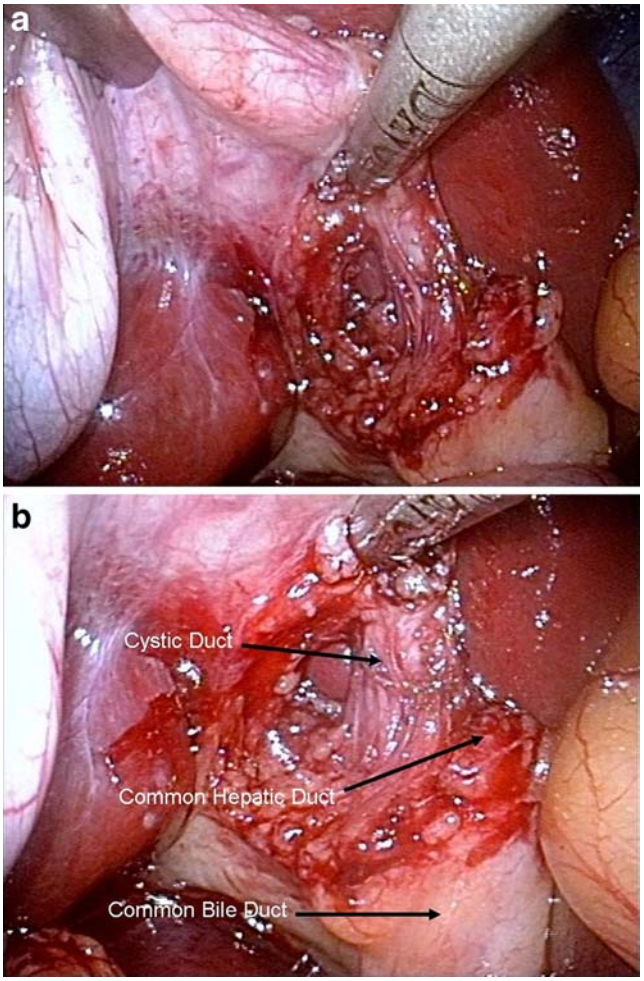

Figure 3 **a** NOTUS cholecystectomy showing the critical view with a grasper giving cephalad retraction and a suction device giving medial retraction. **b** NOTUS cholecystectomy showing the critical structures of the triangle of Calot.

of appropriate flexible instrumentation, and concern over breaking the sterility barrier. Single-access surgical technology is an alternative to NOTES, which is a less invasive platform compared to conventional laparoscopy that may utilize existing instrumentation and visualization systems. This paper describes our technique for performance of a laparoscopic cholecystectomy utilizing three laparoscopic incisions that were all placed within the umbilicus, resulting in no visible abdominal scars.

As the introduction of laparoscopic cholecystectomy, surgeons have continually introduced even less invasive techniques. Kagaya[4] reported performance of laparoscopic cholecystectomy using two abdominal ports rather than the conventional four abdominal-port technique. He utilized a 10-mm port within the infraumbilical position and a 5-mm incision at the subxyphoid region to perform cholecystectomy in 40 patients.[4] Leggett et al.[5] reported laparoscopic cholecystectomy using three abdominal ports (two 3-mm abdominal trocars and a 5-mm umbilical trocar). The three-port microlaparoscopic cholecystectomy did not show any reduction in postoperative pain or improvement in postoperative recovery.[5] More recently, several institutions reported the NOTES hybrid cholecystectomy procedure, which uses a transvaginal trocar in combination with a single abdominal port for retraction, maintenance of pneumoperitoneum, or the use of the laparoscopic clip applier.[6,7] Forgione et al.[6] reported hybrid transvaginal cholecystectomy in three patients. Zornig et al.[7] similarly reported the hybrid transvaginal cholecystectomy with an umbilical port in 20 patients. The mean operating time was

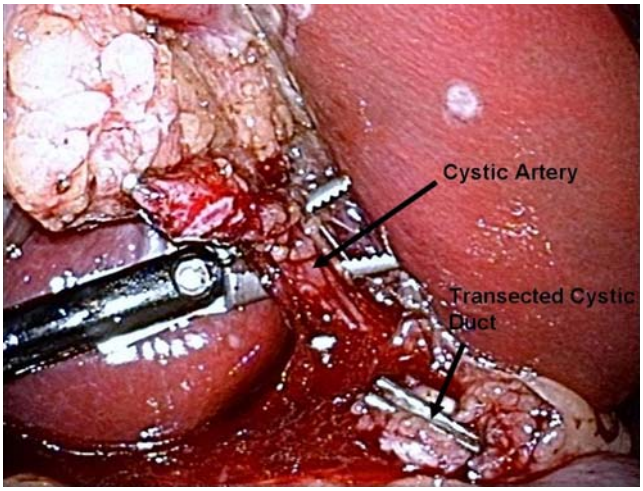

Figure 4 NOTUS cholecystectomy with dissection of the cystic artery after clipping and division of the cystic duct. Using a flexible-tip dissection instrument, we were able to achieve a 90° angle to the cystic artery. A single rigid grasper is used for cephalad retraction of the gallbladder (above the visualization field).

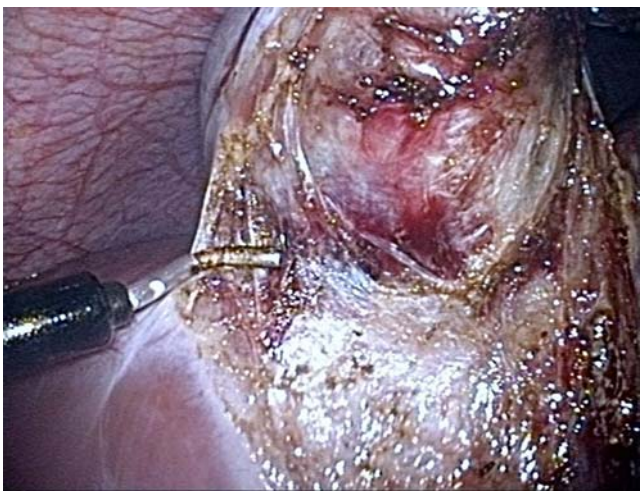

Figure 5 NOTUS cholecystectomy showing removal of the gallbladder from the liver fossa using a flexible-tip L-hook cautery. Although the 5-mm flexible-tip camera, rigid retracting instrument (above the visual field), and the flexible-tip L-hook instrument are introduced at the umbilicus, the flexible-tip L-hook is coming from the left side of the operating field thus improving visualization.

62 min, and there were no intraoperative or postoperative complications. There were no visible abdominal scars, as the ports were placed either transvaginally or transumbilical. Recognition that all of the current NOTES cholecystectomy procedures are hybrid procedures requiring an abdominal trocar led to the concept of transumbilical surgery as a method to eliminate the abdominal scars. Cuesta et al.[8] reported on transumbilical cholecystectomy using two 5-mm umbilical trocars and a 1-mm Kirschner wire introduced in the right subcostal region for retraction of the gallbladder. Their mean operative time was 70 min with no conversion and no postoperative complications.[8] Alternatively, Piskun and Rajpal[9] reported transumbilical cholecystectomy using two 5-mm umbilical ports and two transabdominal sutures for retraction of the gallbladder. Unlike these techniques, we utilized three abdominal ports within the umbilicus, obviating the need for suture or wire retraction within the right costal margin. This technique has been described as NOTUS, as the umbilicus was once a natural orifice. Advantages of our technique include the ability to use a rigid instrument to retract the gallbladder with dynamic retraction provided by the operating surgeon and the ability to use conventional laparoscopic clips rather than flexible endoscopic clips. These simplifications in technique will require a shorter learning curve.

This report documents the feasibility of transumbilical cholecystectomy. Clinical advantages of this approach may eventually require a randomized controlled trial comparing laparoscopic cholecystectomy vs. NOTUS cholecystectomy. However, the major advantage of this method is improved cosmesis without any visible abdominal scars. Disadvantages of NOTUS cholecystectomy include the smaller degree of instrument triangulation compared to conventional laparoscopy and the lack of lateral retraction during dissection of the triangle of Calot. Some of these disadvantages may be overcome with the development of trocars with smaller profiles to enhance the degrees of instrumentation movement and flexible retracting instruments. Despite the limitations of NOTUS cholecystectomy, we were able to perform our operation with a reasonable operative time of 70 min, which should improve once the learning phase of this new technique is overcome.

In conclusion, we have documented the feasibility of NOTUS cholecystectomy. The procedure was performed with existing ports, laparoscopic instrumentation, and visualization platforms. Development of newer instrumentation and visualization platforms may facilitate this new operative approach. Further advantages of NOTUS cholecystectomy compared to conventional laparoscopic cholecystectomy will ultimately require a clinical trial.

References

1. Zorron R, Filqueiras M, Maggioni LC, et al. Transvaginal cholecystectomy: report of the first case. Surg Innov 2007;14:279–83. doi:10.1177/1553350607311090.
2. Zornig C, Emmermann A, von Waldenfels HA, Mofid H. Laparoscopic cholecystectomy without visible scar: combined transvaginal and transumbilical approach. Endoscopy 2007;39:913–5. doi:10.1055/s-2007-966911.
3. Marescaux J, Dallemagne B, Perretta S, et al. Surgery without scars: report of transluminal cholecystectomy in a human being. Arch Surg 2007;142:823–6. doi:10.1001/archsurg.142.9.823.
4. Kagaya T. Laparoscopic cholecystectomy via two ports, using the "twin-port" system. J Hepatobiliary Pancreat Surg 2001;8:76–80. doi:10.1007/s005340170053.
5. Leggett PL, Bissell CD, Churchman-Winn R, Ahn C. Three-port microlaparoscopic cholecystectomy in 159 patients. Surg Endosc 2001;15:293–6. doi:10.1007/s004640000302.
6. Forgione A, Maggioni D, Sansonna F, et al. Transvaginal endoscopic in human beings: preliminary results. J Laparoendosc Adv Surg Tech A 2008;18:345–51. doi:10.1089/lap.2007.0203.
7. Zornig C, Mofid H, Emmermann A, et al. Scarless cholecystectomy with combined transvaginal and transumbilical approach in a series of 20 patients. Surg Endosc 2008;22:1427–9. doi:10.1007/s00464-008-9891-2.
8. Cuesta MA, Berends F, Veenhof AA. The "invisible cholecystectomy". A transumbilical operation without a scar. Surg Endosc 2008;22:1211–3. doi:10.1007/s00464-007-9588-y.
9. Piskun G, Rajpal S. Transumbilical laparoscopic cholecystectomy utilizes no incisions outside the umbilicus. J Laparoendosc Adv Surg Tech A 1999;9:361–4.

J Gastrointest Surg (2009) 13:1129–1137
DOI 10.1007/s11605-008-0797-z

REVIEW ARTICLE

Systematic Review of Minimally Invasive Pancreatic Resection

Christopher D. Briggs · Christopher D. Mann · Glen R. B. Irving · Christopher P. Neal · Mark Peterson · Iain C. Cameron · David P. Berry

Received: 30 October 2008 / Accepted: 11 December 2008 / Published online: 7 January 2009

Abstract
Background Pancreatic resection is associated with a significant morbidity. Efforts to reduce hospital stay and enhance recovery have seen the introduction of minimally invasive surgical techniques. This article reviews the current published literature on the safety and efficacy of minimally invasive surgery of the pancreas.
Methods An electronic search of the PubMed and Embase databases was performed from 1996 to May 2008 to identify all relevant publications; studies meeting predefined inclusion criteria were retrieved and analyzed using a standardized protocol. Data on the safety and efficacy of minimally invasive surgery of the pancreas were recorded and analyzed.
Results Of 565 abstracts reviewed, 39 studies were identified as eligible for inclusion. There were 37 case series and two case control studies. Compared with open pancreatic surgery, minimally invasive pancreatic resection is similar in terms of morbidity and mortality. Blood loss and length of stay are decreased.
Conclusions Laparoscopic distal pancreatic resection and enucleation of insulinoma appear to be safe procedures with reduced hospital stay, though morbidity remains significant. The evidence for laparoscopic pancreaticoduodenectomy is in its infancy, but the authors feel it is unlikely that many centers will achieve sufficient case load to make the introduction of minimally invasive resection feasible.

Keywords Pancreas · Laparoscopic · Minimally invasive

C. D. Briggs (✉) · C. D. Mann · C. P. Neal · D. P. Berry
Cancer Biomarkers and Prevention Group,
Department of Cancer Studies and Molecular Medicine,
Bio centre, University of Leicester,
University Road,
Leicester LE1 7RH, UK
e-mail: Chrisbriggs@doctors.org.uk

G. R. B. Irving · M. Peterson · I. C. Cameron
Department of Hepatobiliary and Pancreatic Surgery,
Royal Hallamshire Hospital,
Sheffield Teaching Hospitals NHS Foundation Trust,
Glossop Road,
Sheffield S10 2JF, UK

D. P. Berry
Department of Hepatobiliary and Pancreatic Surgery,
Leicester General Hospital, University Hospitals of Leicester,
Gwendolen Road,
Leicester LE5 4PW, UK

Introduction

Resection of the pancreas remains one of the most challenging areas of gastro-intestinal surgical practice and is associated with up to a 50% morbidity and 8% mortality rate.[1–3] The traumatic response induced by the large incisions which are required for adequate exposure of the surgical field is thought to make a significant contribution to this morbidity.[4] The introduction of minimally invasive (laparoscopic) surgery in operations such as cholecystectomy and colonic resection has seen a reduction in postoperative pain and increased mobility, enabling enhanced recovery and facilitating early discharge.[5,6] Concerns were raised initially in cancer surgery regarding radicality of resection using the laparoscopic approach. However, evidence from studies in laparoscopic colonic resection suggests these concerns were unfounded.[7] In pancreatic surgery, there is increasing interest in the feasibility of minimal access techniques in an attempt to reduce morbidity and assist postoperative recovery. However, availability of training cases is infrequent as the

incidence of resectable pancreatic disease is low in comparison to other surgical pathologies. In addition, the difficulty of performing these complex resections and reconstructions without the tactile feedback provided by open surgery adds a further barrier to widespread introduction of the technique. In this systematic review, we present the current evidence available on minimally invasive pancreatic resection and evaluate the implications for changes in future hepatobiliary and pancreatic surgical practice.

Methods

Search Strategy

The PubMed and Embase databases were searched electronically from 1996 up to and including May 2008. Search terms used included: pancreas, minimally invasive, laparoscopic, resection, and surgery. Terms were searched both in isolation and in combination to identify all published evidence. Search limits were applied to include articles published in English language, those with abstracts, and human studies only. Articles published in abstract form only, relating to animal or *in vitro* work, case reports, or reporting less than five cases were excluded from the final analysis. All full articles retrieved were also hand searched for further studies identifiable from the reference list. Articles describing hand-assisted techniques were included so long as part or all of the procedure was completed laparoscopically. Review articles and studies of non-resection or necrosectomy-related pancreatic procedures were excluded. In the case of sequential publications with data overlap, the report with the most comprehensive information regarding the study population was selected.

Data Extraction

All identified articles were examined using a predesigned pro forma, and data collected was entered into a database. A list of information gathered on the pro forma is detailed in Table 1. Data was analyzed on an intention to treat basis where possible.

Statistical Analysis

Overall averages are presented as weighted means (range) unless otherwise stated.

Results

Figure 1 details the results of the initial search and the subsequent selection of relevant articles. In the initial search, 866 articles were identified. Manuscripts without abstracts, not in the English language, and those performed in animals were excluded leaving 565 abstracts for review. After application of exclusion criteria, a further 522 publications were excluded—lack of relevance (308), review article (62), case report (73), inclusion of fewer than five cases (14), drainage procedure for cystic disease without resection (24), necrosectomy (23), laparoscopy only (18). A total of 43 full articles were examined. Four further articles were excluded due to data duplication, leaving 39 studies for review.

Table 1 Data Captured on Pro Forma from Retrieved Studies

Captured data
Author
Study design (*randomized controlled trial*, *case control*, *case series*)
Period of inclusion
Number of patients
Age (*mean and range*)
Male: female ratio
Type of operation (*enucleation*, *distal pancreatectomy with splenectomy*, *distal pancreatectomy with splenic preservation*, *pancreaticoduodenectomy*)
Operating time (*mean and ranges*)
Blood loss (*mean and ranges*)
Conversion rate and reason
Morbidity and type
Mortality and type
Length of hospital stay (*mean and range*)
Resected specimen margin status
Number of lymph nodes retrieved
Postoperative pathology

The majority of studies were retrospective case series, though several groups collected data prospectively (10), and there were two case-controlled studies.[8,9] There were no randomized controlled trials. Five studies involved more than one center.[10–14] A total of 801 patients were included in all publications, ranging from five to 127, with a mean of 21 patients per study. The attempted operations included 85 pancreaticoduodenectomies, 130 enucleations, seven central pancreatic resections, 349 distal pancreatectomies with splenic preservation, and 229 distal pancreatectomies with splenectomy. Several studies reported different types of resection as a cohort. During resection-specific analysis reports including less than five operations pertaining to one type of resection were not included.

Pancreaticoduodenectomy

Table 2 shows the four studies which have reported greater than five laparoscopic pancreaticoduodenectomies, with a total of 85 patients in these studies.

Mortality

Of 85 patients in the four studies there were three deaths, giving an overall mortality rate of 3.5%. The deaths were

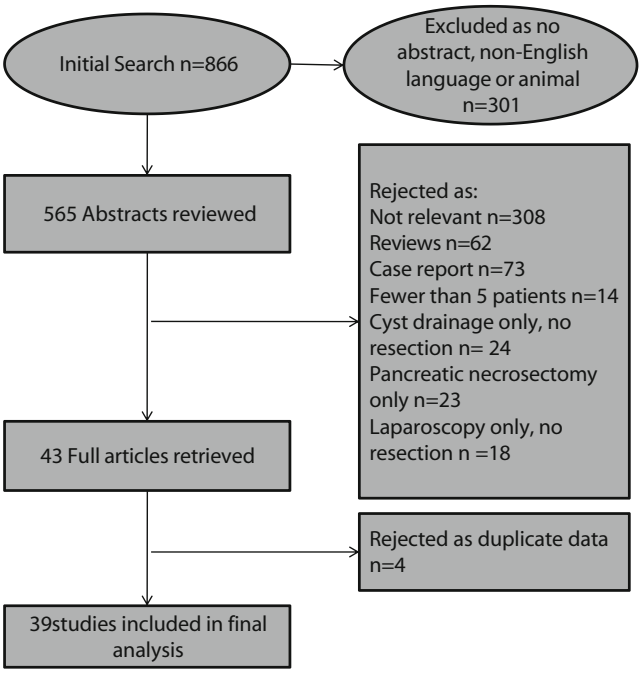

Figure 1 Flow chart detailing results of search strategy and reasons for exclusion.

due to a postoperative myocardial infarction.[15] adult respiratory distress syndrome associated with pancreatic anastamotic leak.[16] and bleeding from a duodenal ulcer.[17]

Morbidity

One group only reported their morbidity as "high" and could not be taken into account in the analysis.[18] Overall morbidity for the remainder was 30.7%, due to 23 complications in 75 patients.

Perioperative Factors

All studies reported mean duration of surgery. Overall weighted mean was 371 min in the 85 patients (243–640 min). Blood loss was reported in three of the four studies,[15–17] overall mean being 126 ml (35–770 ml). Lu et al. did not report conversion in their small series.[17] Of the remaining eighty operations, seven were converted (8.75%). Three studies reported hospital stay,[15,16,18] overall weighted mean was 13.6 days (8–28 days).

Histopathological Factors

Two studies included lymph node yield in their analysis, with an overall mean of 15 per case (8–24).[15,16]

Distal Pancreatectomy

Table 3 shows studies relating to distal pancreatectomy with and without splenic preservation. Morbidity encountered in the laparoscopic distal pancreatectomy studies is summarized in Table 4.

Mortality

Twenty-seven out of the twenty eight studies analysed reported a 0% mortality rate. Edwin et al. reported two perioperative deaths, one patient from multi-organ failure after a complicated, converted operation in which the celiac plexus was excised and reconstructed, and the other patient succumbing to a myocardial infarction 8 days after operation.[19] Overall mortality was, therefore, 0.4%.

Table 2 Laparoscopic Pancreaticoduodenectomy - Results of Published Studies

Reference and inclusion period	No. of patients	Mean age (years)	M:F	Pathology	Op time (mins)	Blood loss (mls)	Conversion rate (%)	Morbidity (%)	Mortality (%)	Hospital Stay (days)	Lymph node yield
Palanivelu et al.[16] Feb 1998–Jan 2006	45	61 (28–0)	25:20	24 Amp, 4 CA, 12 AHOP, 3 DC, 2 CP	370 (270–640)	65 (35–395)	0	26.7	2.2	10.2 (8–28)	13 (8–21)
Dulucq et al.[15] March 1999–June 2005	25	62 (48–76)	9:16	11 AHOP, 3 Amp, 2 DA, 2 CP, 1 NEC, 1 RM, 2 Other	287 (240–331)	107 (59–155)	12	31.8	4.5	16.2 (13–19)	19 (14–24)
Gagner et al.[18] Jan 1992–Jan 1997	10	71 (33–82)	4:6	8 Amp, 2 CP	510	NR	40	"High"	0	22.3	NR
Lu et al.[17] 2002–2006	5	43	4:1	4 DA, 1 AHOP	528	770	NR	60	20	NR	NR

Amp ampullary carcinoma, *CA* cystadenocarcinoma, *AHOP* adenocarcinoma head of pancreas, *DC* distal cholangiocarcinoma, *CP* suspicious lesion in chronic pancreatitis, *ARDS* adult respiratory distress syndrome, *DA* duodenal carcinoma (papillary or adeno), *NEC* neuroendocrine carcinoma, *RM* renal metastasis, *Other* other benign lesion, *NR* not reported or insufficient data

Table 3 Laparoscopic Distal Pancreatectomy with and without Splenectomy—Results of Published Studies

Reference and study period	No. of cases	Mean age (years)	M:F	Post-operative Pathology	No. with spleen preserved	Re-op for splenic infarct?	Mean Op time (min)	Mean Blood loss (ml)	Conversion rate (%)	Morbidity (%)	Mortality (%)	Hospital stay (days)
Corcione et al.[38] April 1999–Oct 2004	14	50.7 (26–68)	NR	2 ATOP, 1 MC, 2 BSC, 8 BMC, 1 PSC	8	No	130 (90–200)	NR	6.7	26.3	0	8.5 (4–45)
Ayav et al.[14] 1996–2003	15	48 (20–77)	12:24	15 IS	12	1	175 (120–240)	NR	53	13.3	0	NR
Gagner et al.[39] Jan 1992–Mar 1996	7	43 (29–74)	NR	5 IS, 1 G, 1 MC	7	0	316 (240–480)	NR	42.9	28.6	0	11.9 (4–33)
Patterson et al.[40] Mar 1993–Dec 2000	15	NR	NR	1 ATOP, 3 Other, 2 SC, 1 MC	3	0	264 (96–396)[a]	200 (20–4,000)[a]	11	26	0	6 (1–26)
D'angelica et al.[20] Dec 2002–Jul 2004	16	60 (29–85)	4:13	3 BMC, 3 CP, 5 Other, 1 SC, 1 IPMN, 1 ATOP, 1 Mets, 1AS	1	0	196 (128–235)	125 (50–1,250)	11.8	25	0	5.5 (4–18)
Cuschieri et al.[41] 1994–1996	5	47.8 (38–54)	3:2	5 CP	0	N/A	300 (240–360)	400 (200–700)	NR	40	0	6 (6–7)
Edwin et al.[19] Mar 1997–May 2002	17	NR	NR	4 ATOP, 4 NT, 2 G, 2 Mets, 1 PSC, 1 AS, 1 SC, 1 BMC, 1 Other	5	0	235 (104–332)[a]	400 (100–1,500)[a]	11.8	52.9	11.8	5.5 (2–22)
Dulucq et al.[21] Apr 1995–Dec 2003	21	58 (24–85)	6:15	9 SC, 1 MC, 2 ATOP, 1 IS, 3 BMC, 3 CP, 2 Other	16	0	154 (110–240)	162 (50–700)	4.8	23	0	10.8 (6–15)
Fernandez-Cruz et al.[42] Feb 1998–Oct 2000	5	39.5 (23–52)	NR	5 CP	5	0	240 (180–300)	450 (300–800)	NR	20	0	6 (5–14)
Fernandez-Cruz et al.[22] Apr 1998–Apr 2007	72	57 (22–83)	NR	8 CP, 3 SC, 3 BMC, 3 MC, 10 IPMN, 13 ATOP, 32 NT	52	1 – (6 no surgery)	225 (125–330)	489 (200–1,300)	7.3	21.7	0	6.5 (5–14)
Fabre et al.[43] NR	13	60 (32–85)	2:11	2 BMC, 3 SC, 5 PSC, 1 ATOP, 1 IS, 1 Other	10	0	280 (180–480)	NR	15	30	0	NR (5–22)
Han et al.[24] May 2000–Jul 2003	5	47.6 (25–64)	1:4	2 SC, 2 BMC, 1 Other	5	0	348 (295–435)	NR	NR	0	0	10.4 (8–16)
Gramatica et al.[12] 1996–2000	5	45.8 (27–70)	0:5	5 IS	4	0	240	NR	NR	33	0	NR
Mabrut et al.[11] 1995–2002	98	52 (8–80)	NR	NR	61	2	202 (65–500)	<300 in 77%	14.3	56	0	7 (3–67)[a]
Misawa et al.[44] Aug 2005–Jun 2006	7	48 (39–56)	3:4	3 BMC, 1 SC, 1 IPMN, 1 splenectomy, 1 NT	0	N/A	NR	NR	NR	28.6	0	9 (7–11)
Misawa et al.[9] May 2004–Dec 2005	8	48.5 (28–72)	2:6	4 BMC, 2 Other, 1 SC, 1 PSC	1	0	255 (120–300)	14 (0–700)	NR	0	0	10 (7–14)
Melotti et al.[23] May 1999–Nov 2005	58	48.9 (33–67)	8:50	19 BMC, 13 SC, 9 NT, 5 ATOP, 3 IPMN, 2 MC, 2 PSC, 5 Other	32	1	165 (120–200)	NR	0	53.4	0	9 (7–12.5)
Park et al.[45] May 1997–Jan 2001	23	48.9 (36–73)	9:14	5 IS, 6 SC, 4 CP, 4 PSC, 4 Other	12	0	222 (108–420)	274 (30–1,200)	8	16	0	4.1 (2–8)
Vezakis et al.[46] Nov 1993–Jun 1997	6	62.5 (30–83)	0:6	1 IS, 3 SC, 1 ATOP, 1 NT	5	0	300 (240–360)	NR	33.3	33.3	0	25.6 (5–60)
Velanovich et al.[47] NR	11	65	4:7	NR	0	N/A	162	NR	18.2	27.3	0	3 (2–9)
Nieuwenhove et al.[48] Mar 2003–Jun 2002	5	53 (37–77)	2:3	2 IS, 3 Other	3	0	260 (240–290)	60 (0–200)	NR	25	0	7.6 (6–9)
Uranues et al.[10] Sep 2003–Feb 2005	5	32.6 (16–56)	0:5	1 BMC, 2 SC, 1 PSC, 1 Other	5	0	174 (170–207)	NR	NR	20	0	NR

Toniato et al.[49] Jan 2000–Sep 2005	8	52 (22–78)	NR	8 IS	5	0	170 (90–280)	NR	12.5	25	0	8 (5–16)
Barlehner et al.[25] Nov 1998–Jul 2001	6	64 (48–81)	3:3	2 ATOP, 1 NT, 1 SC, 2 Other	0	N/A	180 (90–260)	340 (10–1,000)	16.7	0	0	14 (12–17)
Tang et al.[26] 1999–2007	9	61 (18–79)	3:6	5 SC, 1 CP, 1 NT, 2 Other	5	0	180 (120–250)	100 (50–500)	NR	33.3	0	7 (4–53)
Velanovich et al.[8] Oct 2003–2006	15	NR	NR	3 ATOP, 8 SC/BMC, 2 NT, 2 CP	0	N/A	NR	NR	20	20	0	5 (3–9)
Shimizu et al.[50] Mar 1998–Dec 2002	9	56	5:4	2 NT, 2 SC/BMC, 1 PSC, 2 CP, 2 Other	1	0	293	213	22.2	14.3	0	NR
Pierce et al.[51] Jul 2000–Feb 2006	18	55.1 (26–78)	5:13	3 BMC, 3 SC, 4 IPMN, 2 NT, 2 IS, 1GL, 2 Mets, 1 PSC	8	0	233 (146–322)	278 (20–2,500)	5.6	55.6	0	4.8 (2–11)

MC mucinous cystadenocarcinoma, *PSC* Pseudo cyst, *SC* serous cystadenoma, *BMC* benign mucinous cystadenoma, *G* gastrinoma, *GL* glucagonoma, *ATOP* adenocarcinoma tail of pancreas, *IS* insulinoma, *CP* suspicious lesion in chronic pancreatitis, *NT* neuroendocrine tumor, *Mets* metastasis, *AS* accessory spleen, *IPMN* intraductal papillary mucinous neoplasm, *Other* other lesion, *NR* not reported or insufficient data

[a] Median

Morbidity

All 28 studies reported morbidity rates. Out of a total of 496 patients, there were 169 complications; an overall morbidity rate of 34.1%.

Perioperative Factors

Twenty-six of 28 studies reported operating times, with an overall mean duration of 229 minutes (65–500 min). Twelve studies reported blood loss, overall weighted mean was 311 ml (0–4,000 ml) in a total of 229 patients. Nineteen studies reported conversion rates, with an overall mean of 12.1% in 442 patients. Twenty-three publications reported length of hospital stay in a total of 441 patients. The weighted mean was 7.5 days (1–67 days).

Histopathological Factors

Only four studies reported lymph node yield,[20–23] mean weighted total being 13 (2–20). Margin status was recorded in nine studies.[11,19–26] Out of a total of 194 cases, eight specimens (4.1%) were reported to have positive resection margins at histological analysis.

Enucleation

Table 5 shows studies of pancreatic tumor enucleation.

Mortality

There was no reported mortality in any of the published series.

Morbidity

Eight of the 11 studies reported sufficient data which could be analyzed for specific morbidity after enucleation. Out of a total of 101 patients, 48 (47%) suffered complications. The rate of postoperative pancreatic fistula (of any type) was 29.3% and this was the commonest complication.

Perioperative Factors

Eight studies reported mean operating times in a total of 98 patients. The weighted mean duration of surgery was 132 min (50–290 min). Nine out of 11 studies reported conversion rates in enucleation, overall weighted mean conversion rate was 23.3%. Hospital stay was described in six papers with an overall mean of 7.8 days (1–32 days).

Table 4 Morbidity in Distal Pancreatic Resections

Type of morbidity		No. of patients (% incidence)
Specific complications related to surgery	Pancreatic fistula	71 (14.3)
	Intra-abdominal collection	35 (7.1)
	Splenic infarct	8 (1.6)
	Bleeding	6 (1.2)
	Wound infection	3 (0.6)
	Diabetes	2 (0.4)
	Port site hernia	1 (0.2)
	Pancreatitis	1 (0.2)
General complications	Respiratory	18 (3.6)
	Ileus	4 (0.8)
	Pyrexia of unknown source	4 (0.8)
	Urinary	4 (0.8)
	Perforated ulcer	3 (0.6)
	Venous thrombo-embolism	3 (0.6)
	Blood transfusion	2 (0.4)
	Cardiac	2 (0.4)
	Cerebro-vascular accident	1 (0.2)
	Multi-organ failure	1 (0.2)

Discussion

The evolution of many forms of surgery toward the minimally invasive approach has been perhaps the most significant change in surgical practice in the last decade. Operations, such as cholecystectomy, which previously required routine hospital admission for up to a week, can now be safely achieved as day-case procedures.[27] However, the majority of laparoscopic procedures which have met with widespread acceptance by surgeons are performed in the setting of a high incidence of pathology which is amenable to surgical treatment. This enables a high volume of experience for the training surgeon in order to perfect and enhance the operative technique and gain familiarity with the pitfalls which may be encountered.

Pancreatic disease is relatively uncommon, with 10 cases of carcinoma of the pancreas per 100,000 population per year in Europe,[28] with as few as 10% of these patients being suitable for potentially curative resection.[29] The infrequency and complexity of these cases has meant that adoption of minimally invasive approaches has been met with scepticism and caution by the majority of pancreatic surgeons. Many specialists have declined to take up the procedure, instead awaiting evidence of its benefit. This review demonstrates that there are now a considerable number of publications pertaining to laparoscopic pancreatic surgery. However, there are no randomized controlled trials and the majority of series is retrospectively collected and includes very few patients, and so the data should be treated with caution.

With regard to pancreaticoduodenectomy, it is evident that the literature is in its infancy. Few surgeons have even attempted the procedure. The series reported by Dulucq et al. includes 13 totally laparoscopic cases and nine in which a mini-laparotomy was performed to facilitate the reconstruction.[15] Overall, it is apparent that operative variables, specifically duration of surgery and lymph node yield, are comparable to published open series.[30] Blood loss is significantly less and hospital stay shorter in comparison to the largest open series reported by Yeo et al. in 1997.[1] It should be noted that the surgical margins (one of the key concerns of those not advocating laparoscopic resection for malignant disease) were all negative in the series reporting them. If the morbidity rate of 26.7% in Palanivelu et al.'s series from India could be reproduced in other studies, it

Table 5 Laparoscopic Enucleation of Pancreatic Tumors—Results of Published Studies

Reference and study period	No. of cases	Mean age (years)	M:F	Mean Op time (mins)	Mean blood loss (mls)	Conversion rate (%)	Morbidity (%)	Mortality (%)	Hospital stay (days)
Ayav et al.[14] 1996–2003	19	48 (20–77)	NR	115 (50–190)	NR	10.5	42 NR	0	11 (5–32)
Edwin et al.[19] Mar 1997–May 2002	6	NR	NR	120 (60–240)	100 (100–300)	NR	NR	0	5.5 (2–22)
Berends et al.[13] Feb 1996–Feb 1999	9	42 (16–72)	2:7	180 (150–210)	<100 in all	44.4	66.6	0	7 (3–21)[a]
Fernandez-Cruz et al.[22] Apr 1998–Apr 2007	20	NR	NR	120 [NR]	220 [NR]	NR	40	0	5.5 (5–7)
Mabrut et al.[11] 1995–2002	24	NR	NR	120 (65–290)	NR	12.5	33.3	0	NR
Jaroszewski et al.[52] Sep 1997–Apr 2002	6	NR	NR	NR	NR	50	33.3	0	NR
Sweet et al.[53] Jul 2000–Jun 2005	9	39 (18–56)	3:6	NR	NR	22	77.8	0	4.4 (1–15)
Iihara et al.[54] NR	6	NR	NR	170 (140–240)	15 (10–30)	16.7	66.6	0	NR
Liu et al.[55] May 2000–Oct 2006	9	NR	NR	159 [NR]	77 [NR]	33.3	22.2	0	11.8 [NR]
Toniato et al.[49] Jan 2000–Sep 2005	5	NR	NR	NR	NR	20	NR	NR	NR
Schraibman et al.[56] NR	5	(14–45)	NR	130 (100–150)	"Minimal"	0	NR	NR	NR

NR not reported or insufficient data to analyze separately
[a] Median

would be an improvement on current open surgical practice.[16] It should be noted that all the patients in this series were graded as American Society of Anesthesiologists I or II, and the results may not be representative of the general population. It is clear that in all these studies, cases were highly selected, and it is debatable whether the results can be transferred into a wider population. In addition it remains unclear whether or not laparoscopic resection can be used in all pancreatic pathologies, for instance when portal vein invasion is present.

In contrast to pancreaticoduodenectomy, distal pancreatectomy has sparked widespread interest. This is almost certainly due to the easier technical nature of the procedure given that there is no necessity to perform a pancreatic anastamosis. Twenty-eight groups have published data on outcome in 496 patients, giving a substantial body of evidence regarding the safety and efficacy of the procedure. Duration of surgery, blood loss, mortality, and length of hospital stay compare favorably with the published literature in open surgery.[31,32] The morbidity associated with pancreatic resection appears similar to open series.[31,32] In common with open distal pancreatectomy, formation of pancreatic fistulae and abdominal collections are the commonest complications.[31,32]

Of note is the experience of one group in resection of the central portion of the pancreas which did not fit easily into any of our result sub-classification. In their series of six resections, Sa Cunha et al. achieved similar results to that of distal pancreatectomy in terms of morbidity, conversion rate, mortality, and duration of operation, though hospital stay was longer (mean 18 days).[33] This technique is used less frequently than complete distal resection due to concern regarding margins in malignant disease. However, in benign pathology, it is worthy of further investigation given the parenchymal preservation and potential for better long term endocrine and exocrine pancreatic function.[34,35]

Laparoscopic enucleation of neuroendocrine and benign cystic lesions has also gained popularity, though the most significant series to date amounts to only 24 cases from a multicenter study.[11] In comparison to open surgical resection, the morbidity associated with laparoscopic enucleation remains similar at nearly 50%, and one third of patients will still develop a pancreatic fistula.[36] A decreased length of stay was not observed when compared to the open series.[36,37]

No survival analysis has been presented in this review. The studies identified are generally small and incorporate a wide range of benign and malignant pathologies. Though this allows the reviewers to infer that the minimally invasive technique can be used in a variety of benign and malignant conditions, it also serves to confound survival analysis. Extrapolation of survival data from the heterogeneous populations would provide little evidence as to the long term outcome in comparison to open techniques. This highlights the need for a randomized, multicenter study comparing laparoscopic and open surgery in malignant disease.

Conclusion

Experience in minimally invasive pancreatic surgery remains limited to a few laparoscopic surgeons in different centers around the world. The low incidence of suitable cases may prevent widespread uptake. The lack of large studies, or randomized controlled trials, indicates the need for multicenter cooperation in order to clarify the role of this technically demanding and difficult surgery. At present the minimally invasive approach in distal pancreatectomy may confer benefit over traditional surgical techniques in terms of hospital stay, blood loss and mortality, however, the case for improved outcomes in laparoscopic pancreaticoduodenectomy and laparoscopic enucleation remains to be proven.

Conflict of interest None declared.

References

1. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, Hruban RH, Ord SE, Sauter PK, Coleman J, Zahurak ML, Grochow LB, Abrams RA. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 1997;226(3):248–257. discussion 257–260. doi:10.1097/00000658-199709000-00004.
2. Iacono C, Accordini S, Bortolasi L, Facci E, Zamboni G, Montresor E, Marinello PD, Serio G. Results of pancreaticoduodenectomy for pancreatic cancer: extended versus standard procedure. World J Surg 2002;26(11):1309–1314. doi:10.1007/s00268-002-5976-6.
3. Gazzaniga GM, Cappato S, Papadia F, Mori L, Filauro M. D1 versus D2 pancreatoduodenectomy in surgical therapy of pancreatic head cancer. Hepatogastroenterology 2001;48(41):1471–1478.
4. Mimica Z, Pogorelic Z, Perko Z, Srsen D, Stipic R, Dujmovic D. Effect of surgical incision on pain and respiratory function after abdominal surgery: a randomized clinical trial. Hepatogastroenterology 2007;54(80):2216–2220.
5. Buchanan GN, Malik A, Parvaiz A, Sheffield JP, Kennedy RH. Laparoscopic resection for colorectal cancer. Br J Surg 2008;95 (7):893–902. doi:10.1002/bjs.6019.
6. Keus F, de Jong JA, Gooszen HG, van Laarhoven CJ. Laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis. Cochrane Database Syst Rev 2006;4: CD006231.
7. Kuhry E, Schwenk W, Gaupset R, Romild U, Bonjer J. Long-term outcome of laparoscopic surgery for colorectal cancer: A cochrane systematic review of randomised controlled trials. Cancer Treat Rev 2008;34(6):498–504.
8. Velanovich V. Case-control comparison of laparoscopic versus open distal pancreatectomy. J Gastrointest Surg 2006;10(1):95–98. doi:10.1016/j.gassur.2005.08.009.

9. Misawa T, Shiba H, Usuba T, Nojiri T, Kitajima K, Uwagawa T, Toyama Y, Ishida Y, Ishii Y, Yanagisawa A, Kobayashi S, Yanaga K. Systemic inflammatory response syndrome after hand-assisted laparoscopic distal pancreatectomy. Surg Endosc 2007;21 (8):1446–1449. doi:10.1007/s00464-006-9149-9.
10. Uranues S, Alimoglu O, Todoric B, Toprak N, Auer T, Rondon L, Sauseng G, Pfeifer J. Laparoscopic resection of the pancreatic tail with splenic preservation. Am J Surg 2006;192(2):257–261. doi:10.1016/j.amjsurg.2006.01.031.
11. Mabrut JY, Fernandez-Cruz L, Azagra JS, Bassi C, Delvaux G, Weerts J, Fabre JM, Boulez J, Baulieux J, Peix JL, Gigot JF. Laparoscopic pancreatic resection: results of a multicenter European study of 127 patients. Surgery 2005;137(6):597–605. doi:10.1016/j.surg.2005.02.002.
12. Gramatica L Jr, Herrera MF, Mercado-Luna A, Sierra M, Verasay G, Brunner N. Videolaparoscopic resection of insulinomas: experience in two institutions. World J Surg 2002;26(10):1297–1300. doi:10.1007/s00268-002-6711-z.
13. Berends FJ, Cuesta MA, Kazemier G, van Eijck CH, de Herder WW, van Muiswinkel JM, Bruining HA, Bonjer HJ. Laparoscopic detection and resection of insulinomas. Surgery 2000;128(3):386–391. doi:10.1067/msy.2000.107413.
14. Ayav A, Bresler L, Brunaud L, Boissel P. Laparoscopic approach for solitary insulinoma: a multicentre study. Langenbecks Arch Surg 2005;390(2):134–140. doi:10.1007/s00423-004-0526-3.
15. Dulucq JL, Wintringer P, Mahajna A. Laparoscopic pancreaticoduodenectomy for benign and malignant diseases. Surg Endosc 2006;20(7):1045–1050. doi:10.1007/s00464-005-0474-1.
16. Palanivelu C, Jani K, Senthilnathan P, Parthasarathi R, Rajapandian S, Madhankumar MV. Laparoscopic pancreaticoduodenectomy: technique and outcomes. J Am Coll Surg 2007;205(2):222–230. doi:10.1016/j.jamcollsurg.2007.04.004.
17. Lu B, Cai X, Lu W, Huang Y, Jin X. Laparoscopic pancreaticoduodenectomy to treat cancer of the ampulla of Vater. JSLS 2006;10(1):97–100.
18. Gagner M, Pomp A. Laparoscopic pancreatic resection: Is it worthwhile? J Gastrointest Surg 1997;1(1):20–25. discussion 25-26. doi:10.1007/s11605-006-0005-y.
19. Edwin B, Mala T, Mathisen O, Gladhaug I, Buanes T, Lunde OC, Soreide O, Bergan A, Fosse E. Laparoscopic resection of the pancreas: a feasibility study of the short-term outcome. Surg Endosc 2004;18(3):407–411. doi:10.1007/s00464-003-9007-y.
20. D'Angelica M, Are C, Jarnagin W, DeGregoris G, Coit D, Jaques D, Brennan M, Fong Y. Initial experience with hand-assisted laparoscopic distal pancreatectomy. Surg Endosc 2006;20(1):142–148. doi:10.1007/s00464-005-0209-3.
21. Dulucq JL, Wintringer P, Stabilini C, Feryn T, Perissat J, Mahajna A. Are major laparoscopic pancreatic resections worthwhile? A prospective study of 32 patients in a single institution. Surg Endosc 2005;19(8):1028–1034. doi:10.1007/s00464-004-2182-7.
22. Fernandez-Cruz L, Cosa R, Blanco L, Levi S, Lopez-Boado MA, Navarro S. Curative laparoscopic resection for pancreatic neoplasms: a critical analysis from a single institution. J Gastrointest Surg 2007;11(12):1607–1621. discussion 1621-1602. doi:10.1007/s11605-007-0266-0.
23. Melotti G, Butturini G, Piccoli M, Casetti L, Bassi C, Mullineris B, Lazzaretti MG, Pederzoli P. Laparoscopic distal pancreatectomy: results on a consecutive series of 58 patients. Ann Surg 2007;246 (1):77–82. doi:10.1097/01.sla.0000258607.17194.2b.
24. Han HS, Min SK, Lee HK, Kim SW, Park YH. Laparoscopic distal pancreatectomy with preservation of the spleen and splenic vessels for benign pancreas neoplasm. Surg Endosc 2005;19 (10):1367–1369. doi:10.1007/s00464-004-8158-9.
25. Barlehner E, Anders S, Schwetling R. Laparoscopic resection of the left pancreas: technique and indication. Dig Surg 2002;19 (6):507–510. doi:10.1159/000067606.
26. Tang CN, Tsui KK, Ha JP, Wong DC, Li MK. Laparoscopic distal pancreatectomy: a comparative study. Hepatogastroenterology 2007;54(73):265–271.
27. Gurusamy K, Junnarkar S, Farouk M, Davidson BR. Meta-analysis of randomized controlled trials on the safety and effectiveness of day-case laparoscopic cholecystectomy. Br J Surg 2008;95(2):161–168. doi:10.1002/bjs.6105.
28. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: A combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. Eur J Cancer 2008;44(10):1345–1389. doi:10.1016/j.ejca.2007.12.015.
29. Stojadinovic A, Brooks A, Hoos A, Jaques DP, Conlon KC, Brennan MF. An evidence-based approach to the surgical management of resectable pancreatic adenocarcinoma. J Am Coll Surg 2003;196(6):954–964. doi:10.1016/S1072-7515(03)00010-3.
30. Karanicolas PJ, Davies E, Kunz R, Briel M, Koka HP, Payne DM, Smith SE, Hsu HP, Lin PW, Bloechle C, Paquet KJ, Guyatt GH. The pylorus: take it or leave it? Systematic review and meta-analysis of pylorus-preserving versus standard whipple pancreaticoduodenectomy for pancreatic or periampullary cancer. Ann Surg Oncol 2007;14(6):1825–1834. doi:10.1245/s10434-006-9330-3.
31. Knaebel HP, Diener MK, Wente MN, Buchler MW, Seiler CM. Systematic review and meta-analysis of technique for closure of the pancreatic remnant after distal pancreatectomy. Br J Surg 2005;92(5):539–546. doi:10.1002/bjs.5000.
32. Lillemoe KD, Kaushal S, Cameron JL, Sohn TA, Pitt HA, Yeo CJ. Distal pancreatectomy: indications and outcomes in 235 patients. Ann Surg 1999;229(5):693–698. discussion 698-700. doi:10.1097/00000658-199905000-00012.
33. Sa Cunha A, Rault A, Beau C, Collet D, Masson B. Laparoscopic central pancreatectomy: single institution experience of 6 patients. Surgery 2007;142(3):405–409. doi:10.1016/j.surg.2007.01.035.
34. Johnson MA, Rajendran S, Balachandar TG, Kannan DG, Jeswanth S, Ravichandran P, Surendran R. Central pancreatectomy for benign pancreatic pathology/trauma: is it a reasonable pancreas-preserving conservative surgical strategy alternative to standard major pancreatic resection? ANZ J Surg 2006;76(11):987–995. doi:10.1111/j.1445-2197.2006.03916.x.
35. Efron DT, Lillemoe KD, Cameron JL, Yeo CJ. Central pancreatectomy with pancreaticogastrostomy for benign pancreatic pathology. J Gastrointest Surg 2004;8(5):532–538. doi:10.1016/j.gassur.2004.03.004.
36. Park BJ, Alexander HR, Libutti SK, Huang J, Royalty D, Skarulis MC, Jensen RT, Gorden P, Doppman JL, Shawker TH, Fraker DL, Norton JA, Bartlett DL. Operative management of islet-cell tumors arising in the head of the pancreas. Surgery 1998;124(6):1056–1061. discussion 1061-1052. doi:10.1067/msy.1998.92171.
37. Talamini MA, Moesinger R, Yeo CJ, Poulose B, Hruban RH, Cameron JL, Pitt HA. Cystadenomas of the pancreas: is enucleation an adequate operation? Ann Surg 1998;227(6):896–903. doi:10.1097/00000658-199806000-00013.
38. Corcione F, Marzano E, Cuccurullo D, Caracino V, Pirozzi F, Settembre A. Distal pancreas surgery: outcome for 19 cases managed with a laparoscopic approach. Surg Endosc 2006;20 (11):1729–1732. doi:10.1007/s00464-005-0839-5.
39. Gagner M, Pomp A, Herrera MF. Early experience with laparoscopic resections of islet cell tumors. Surgery 1996;120 (6):1051–1054. doi:10.1016/S0039-6060(96)80054-7.
40. Patterson EJ, Gagner M, Salky B, Inabnet WB, Brower S, Edye M, Gurland B, Reiner M, Pertsemlides D. Laparoscopic pancreatic resection: single-institution experience of 19 patients. J Am Coll Surg 2001;193(3):281–287. doi:10.1016/S1072-7515(01)01018-3.
41. Cuschieri A, Jakimowicz JJ, van Spreeuwel J. Laparoscopic distal 70% pancreatectomy and splenectomy for chronic pancreatitis.

Ann Surg 1996;223(3):280–285. doi:10.1097/00000658-199603000-00008.
42. Fernandez-Cruz L, Saenz A, Astudillo E, Pantoja JP, Uzcategui E, Navarro S. Laparoscopic pancreatic surgery in patients with chronic pancreatitis. Surg Endosc 2002;16(6):996–1003. doi:10.1007/s00464-001-9065-y.
43. Fabre JM, Dulucq JL, Vacher C, Lemoine MC, Wintringer P, Nocca D, Burgel JS, Domergue J. Is laparoscopic left pancreatic resection justified? Surg Endosc 2002;16(9):1358–1361. doi:10.1007/s00464-001-9206-3.
44. Misawa T, Shiba H, Usuba T, Nojiri T, Uwagawa T, Ishida Y, Ishii Y, Yanaga K. Safe and quick distal pancreatectomy using a staggered six-row stapler. Am J Surg 2008;195(1):115–118. doi:10.1016/j.amjsurg.2007.01.038.
45. Park AE, Heniford BT. Therapeutic laparoscopy of the pancreas. Ann Surg 2002;236(2):149–158. doi:10.1097/00000658-200208000-00002.
46. Vezakis A, Davides D, Larvin M, McMahon MJ. Laparoscopic surgery combined with preservation of the spleen for distal pancreatic tumors. Surg Endosc 1999;13(1):26–29. doi:10.1007/s004649900891.
47. Velanovich V. The lasso technique for laparoscopic distal pancreatectomy. Surg Endosc 2006;20(11):1766–1771. doi:10.1007/s00464-004-8704-5.
48. Van Nieuwenhove Y, Vandaele S, Op de Beeck B, Delvaux G. Neuroendocrine tumors of the pancreas. Surg Endosc 2003;17(10):1658–1662. doi:10.1007/s00464-002-9268-x.
49. Toniato A, Meduri F, Foletto M, Avogaro A, Pelizzo M. Laparoscopic treatment of benign insulinomas localized in the body and tail of the pancreas: a single-center experience. World J Surg 2006;30(10):1916–1919. discussion 1920-1911. doi:10.1007/s00268-005-0645-1.
50. Shimizu S, Tanaka M, Konomi H, Mizumoto K, Yamaguchi K. Laparoscopic pancreatic surgery: current indications and surgical results. Surg Endosc 2004;18(3):402–406. doi:10.1007/s00464-003-8164-3.
51. Pierce RA, Spitler JA, Hawkins WG, Strasberg SM, Linehan DC, Halpin VJ, Eagon JC, Brunt LM, Frisella MM, Matthews BD. Outcomes analysis of laparoscopic resection of pancreatic neoplasms. Surg Endosc 2007;21(4):579–586. doi:10.1007/s00464-006-9022-x.
52. Jaroszewski DE, Schlinkert RT, Thompson GB, Schlinkert DK. Laparoscopic localization and resection of insulinomas. Arch Surg 2004;139(3):270–274. doi:10.1001/archsurg.139.3.270.
53. Sweet MP, Izumisato Y, Way LW, Clark OH, Masharani U, Duh QY. Laparoscopic enucleation of insulinomas. Arch Surg 2007;142(12):1202–1204. discussion 1205. doi:10.1001/archsurg.142.12.1202.
54. Iihara M, Obara T. Recent advances in minimally invasive pancreatic surgery. Asian J Surg 2003;26(2):86–91.
55. Liu H, Peng C, Zhang S, Wu Y, Fang H, Sheng H, Peng S. Strategy for the surgical management of insulinomas: analysis of 52 cases. Dig Surg 2007;24(6):463–470. doi:10.1159/000111822.
56. Schraibman V, Goldenberg A, de Matos Farah JF, Apodaca FR, Goldman S, Lobo EJ. Laparoscopic enucleation of pancreatic insulinomas. J Laparoendosc Adv Surg Tech A 2007;17(4):399–401. doi:10.1089/lap.2006.0110.

J Gastrointest Surg (2009) 13:1138–1146
DOI 10.1007/s11605-009-0855-1

REVIEW ARTICLE

The Omentum: Anatomical, Metabolic, and Surgical Aspects

Danielle Collins · Aisling M. Hogan · Donal O'Shea · Des C. Winter

Received: 12 January 2009 / Accepted: 26 February 2009 / Published online: 17 March 2009

Abstract
Introduction The omentum is acknowledged to have diverse functions in the pathophysiology of intra-abdominal disease. Its angiogenic properties act as a natural defense mechanism in peritonitis and intra-abdominal sepsis. With advancing technology the omentum is revealing itself as a new player in the field of molecular surgery with special reference to cancer, obesity and tissue reconstruction. This article reviews the existing and potential surgical applications of the omentum.

Keywords Omentum · Inflammation · Reconstruction · Metabolic

Introduction

The omentum is known as the "policeman of the abdomen," a protective agent that moves around the peritoneal cavity to areas where "mischief is brewing."[1] Once thought of as just a large amount of redundant fat overlying the intestines, surgeons' attitudes towards the omentum have changed. It is recognized as an organ in its own right with many diverse functions ranging from its ability to attenuate the spread of sepsis in peritonitis to acting as a source of angiogenic and hemostatic factors involved in tissue healing and repair. The omentum has been identified as a source of adult stem cells which may have future prospects in the fields of tissue engineering and the synthesis of vascular grafts. Its regenerative properties have been exploited in virtually every field of surgery from the reconstruction of complex wounds to the protection of gastrointestinal anastomosis.

Anatomy and Embryology

Recognition of the omentum dates back to Egyptian times, and it was termed the great epiploon by Aristotle.[2] It originates embryologically from the dorsal mesogastrium and is divided anatomically into the greater and lesser omenta. The greater omentum is a double sheet of peritoneum that descends from the greater curvature of the stomach, overlying the small intestine and then folds back on itself to fuse with the peritoneum on the anterior surface of the transverse colon. The lesser omentum extends between the liver and the lesser curvature of the stomach forming the anterior boundary of the lesser sac (Fig. 1). The blood supply of the omentum is from the right left and middle omental arteries which originate from the right and left gastroepiploic arteries. The larger right omental artery supplies the anterior surface, while the smaller left omental artery supplies the posterior surface.[3]

D. Collins · A. M. Hogan · D. C. Winter
Institute for Clinical Outcomes, Research and Education (iCore),
St Vincent's University Hospital,
Elm Park,
Dublin 4, Ireland

D. O'Shea
Department of Endocrinology, St Vincent's University Hospital,
Elm Park,
Dublin 4, Ireland

D. Collins (✉)
Department of Surgery, St Vincent's Hospital,
Elm Park,
Dublin 4, Ireland
e-mail: daniellecol@gmail.com

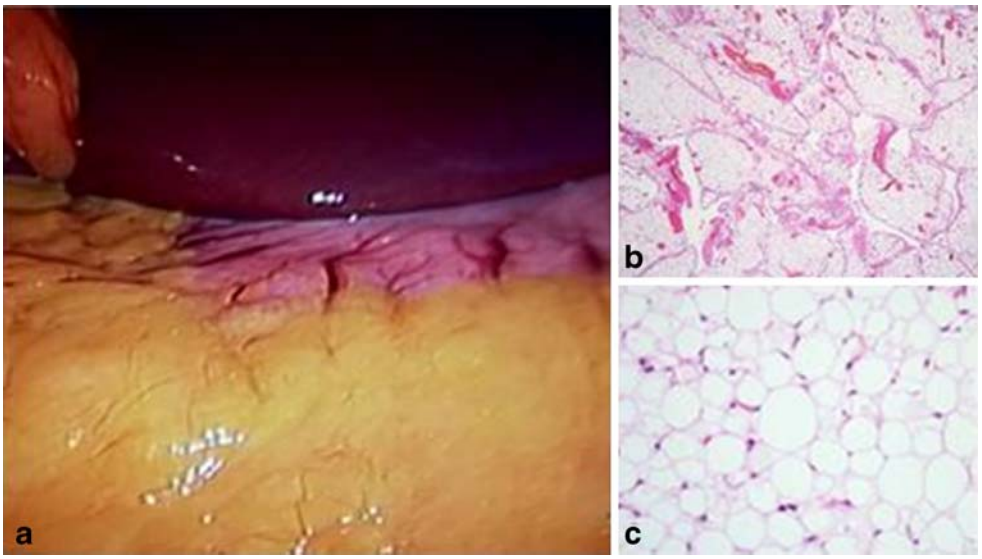

Figure 1 **a** Laparoscopic image of the greater omentum, stomach, and right lobe of liver. **b** Hematoxylin and eosin staining of omentum (×4 magnification). **c** Omental adiopcytes (×40 magnification).

Ultrastructure

The omentum is comprised of two mesothelial sheets enclosing adipocytes and loose connective tissue with aggregates of mononuclear phagocytic cells.

Microscopically, it is composed of two distinct tissue types: thin fenestrated translucent membranes and adipose-rich areas.[4,5] The function of the translucent areas has not been fully evaluated; however, they are thought to be involved in fluid and solute transport as well as in omental adhesion to areas of inflammation. The adipose region of the omentum is home to so-called milky spots or "taches laiteuses" described by Ranvier[6] which play a role in the clearance of bacteria and also provide a site for proliferation and maturation of macrophages and B cells.[7]

Milky Spots

At a microscopic level, the milky spots contain a glomerular like capillary network of blood vessels which enables fluid exchange between the peritoneal cavity, the bloodstream, and the surrounding omental tissue.[8] Scanning electron microscopy shows that omental milky spots are characterized by discontinuous layers of mesothelial cells and leukocytes. The presence of pores or stomata within the connective tissue layer of milky spots allows for direct communication with the peritoneal cavity.[9] Milky spots consist of relatively uniform vascularized accumulations of mononuclear cells comprising macrophages (70%), B cells (10%), T cells (10%), and mast cells.[10] Developing milky spots contain macrophages in different stages of maturation formed during the 20th to 35th weeks of gestation.[11,12] They are considered to be the site where the origin of peritoneal macrophages originate and differentiate.[13–15]

Activated Omentum

The omentum is the primary peritoneal defense organ responsible for the absorption and clearance of bacteria and debris from the peritoneal cavity. Although it is not inherently motile, experimental models have shown that, in response to foreign matter or inflammation, it adheres to and walls off the area of insult. When exposed to a foreign stimulus, omental blood flow increases, and the proportion of stromal tissue expands.[16] The stroma produces cells expressing stem cell markers[17–19] as well as inflammatory, hemostatic, and chemotactic[20] substances such as vascular endothelial growth factor and basic fibroblast growth factor (bFGF).[21] These activated stromal cells engraft to injured sites,[22] leading to the recruitment of inflammatory cells[23] within the peritoneal cavity, thus promoting tissue repair.

The mechanism for omental adhesion involves the formation of a fibrin exudate at the site of injury forming a bridge between it and the injured site. The fibrin scaffold encourages the migration of leukocytes especially macrophages, neutrophils, and fibroblasts to the site of injury leading to collagen deposition around the offending zone.[24] The use of an omental patch, for example in the treatment of perforated duodenal ulcers, gives rise to accelerated ulcer healing and inhibits ulcer recurrence. Experimental wound models show omental transposition promotes healing due to transforming growth factor-β1 and bFGF mediated angiogenesis.[25,26] Interestingly, this same physiological pathway is involved in the

formation of omental adhesions following inflammation or surgery. From a therapeutic point of view, selectively inhibiting the cytokines involved may hold promise in preventing adhesion formation.[27–30]

Omentum in Cancer and Tumorigenesis

Primary tumors of the omentum are rare; however, it is a well-known site of metastases of carcinomas of the ovaries, stomach, and colon. Omentectomy is frequently performed for ovarian epithelial carcinomas as a means of staging the disease as well as to prevent local recurrence[31] and has been advocated for tumors that metastasize via the peritoneal cavity.[32,33]

Although the omentum plays a major role in tumor cell spread by recognizing and trapping cells in milky spots, few studies have been performed that elucidate the cellular reactions and mechanism involved. Intraperitoneally injected tumor cells preferentially localize to milky spots[34] within a number of hours where they encounter host macrophages with tumoricidal capabilities.[35,36] It has therefore been proposed that omentectomy should be avoided in order to permit the cytotoxic actions of these cells. However, in models of minimal residual disease, omental macrophages are unable to effectively eliminate tumor cells from the peritoneal cavity.[37] As tumor cell proliferation in milky spots is the first step in the progression to peritoneal carcinomatosis,[38–41] should omentectomy be advised for the management of all intra-abdominal tumors? Or does removing the omentum unnecessarily impair peritoneal defense mechanisms?

Role of the Omentum in Obesity

Intra-abdominal obesity is recognized as an independent risk factor for cardiovascular disease, diabetes, and certain cancers.[42,43] The proposed hypothesis is that obesity causes a state of low-grade inflammation leading to thrombosis, atherosclerosis, and insulin resistance.[44] This immune-inflammatory hypothesis is further supported by evidence that omental fat contains more macrophages than other fat depots.[45] Visceral fat is functionally and metabolically distinct from other adipose tissue stores,[46] and patients with intra-abdominal fat have higher plasma glucose and triglyceride levels than patients with predominantly subcutaneous fat.[47,48] In comparative studies of adipose tissue taken from the omentum and from peripheral sites, it has been demonstrated that visceral fat secretes pro-inflammatory mediators such as platelet activator inhibitor-1, tumor necrosis factor α (TNFα), transforming growth factor β[49,50] complement,[51] and Il-18.[52] At a genomic level, microarray studies have identified differences in gene expression in omental fat including a down-regulation of genes involved in activation of lipolysis.[53]

In addition, omental adipose tissue is capable of increasing circulating glucocorticoids which predispose to obesity and insulin resistance, a process which had been termed "Cushing's disease of the omentum."[54]

Further investigation is required into how intra-abdominal adipose tissue causes metabolic dysfunction in humans. Recent work demonstrates that the omentum is a source of adipokines such as leptin, RANTES,[55] and resistin,[56] which may provide the link into how intra-abdominal obesity causes metabolic dysfunction (Table 1). Alternatively, the increased production of free fatty acids entering the portal system may alter the effects of the liver on insulin regulation[57] leading to insulin resistance.

In addition, omental microvascular endothelial cells (MVEC) provide a source of pre-adipocytes capable of differentiating into adipocytes. The function of these stem cells within omental tissue is unknown; however, it does provide a continued source of adipocytes to the omentum.

It is interesting to note that "visceral fat syndrome" may actually be amenable to surgical management. Omentectomy eliminates an often massive, metabolically detrimental visceral fat depot. It has been suggested that omentectomy in combination with roux-en-y gastric bypass ameliorates insulin resistance and diabetes, although results

Table 1 Adipokines and Cytokines Produced by Omentum

	Function
Resistin[56]	Insulin resistance and glucose intolerance
Adiponectin[100]	Insulin sensitizing adipokine; reduced in visceral obesity
RANTES[101]	Recruitment of T cells and chronic inflammation
MCP-1	Macrophage recruitment and insulin resistance
MIP	Macrophage recruitment and insulin resistance
IL-6[102]	Inflammatory mediator
TNFα[103]	Inflammatory mediator
GRO[55]	Skeletal muscle insulin resistance
TIMP-1	Skeletal muscle insulin resistance

RANTES: regulated on activation, normal T cell expressed and secreted, *MCP* monocyte chemoattractant protein, *MIP* macrophage inflammatory protein, *GRO* growth-related antigen, *TIMP* tissue inhibitor of metalloproteinases

Table 2 Outcome of Omentopexy in Abdomino-Perineal Resection

Study	Year	No of Patients	Intervention		Outcome at 3months	
			Omentopexy	No omentopexy	Omentopexy	No Omentopexy
De Broux [104]	2005	92	92	–	100%	84%
Hay [105]	1997	165	64	101	87%	82%
Wang [106]	1994	103	21	82	100% healed	–
Rice [107]	1992	20	20	–	100% healed	–
John [108]	1991	74	38	36	87%	69%
Poston [109]	1991	53	28	25	100% healed	–
Smith [110]	1988	11	11	–	100% healed	–
Moreaux [111]	1984	55	55	–	100% healed	–
Page [112]	1980	26	26	–	100% healed	–

are conflicting. Thörne et al. carried out a pilot study of 50 patients and found a significant improvement in glycemic control in the omentectomy group;[58] however, in a randomized trial of 70 patients, Csendes et al. did not demonstrate a benefit[59] at 2-year follow-up. Given the low numbers associated with these studies as well as the confounding factor of jejunal bypass, it is difficult to attribute improvements in metabolic control solely to omentectomy.

Gastrointestinal Surgery

In gastrointestinal (GI) operations, omentum is used to safeguard colonic anastomosis, in the management of perforated duodenal and gastric ulceration, and as a reconstructive tissue in abdomino-perineal resections. In addition, its hemostatic properties have been employed in hepatico-pancreatic surgery to minimize postoperative bleeding following hepatectomy or pancreaticoduodenectomy.[60]

Gastrointestinal Anastomosis

Controversy exists as to whether reinforcing colonic anastomosis using omentum decreases the incidence of anastomotic leakage. In the late 1800s, Senn concluded that protecting surgical wounds with omentum was simply imitating nature's process in protecting the peritoneal cavity against perforation and in hastening the healing of the visceral wound.[61] Studies in animal models have demonstrated that wrapping the omentum around an anastomosis can promote healing,[62,63] but in clinical studies, omental wrap has only proved beneficial in upper GI surgery.[64] In low rectal anastomosis, using omentum to exclude the pelvic dead space intuitively would appear to decrease complication rates as well as diverting any small-bowel loops away from potential radiotherapy fields.[65–67] Tocchi et al.[68] found a decreased incidence in clinical anastomotic leak in patients who underwent omentopexy for colorectal anastomosis in a prospective study of 112 patients (Table 2). However, in a prospective randomized trial of 712 patients undergoing colonic anastomosis, it was found that omentoplasty did not decrease the rate of anastomotic failure.[69]

The Use of Omentopexy in Abdominoperineal Resection

Abdominoperineal resection (APR) especially following radiotherapy has a reported perineal wound complication rate in the order of 35–41%.[70,71] One of the major contributing factors is that the pelvis acts as a physiological dead space where fluid can accumulate and provide a medium for bacterial growth and subsequent abscess formation. It is suggested that omentoplasty in APR does

Table 3 Applications for Omental Transposition

Speciality	Reference	Indication for Omental Transposition
Neurosurgery	[93,94]	Alzheimers's disease, Moyamoya disease, spinal cord transaction
Urology	[86]	Management of complex urinary fistula
Gynecology	[87,88]	J-flap following radical abdominal hysterectomy
Vascular Surgery	[89–92]	Extremity revascularization in Buerger's disease, aortic interposition graft following aortoenteric fistula

confer benefit, but this evidence is either from case series or small number cohort studies lacking adequate controls. In a review of omentoplasty in APR,[72] Nilsson reported statistically improved perineal healing rates with omentoplasty; however, the lack of a suitable randomized controlled trial means that a meaningful conclusion cannot be drawn.

Does Omentectomy Impair Peritoneal Defenses?

In a retrospective study of patients undergoing proctocolectomy with ileo-anal anastomosis, those who underwent omentectomy at the time of their procedure had a poorer outcome with regard to postoperative sepsis and sepsis requiring reoperation. It was concluded from the study that the omentum should be retained in this type of operation.[73]

In rodent models, however, omentectomy does not decrease the bactericidal activity of peritoneal fluid,[74] nor does it increase bacterial counts in a model of cecal perforation.[75] The same group looked at the effect of omentectomy on the inflammatory phase of anastomotic healing and found that there was no difference between rats subjected to omentectomy.[76] In fact, they showed that following omentectomy, systemic compensatory mechanisms lead to the recruitment of peripheral leukocytes which mediate the healing process.

Reconstruction

The regenerative properties of the omentum have been exploited by surgeons for over a century, ranging from the protection of anastomosis in gastrointestinal surgery, revascularization of arterial ulcers, to the reconstruction of head and neck deformities.[77] The advantage of the omentum is that it is an accessible and versatile source of growth factors, angiogenic factors, and leukocytes. It can be lengthened considerably by careful dissection to produce a mobile organ.[78] The omentum can be transformed into a pedicled flap based on both the right and left gastroepiploic arteries. In this way, it can be grafted to distant sites such as the chest wall, perineum, or thigh. Briefly, the omentum is detached from the transverse colon and greater curvature of the stomach. It can be further lengthened by dividing along the various smaller vascular arcades.[79–81] Donor site complications (wound infection, hernia) occur in up to 18% of patients but generally carry low morbidity.[82] Omental harvesting usually requires laparotomy, but with the advent of laparoscopic surgery, the morbidity from harvesting omental grafts has decreased.[83]

Complex Wounds

Recently omental pedicled grafts have been successfully used in the management of complex extraperitoneal wounds such as large chest wall defects.[84] Schrager et al. have reported an 88% success rate with the use of omental grafts for both the protection of high-risk thoracic anastomosis as well as for reconstruction of infected chest wall wounds.[85]

In other surgical disciplines, successful cases of omental transposition have been described in the fields of neurosurgery, gynecology, urology, and vascular surgery (Table 3).[86–94]

Future Prospects

With expanding knowledge in the fields of stem cell research and tissue reconstruction, the omentum may prove to be an exciting option for adult stem cell harvesting as well as a medium for tissue engineering. MVEC isolated and cultured from human omentum have been used to construct an endothelial lining for synthetic vascular grafts.[95] In a similar way, these angiogenic capabilities may be harnessed for pancreatic islet cell transplantation.[96–98] Furthermore, the omentum may be used as a scaffold for the formation of new organs. Although in its infancy, it has been demonstrated that the omentum can act as an in vivo bioreactor for bladder reconstruction.[99]

Conclusion

In this era of molecular surgery, our understanding of the diverse functions of the omentum both as a lymphoid organ and as a regulator of metabolism is evolving. Its function in controlling the spread of intra-abdominal tumors remains to be defined. Milky spot macrophages and B cells have demonstrated cytotoxic actions in vitro and may represent a new target for anticancer therapy. From a surgical perspective, it plays an important role in tissue healing, and these properties may be harnessed for tissue engineering and transplantation. Finally, as the properties of omental adipocytes are revealed, surgery may prove to be important in the management of obesity-related metabolic disorders.

Acknowledgments Images courtesy of Dr Leona Doyle

References

1. Morison R. Remarks on some functions of the omentum. BMJ 1906;1:76–78.

2. Aristotle. On the parts of animals. Book IV 350 BC
3. Taranu T, Taranu T, Varlam H, et al. The arterial system of the greater omentum. Rev Med Chir Soc Med Nat 1998;102:139–142.
4. Ryan GB, Grobety J, Majno G. Postoperative peritoneal adhesions. A study of the mechanisms. Am J Pathol 1971;65:117–148.
5. Wilkosz S, Ireland G, Khwaja N, Walker M, Butt R, de Giorgio-Miller A, Herrick SE. A comparative study of the structure of human and murine greater omentum. Anat Embryol (Berl) 2005;209:251–261. doi:10.1007/s00429-004-0446-6.
6. Ranvier L. Recherches sur la formation des milles du grand epiplon. Arch Physiol 1880;1:421–428.
7. Van Vugt E, Van Rijthoven EA, Kamperdijk EW, Beelen RH. Omental milky spots in the local immune response in the peritoneal cavity of rats. Anat Rec 1996;244:235–245. doi:10.1002/(SICI)1097-0185(199602)244:2<235::AID-AR11>3.0.CO;2-Q.
8. Liebermann-Meffert D, White H, editors. The greater Omentum: Anatomy, Physiology, Pathology, Surgery, with an Historical Survey. New York, Springer, 1983, pp1–369.
9. Cui L, Johkura K, Liang Y, Teng R, Ogiwara N, Okouchi Y, et al. Biodefense function of omental milky spots through cell adhesion molecules and leukocyte proliferation. Cell Tissue Res 2002;310:321–330. doi:10.1007/s00441-002-0636-6.
10. Krist LF, Eestermans IL, Steenbergen JJ, Hoefsmit EC, Cuesta MA, Meyer S, et al. Cellular composition of milky spots in the human greater omentum: an immunochemical and ultrastructural study. Anat Rec 1995;241:163–174. doi:10.1002/ar.1092410204.
11. Krist LF, Koenen H, Calame W, van der Harten JJ, van der Linden JC, Eestermans IL, et al. Ontogeny of milky spots in the human greater omentum: an immunochemical study. Anat Rec 1997;249:399–404. doi:10.1002/(SICI)1097-0185(199711)249:3<399::AID-AR11>3.0.CO;2-J.
12. Wijffels JF, Hendrickx RJ, Seetenbergen JJ, Eestermans IL, Beelen RH, et al. Milky spots in the omentum may play an important role in the origin of peritoneal macrophages. Res Immunol 1992;143:401–409. doi:10.1016/S0923-2494(05)80072-0.
13. Beelen RHJ, Fluitsma DM, Hoefsmit EC. Peroxidatic activity of mononuclear phagocytes developing in omentum milky spots. J Reticuloendothel Soc 1980b;28:601–609.
14. Mandache E, Moldoveanu E, Savi G. The involvement of omentum and its milky spots in the dynamics of peritoneal macrophages. Morphol Embryol (Bucur) 1985;31:137–142.
15. Zhu H, Naito M, Umezu H, Moriyama H, Takatsuka H, Takahashi K, et al. Macrophage differentiation and expression of macrophage colony-stimulating factor in murine milky spots and omentum after macrophage elimination. J Leukoc Biol 1997;61:436–444.
16. Doherty NS, Griffiths RJ, Hakkinen JP, Scampoli DN, Milici AJ. Post-capillary venules in the "milky spots" of the greater omentum are the major site of plasma protein and leukocyte extravasation in rodent models of peritonitis. Inflamm Res 1995;44:169–177. doi:10.1007/BF01782815.
17. Litbarg NO, Gudehithlu KP, Sethupathi P, Arruda JAL, Dunea G, Singh AK. Activated omentum becomes rich in factors that promote healing and tissue regeneration. Cell Tissue Res 1997;328:487–497. doi:10.1007/s00441-006-0356-4.
18. Zhang QX, Magovern CJ, Mack CA, Budenbender KT, Ko W, Rosengart TK. Vascular endothelial growth factor is the major angiogenic factor in omentum: mechanism of the omentum-mediated angiogenesis. J Surg Res 1997;67:147–154.
19. García-Gómez I, Goldsmith HS, Angulo J, Prados A, López-Hervás P, Cuevas B, et al. Angiogenic capacity of human omental stem cells. Neurol Res 2005;27:807–811. doi:10.1179/016164105X63674.
20. Logmans A, Schoenmakers CH, Haensel SM, et al. High tissue factor concentration in the omentum, a possible cause of its hemostatic properties. Eur J Clin Invest 1996;26:82–83. doi:10.1046/j.1365-2362.1996.107247.x.
21. Bikfalvi A, Alterio J, Inyang AL, Dupuy E, Laurent M, Hartmann MP, et al. Basic fibroblast growth factor expression in human omental microvascular endothelial cells and the effect of phorbol ester. J Cell Physiol 1990;144:151–158. doi:10.1002/jcp.1041440120.
22. Singh AK, Patel J, Litbarg NO, Gudehithlu KP, Sethupathi P, Arruda JA, Dunea G, et al. Stromal cells cultured from omentum express pluripotent markers, produce high amounts of VEGF, and engraft to injured sites. Cell Tissue Res 2008;332:81–88. doi:10.1007/s00441-007-0560-x.
23. Shimotsuma M, Simpson-Morgan MW, Takahashi T, Hagiwara A. Activation of omental milky spots and milky spot macrophages by intraperitoneal administration of a streptococcal preparation, OK432. Cancer Res 1992;52:5400–5402.
24. Florey H, Walker JL, Carleton HM. The nature of the movement of the omentum. J Pathol Bacteriol 1926;29:97–106. doi:10.1002/path.1700290111.
25. Oloumi MM, Derakhshanfar A, Molaei M, Tayyebi M. The angiogenic potential of autogenous free omental graft in experimental tibial defects in rabbit: Short-term preliminary histopathological study. J Exp Anim Sci 2006;43(3):179–187. doi:10.1016/j.jeas.2006.02.002.
26. Matoba Y, Katayama H, Ohami H. Evaluation of omental implantation for perforated gastric ulcer therapy: findings in a rat model. J Gastroenterol 1996;31:777–784. doi:10.1007/BF02358602.
27. Epstein JC, Wilson MS, Wilkosz S, Ireland G, O'Dwyer ST, Herrick SE. Human peritoneal adhesions show evidence of tissue remodeling and markers of angiogenesis. Dis Colon Rectum 2006;49:1885–1892.
28. Cahill RA, Wang JH, Soohkai S, Redmond HP. Mast cells facilitate local VEGF release as an early event in the pathogenesis of postoperative peritoneal adhesions. Surgery 2006;140:108–112. doi:10.1016/j.surg.2006.01.020.
29. Chung DR, Chitnis T, Panzo RJ, Kasper DL, Sayegh MH, Tzianabos AO. CD4+ T cells regulate surgical and postinfectious adhesion formation. J Exp Med. 2002;195:1471–1478. doi:10.1084/jem.20020028.
30. Cahill RA, Redmond HP. Cytokine orchestration in post-operative peritoneal adhesion formation. World J Gastroenterol 2008;14:4861–4866. doi:10.3748/wjg.14.4861.
31. Benedet JL, Bender H, Jones H III, et al. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO committee on gynecologic oncology. Int J Gynaecol Obstet 2000;70:209–262. doi:10.1016/S0020-7292(00)90001-8.
32. Hagiwara A, Sawai K, Sakakura C, Hagiwara A, Sawai K, Sakakura C, Shirasu M, Ohgaki M, Yamasaki J, et al. Complete omentectomy and extensive lymphadenectomy with gastrectomy improves the survival of gastric cancer patients with metastases in the adjacent peritoneum. Hepatogastroenterology 1998;45:1922–1929.
33. Lawrence RJ, Loizidou M, Cooper AJ, et al. Importance of the omentum in the development of intra-abdominal metastases. Br J Surg 1991;78:117. doi:10.1002/bjs.1800780135.
34. Hagiwara A, Takahashi T, Sawai K, Taniguchi H, Shimotsuma M, Okano S, et al. Milky spots as the implantation site for malignant cells in peritoneal dissemination in mice. Cancer Res 1993;53:687–692.
35. Dullens HF, Rademakers LH, Doffemont M, Van Veen PT, Bulder R, Den Otter W. Involvement of the omental lymphoid organ in the induction of peritoneal immunity against tumor cells. Invasion Metastasis 1993;13:267.

36. Krist LF, Kerremans M, Koenen HJ. Novel isolation and purifcation method to study functional cytotoxicity of macrophages from milky spots in the greater omentum. J Immunol Methods 1995b;184:253. doi:10.1016/0022-1759(95)00096-S.
37. Oosterling SJ, van der Bij GJ, Bögels M, van der Sijp JR, Beelen RH, Meijer S, et al. Ability of omental milky spots to prevent peritoneal tumor outgrowth supports omentectomy in minimal residual disease. Cancer Immunol Immunother 2006;55 (9):1043–1051. doi:10.1007/s00262-005-0101-y.
38. Dullens HF, Rademakers LH, Cluistra S, Van Os R, Dux K, Den Besten PJ, Den Otter W. Parathymical lymph nodes during growth and rejection of intraperitoneally inoculated tumour cells. Invasion Metastasis 1991;11:216.
39. Tsjujimoto H, Hagiwara A, Shimutsuma M. Role of milky spots as selective implantation sites for malignant cells in peritoneal dissemination in mice. J Cans Res Clin Oncol 1996;122:590. doi:10.1007/BF01221190.
40. Lopes Cardozo AM, Gupta A, Koppe MJ. Metastatic pattern of CC531 colon carcinoma cells in the abdominal cavity: an experimental model of peritoneal carcinomatosis in rats. Eur J Surg Oncol 2001;27:359–363. doi:10.1053/ejso.2001.1117.
41. Krist LF, Kerremans M, Broekhuis-Fluitsma DM, Eestermans IL, Meyer S, Beelen RH. Milky spots in the greater omentum are predominant sites of local tumour cell proliferation and accumulation in the peritoneal cavity. Cancer Immunol Immunother 1998;47:205–212. doi:10.1007/s002620050522.
42. Bjorntorp P. Metabolic implications of body fat distribution. Diabetes Care 1991;14:1132–1143. doi:10.2337/diacare. 14.12.1132.
43. Matsuzawa Y, Fujioka S, Tokunaga K, Tarui S. Classification of obesity with respect to morbidity. Proc Soc Exp Biol Med 1992;200:197–201.
44. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, Capeau J, Feve B. Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw 2006;17(1):4–12.
45. Harman-Boehm I, Blüher M, Redel H, Sion-Vardy N, Ovadia S, Avinoach E, Shai I, Klöting N, Stumvoll M, Bashan N, Rudich A. Macrophage infiltration into omental versus subcutaneous fat across different populations: effect of regional adiposity and the comorbidities of obesity. J Clin Endocrinol Metab 2007;92:2240–2247. doi:10.1210/jc.2006-1811.
46. Vohl MC, Sladek R, Robitaille J, Gurd S, Marceau P, Richard D, Hudson TJ, Tchernof A. A survey of genes differentially expressed in subcutaneous and visceral adipose tissue in men. Obes Res 2004;12(8):1217–1222. doi:10.1038/oby.2004.153.
47. Fujioka S, Matsuzawa Y, Tokunaga K, Tarui S. Contribution of intraabdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. Metabolism 1987;36:54–59. doi:10.1016/0026-0495(87)90063-1.
48. Kanai H, Matsuzawa Y, Kotani K, Keno Y, Kobatake T, Nagai Y. Close correlation of intra-abdominal fat accumulation to hypertension in obese women. Hypertension 1990;16:484–490.
49. He G, Pedersen SB, Bruun JM, Lihn AS, Jensen PF, Richelsen B. Differences in plasminogen activator inhibitor 1 in subcutaneous versus omental adipose tissue in non-obese and obese subjects. Horm Metab Res 2003;35(3):178–182. doi:10.1055/s-2003-39078.
50. Alessi MC, Bastelica D, Morange P, Berthet B, Leduc I, Verdier M, Geel O, Juhan-Vague I. Plasminogen activator inhibitor 1, transforming growth factor-beta1, and BMI are closely associated in human adipose tissue during morbid obesity. Diabetes 2000;49(8):1374–1380. doi:10.2337/diabetes.49.8.1374.
51. Gabrielsson BG, Johansson JM, Lönn M, Jernås M, Olbers T, Peltonen M, Larsson I, Lönn L, Sjöström L, Carlsson B, Carlsson LM. High expression of complement components in omental adipose tissue in obese men. Obes Res 2003;11(6):699–708. doi:10.1038/oby.2003.100.
52. Darimont C, Avanti O, Blancher F, Wagniere S, Mansourian R, Zbinden I, Leone-Vautravers P, Fuerholz A, Giusti V, Macé K. Contribution of mesothelial cells in the expression of inflammatory-related factors in omental adipose tissue of obese subjects. Int J Obes (Lond) 2008;32(1):112–120.
53. Gómez-Ambrosi J, Catalán V, Diez-Caballero A, Martinez-Cruz LA, Gil MJ, García-Foncillas J, Cienfuegos JA, Salvador J, Mato JM. Frühbeck Gene expression profile of omental adipose tissue in human obesity. G FASEB J 2004;18:215–217.
54. Bujalska IJ, Kumar S, Stewart PM. Does central obesity reflect "Cushing's disease of the omentum"? Lancet 1997;349 (9060):1210–1213. doi:10.1016/S0140-6736(96)11222-8.
55. Maury E, Ehala-Aleksejev K, Guiot Y, Detry R, Vandenhooft A, Brichard SM. Adipokines oversecreted by omental adipose tissue in human obesity. Am J Physiol Endocrinol Metab 2007;293(3): E656–E665. doi:10.1152/ajpendo.00127.2007.
56. McTernan CL, McTernan PG, Harte AL, Levick PL, Barnett AH, Kumar S. Resistin, central obesity, and type 2 diabetes. Lancet 2002;359:46–47. doi:10.1016/S0140-6736(02)07281-1.
57. Bergman RN, Van Citters GW, Mittelman SD, Dea MK, Hamilton-Wessler M, Kim SP, Ellmerer M. Central role of the adipocyte in the metabolic syndrome. J Investig Med 2001;49 (1):119–126. doi:10.2310/6650.2001.34108.
58. Thörne A, Lönnqvist F, Apelman J, et al. A pilot study of long-term effects of a novel obesity treatment: omentectomy in connection with adjustable gastric banding. Int J Obes Relat Metab Disord 2002;26:193–199. doi:10.1038/sj.ijo.0801871.
59. Csendes A, Maluenda F, Burgos AM. Prospective Randomized Study Comparing Patients with Morbid Obesity Submitted to Laparotomic Gastric Bypass with or without Omentectomy. Obes Surg 2008;PMID: 18712575.
60. Maeda A, Ebata T, Kanemoto H, et al. Omental flap in pancreaticoduodenectomy for protection of splanchnic vessels. World J Surg 2005;29:1122–1126. doi:10.1007/s00268-005-7900-3.
61. Senn N. An experimental contribution to intestinal surgery with special reference to the treatment of intestinal obstruction. Ann Surg 1888;7:171–186.
62. Adams W, Ctercteko G, Bilous M. Effect of an omental wrap on the healing and vascularity of compromised intestinal anastomoses. Dis Colon Rectum 1992;35:731–738. doi:10.1007/BF02050320.
63. Katsikas D, Sechas M, Antypas G, et al. Beneficial effect of omental wrapping of unsafe intestinal anastomoses. An experimental study in dogs. Int Surg 1977;62(8):435–437.
64. Bhat MA, Dar MA, Lone GN, Dar AM. Use of pedicled omentum in esophagogastric anastomosis for prevention of anastomotic leak. Ann Thorac Surg 2006;82:1857–1862. doi:10.1016/j.athoracsur.2006.05.101.
65. Ferguson CM. Use of omental pedicle grafts in abdominoperineal resection. Am Surg 1990;56(5):310–312.
66. Logmans A, Lent van M, Geel van AN, Olofsel- van Acht M, et al. The pedicled omentoplasty, a simple and effective surgical technique to acquire a safe pelvic radiation field; theoretical and practical aspects. Radiother Oncol 1994;33:269–271. doi:10.1016/0167-8140(94)90364-6.
67. Lechner P, Cesnik H. Abdominopelvic omentopexy: preparatory procedure for radiotherapy in rectal cancer. Dis Colon Rectum 1992;35(12):1157–1160. doi:10.1007/BF02251968.
68. Tocchi A, Mazzoni G, Lepre L, Costa G, Liotta G, Agostini N, et al. Prospective evaluation of omentoplasty in preventing leakage of colorectal anastomosis. Dis Colon Rectum 2000;43:951–955. doi:10.1007/BF02237357.
69. Merad F, Hay JM, Fingerhut A, et al. Omentoplasty in the prevention of anastomotic leakage after colonic or rectal resection: a prospective randomized study in 712 patients. French Associa-

tions for Surgical Research. Ann Surg 1998;227:179–186. doi:10.1097/00000658-199802000-00005.
70. Christian CK, Kwaan MR, Betensky RA, et al. Risk factors for perineal wound complications following abdominoperineal resection. Dis Colon Rectum 2005;48:43–48. doi:10.1007/s10350-004-0855-x.
71. Bullard KM, Trudel JL, Baxter NN, et al. Primary perineal wound closure after preoperative radiotherapy and abdominoperineal resection has a high incidence of wound failure. Dis Colon Rectum 2005;48:438–443. doi:10.1007/s10350-004-0827-1.
72. Nilsson PJ. Omentoplasty in abdominoperineal resection: a review of the literature using a systematic approach. Dis Colon Rectum 2006;49:1354–1361. doi:10.1007/s10350-006-0643-x.
73. Ambroze WL Jr, Wolff BG, Kelly KA, et al. Let sleeping dogs lie: role of the omentum in the ileal pouch-anal anastomosis procedure. Dis Colon Rectum 1991;34:563–565. doi:10.1007/BF02049895.
74. Agalar F, Sayek I, Cakmakçi M, Hasçelik G, Abbasoglu O. Effect of omentectomy on peritoneal defence mechanisms in rats. Eur J Surg 1997;163:605–609.
75. Agca B, Paksoy M, Polat E, et al. Influence of omentectomy on peritoneal defense mechanisms in an experimental model of intra-abdominal infection. Eur Surg Res 2003;35:35–40. doi:10.1159/000067033.
76. Paksoy M, Hamzaoglu I, Cubukçu A, Uzun H, Agca B, Polat E, et al. The influence of omentectomy on the inflammatory phase of anastomotic healing. Hepatogastroenterology 2001;48:1359–1363.
77. Losken A, Carlson GW, Culbertson JH, et al. Omental free flap reconstruction in complex head and neck deformities. Head Neck 2002;24:326–331. doi:10.1002/hed.10082.
78. Ross WE, Pardo AD. Evaluation of an omental pedicle extension technique in the dog. Vet Surg 1993;22:37–43. doi:10.1111/j.1532-950X.1993.tb00366.x.
79. Das SK. The size of the human omentum and methods of lengthening it for transplantation. Br J Plast Surg 1976;29:144–170. doi:10.1016/0007-1226(76)90045-X.
80. Alday ES, Goldsmith HS. Surgical technique for omental lengthening based on arterial anatomy. Surg Gynecol Obstet 1972;135:103–107.
81. Topor B, Acland RD, Kolodko V, Galandiuk S. Omental transposition for low pelvic anastomoses. Am J Surg 2001;182:460–464. doi:10.1016/S0002-9610(01)00764-4.
82. Hultman CS, Carlson GW, Losken A, Jones G, Culbertson J, Mackay G, et al. Utility of the omentum in the reconstruction of complex extraperitoneal wounds and defects: donor-site complications in 135 patients from 1975 to 2000. Ann Surg 2002;235:782–795. doi:10.1097/00000658-200206000-00005.
83. Domene CE, Vlope P, Onari P, Szachnowicz S, Birbojm I, Barreira LF, et al. Omental flap obtained by laparoscopic surgery for reconstruction of the chest wall. Surg Laparosc Endosc 1998;8:215–218. doi:10.1097/00019509-199806000-00011.
84. Skoracki RJ, Chang DW. Reconstruction of the chest wall and thorax. J Surg Oncol 2006;94:455–465. doi:10.1002/jso.20482.
85. Shrager JB, Wain JC, Wright CD, Donahue DM, Vlahakes GJ, Moncure AC, et al. Omentum is highly effective in the management of complex cardiothoracic surgical problems. J Thorac Cardiovasc Surg 2003;125:526–532. doi:10.1067/mtc.2003.12.
86. Katz R, Borkowski T, Hoznek A, Salomon L, de la Taille A, Abbou CC. Operative management of rectal injuries during laparoscopic radical prostatectomy. Urology 2003;62:310–313. doi:10.1016/S0090-4295(03)00326-1.
87. Fujiwara K, Kigawa J, Hasegawa K, Nishimura R, Umezaki N, Ando M, et al. Effect of simple omentoplasty and omentopexy in the prevention of complications after pelvic lymphadenectomy. Int J Gynecol Cancer 2003;13:61–66. doi:10.1046/j.1525-1438.2003.13029.x.
88. Patsner B, Hackett TE. Use of the omental J-flap for prevention of postoperative complications following radical abdominal hysterectomy: Report of 140 cases and literature review. Gynecol Oncol 1997;65:405–407. doi:10.1006/gyno.1997.4700.
89. Casten DF, Alday ES. Omental transfer for revascularization of the extremities. Surg Gynecol Obstet 1971;123:301–304.
90. Singh I, Ramteke VK. The role of omental transfer in Buerger's disease: New Delhi's experience. Aust N Z J Surg 1996;66:372–376. doi:10.1111/j.1445-2197.1996.tb01214.x.
91. Talwar S, Jain S, Porwal R, et al. Pedicled omental transfer for limb salvage in Buerger's disease. Int J Cardiol 2000;72:127–132. doi:10.1016/S0167-5273(99)00179-5.
92. Kitayama J, Morota T, Kaisaki S, Ishigami H, Yamashita H, Ishikawa M, et al. Complete coverage of in situ aortograft by total omental pedicle flap as the most reliable treatment of aortoesophageal fistula. Am J Surg 2006;192:130–134. doi:10.1016/j.amjsurg.2005.09.011.
93. Karasawa J, Touho H, Ohnishi H, Miyamoto S, Kikuchi H, Nakayama H. Cerebral revascularization using omental transplantation for childhood moyamoya disease. J Neurosurg 1993;79:192–196.
94. Goldsmith HS. Omental transposition in treatment of Alzheimer disease. J Am Coll Surg 2007;205:800–804. doi:10.1016/j.jamcollsurg.2007.06.294.
95. Salacinski HJ, Punshon G, Krijgsman B, Hamilton G, Seifalian AM. A hybrid compliant vascular graft seeded with microvascular endothelial cells extracted from human omentum. Artif Organs 2001;25:974–982. doi:10.1046/j.1525-1594.2001.06716.x.
96. Kobayashi T, Aomatsu Y, Iwata H, Kin T, Kanehiro H, Hisanga M, et al. Survival of microencapsulated islets at 400 days posttransplantation in the omental pouch of NOD mice. Cell Transplant 2006;15:359–365. doi:10.3727/000000006783981954.
97. Cheng Y, Liu YF, Zhang JL, Li TM, Zhao N. Elevation of vascular endothelial growth factor production and its effect on revascularization and function of graft islets in diabetic rats. World J Gastroenterol 2007;13:2862–2866.
98. Sigrist S, Mechine-Neuville A, Mandes K, Calenda V, Legeay G, Bellocq JP, et al. Induction of angiogenesis in omentum with vascular endothelial growth factor: influence on the viability of encapsulated rat pancreatic islets during transplantation. J Vasc Res 2003;40:359–367. doi:10.1159/000072700.
99. Baumert H, Simon P, Hekmati M, Fromont G, Levy M, Balaton A, et al. Development of a seeded scaffold in the great omentum: feasibility of an in vivo bioreactor for bladder tissue engineering. Eur Urol 2007;52:884–890. doi:10.1016/j.eururo.2006.11.044.
100. Motoshima H, Wu X, Sinha MK, Hardy VE, Rosato EL, Barbot DJ, Rosato FE, Goldstein BJ. Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. J Clin Endocrinol Metab 2002;87(12):5662–5667. doi:10.1210/jc.2002-020635.
101. Matter CM, Handschin C. RANTES (regulated on activation, normal T cell expressed and secreted), inflammation, obesity, and the metabolic syndrome. Circulation 2007;115(8):1029–1038. doi:10.1161/CIRCULATIONAHA.106.685230.
102. Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab 1998;83(3):847–850. doi:10.1210/jc.83.3.847.
103. GS Hotamisligil, NS Shargill, and BM Spiegelman Science 1 January 1993:Vol. 259. no. 5091, pp. 87 – 91 Adipose expression of

tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. GS Hotamisligil, NS Shargill, and BM Spiegelman
104. De Broux E, Parc Y, Rondelli F, Dehni N, Tiret E, Parc R. Sutured perineal omentoplasty after abdominoperineal resection for adenocarcinoma of the lower rectum. Dis Colon Rectum 2005;48:476–481. doi:10.1007/s10350-004-0784-8.
105. Hay JM, Fingerhut A, Paquet JC, Flamant Y. Management of the pelvic space with or without omentoplasty after abdominoperineal resection for carcinoma of the rectum: a prospective multicenter study. The French Association for Surgical Research. Eur J Surg 1997;163:199–206.
106. Wang JY, Huang CJ, Hsieh JS, Huang YS, Juang YF, Huang TJ. Management of the perineal wounds following excision of the rectum for malignancy. Gaoxiong Yi Xue Ke Xue Za Zhi 1994;10:177–181.
107. Rice ML, Hay AM, Hurlow RH. Omentoplasty in abdominoperineal resection of the rectum. Aust N Z J Surg 1992;62:147–149.
108. John H, Buchmann P. Improved perineal wound healing with the omental pedicle graft after rectal excision. Int J Colorectal Dis 1991;6:193–196. doi:10.1007/BF00341389.
109. Poston GJ, Smith SR, Baker WN. Retrocolic pelvic omentoplasty in abdominoperineal excision of the rectum. Ann R Coll Surg Engl 1991;73:229–232.
110. Smith SR, Swift I, Gompertz H, Baker WN. Abdominoperineal and anterior resection of the rectum with retrocolic omentoplasty and no drainage. Br J Surg 1988;75:1012–1015. doi:10.1002/bjs.1800751020.
111. Moreaux J, Horiot A, Barrat F, Mabille J. Obliteration of the pelvic space with pedicled omentum after excision of the rectum for cancer. Am J Surg 1984;148:640–644. doi:10.1016/0002-9610(84)90342-8.
112. Page CP, Carlton PK Jr, Becker DW. Closure of the pelvic and perineal wounds after removal of the rectum and anus. Dis Colon Rectum 1980;23:2–9. doi:10.1007/BF02587192.

J Gastrointest Surg (2009) 13:1147–1148
DOI 10.1007/s11605-008-0709-2

MULTIMEDIA ARTICLE

Laparoscopic Left Hepatectomy with Intraoperative Biliary Exploration for Hepatolithiasis

Giuseppe Di Giuro · Ruben Balzarotti · Panagiotis Lainas · Dominique Franco · Ibrahim Dagher

Received: 30 June 2008 / Accepted: 8 September 2008 / Published online: 21 October 2008

Abstract Major liver resections remain a challenge for liver surgeons. This video illustrates, step by step, a totally laparoscopic technique for left hepatectomy with intraoperative exploration of the remaining biliary tree in a patient with unilateral hepatolithiasis.

Keywords Laparoscopy · Left hepatectomy · Hepatolithiasis · Vascular control · Major liver resection

Introduction

Primary intrahepatic bile duct dilatation is a rare congenital disorder in Western countries predisposing to intrahepatic lithiasis, cholangitis, and cholangiocarcinoma.[1] In symptomatic patients with unilateral disease, liver resection should be considered as a curative treatment.[2] Laparoscopy could allow both liver resection and exploration of the remaining biliary tree. We recently developed totally laparoscopic techniques for formal left and right hepatectomies, with extraparenchymal division of the ipsilateral hepatic duct before liver transection.[3,4] This video illustrates, step by step, our totally laparoscopic technique for left hepatectomy with intraoperative exploration of the remaining biliary tree in a patient with unilateral hepatolithiasis.

Materials and Methods

A 35-year-old woman with hepatolithiasis of the left liver was referred for surgical treatment. The video shows the four distinct steps of the operation: division of the left branches of the hepatic artery and portal vein, division of the left biliary duct and cholangioscopy by the biliary stump, control of the left hepatic vein, and parenchymal transection. The technique for vascular control of the inflow and outflow as well as for parenchymal transection is clearly illustrated.

Results

We have performed laparoscopic liver resections for hepatolithiasis in six patients, from which four underwent laparoscopic left hepatectomy. In this patient, the exploration of the remaining biliary tree allowed the extraction

Electronic supplementary material The online version of this article (doi:10.1007/s11605-008-0709-2) contains supplementary material, which is available to authorized users.

G. Di Giuro · R. Balzarotti · P. Lainas · D. Franco · I. Dagher
Department of General Surgery,
Antoine Béclère Hospital, AP-HP,
Clamart 92140, France

D. Franco · I. Dagher
Univ Paris-Sud,
Orsay 91405, France

I. Dagher (✉)
Department of Surgery, Antoine Béclère Hospital,
157 rue de la Porte de Trivaux,
92141 Clamart cedex, France
e-mail: ibrahim.dagher@abc.aphp.fr

of two stones, one from the common bile duct and one from the right hepatic duct close to the biliary confluence. After clearance of the biliary tree, the endoluminal aspect was normal. Duration of the operation was 210 min. Operative blood loss was less than 50 ml. No drainage was used. The patient had an uneventful postoperative stay and was discharged 4 days after surgery.

Conclusions

Laparoscopic liver resection is feasible and safe for patients with unilateral hepatolithiasis. In addition, the clearance of the remaining biliary tree can be performed by the stump of the biliary canal or by choledochotomy.

References

1. Mabrut JY, Partensky C, Jaeck D, Oussoultzoglou E, Baulieux J, Boillot O, Lerut J, de Ville de Goyet J, Hubert C, Otte JB, Audet M, Ducerf C, Gigot JF. Congenital intrahepatic bile duct dilatation is a potentially curable disease: long-term results of a multi-institutional study. Ann Surg 2007;246:236–245. doi:10.1097/SLA.0b013e3180f61abf.
2. Herman P, Perini MV, Machado MA, Bacchella T, Pugliese V, Saad WA, da Cunha JE, Machado MC, Rodrigues JG. Liver resection as the definitive treatment for unilateral non-oriental primary intrahepatic lithiasis. Am J Surg 2006;191:460–464. doi:10.1016/j.amjsurg.2005.08.036.
3. Dagher I, Franco D. Left hepatectomy: laparoscopic technique. J Chir (Paris) 2007;144:432–433. doi:10.1016/S0021-7697(07)74001-2.
4. Dagher I, Caillard C, Proske JM, Carloni A, Lainas P, Franco D. Laparoscopic right hepatectomy: original technique and results. J Am Coll Surg 2008;206:756–760.

J Gastrointest Surg (2009) 13:1149–1150
DOI 10.1007/s11605-009-0813-y

MULTIMEDIA ARTICLE

Human NOTES Cholecystectomy: Transgastric Hybrid Technique

Edward D. Auyang · Eric S. Hungness · Khashayar Vaziri · John A. Martin · Nathaniel J. Soper

Received: 5 December 2008 / Accepted: 12 January 2009 / Published online: 7 February 2009

Abstract
Background Natural orifice translumenal endoscopic surgery (NOTES) is an emerging field in minimally invasive surgery that is driving the development of new technology and techniques. There are several proposed benefits to the NOTES approach, including potentially decreased abdominal pain, wound infections, and hernia formation Ko and Kalloo (Chin J Dig Dis 7:67–70, 2006); Wagh et al. (Clin Gastroenterol Hepatol 3(9):892–896, 2005); ASGE/SAGES Working Group on Natural Orifice Transluminal Endoscopic Surgery (Gastrointest Endosc 63(2):199–203, 2006); and Pearl and Ponsky (J GI Surg 12:1293–1300, 2008). Cholecystectomy has been one of the most commonly performed NOTES procedures to date, with the majority being performed through the transvaginal approach Marescaux et al. (Arch Surg 142:823–826, 2007); Zorron et al. (Surg Endosc 22:542–547, 2008); and Ramos et al. (Endoscopy 40:572–575, 2008). Transgastric approaches for cholecystectomy have been shown to be technically feasible in animal models and in several unpublished human patients Sumiyama et al. (Gastrointest Endosc 65 (7):1028–1034, 2007). This video demonstrates the technique by which we perform transgastric NOTES hybrid cholecystectomy in human patients.
Method Patients with symptomatic gallstone disease are enrolled under an IRB approved protocol. A diagnostic EGD is performed to confirm normal anatomy. Peritoneal access is gained using a needle-knife cautery and balloon dilation under laparoscopic visualization. Dissection of the critical view of safety is performed endoscopically. The cystic duct and artery are clipped laparoscopically and the gallbladder is dissected off of the liver. The gastrotomy is closed intralumenally and over-sewed laparoscopically. The gallbladder is extracted out the mouth.
Results This technique was used to successfully perform four NOTES hybrid transgastric cholecystectomies without operative complications.
Conclusions NOTES hybrid transgastric cholecystectomy can be performed safely in human patients. This procedure is still technically challenging given the current instrumentation that is available. In order to perform a pure NOTES transgastric cholecystectomy, a safe blind access method, improved retraction, endoscopic hemostatic clips, and reliable closure methods need to be developed.

Presented at SSAT/DDW, May 2008, San Diego, CA.

Electronic supplementary material The online version of this article (doi:10.1007/s11605-009-0813-y) contains supplementary material, which is available to authorized users.

E. D. Auyang · E. S. Hungness · J. A. Martin · N. J. Soper (✉)
Department of Surgery,
Northwestern University Feinberg School of Medicine,
Galter 3-150,
251 E. Huron Street,
Chicago, IL 60611-2908,
USA
e-mail: nsoper@nmh.org

J. A. Martin
Department of Medicine,
Northwestern University Feinberg School of Medicine,
Chicago, IL, USA

K. Vaziri
Department of Surgery, George Washington University,
Washington, DC, USA

Keywords NOTES · Transgastric · Cholecystectomy · Natural · Orifice · Translumenal

References

1. Ko CW, Kalloo AN. Per-oral transgastric abdominal surgery. Chin J Dig Dis 2006;7:67–70. doi:10.1111/j.1443-9573.2006.00256.x.
2. Wagh MS, Merrifield BF, Thompson CC. Endoscopic transgastric abdominal exploration and organ resection: initial experience in a porcine model. Clin Gastroenterol Hepatol 2005;3(9):892–896. doi:10.1016/S1542-3565(05)00296-X.
3. ASGE/SAGES Working Group on Natural Orifice Transluminal Endoscopic Surgery. White Paper, October 2005. Gastrointest Endosc 2006;63(2):199–203. doi:10.1016/j.gie.2005.12.007.
4. Pearl JP, Ponsky JL. Natural orifice translumenal endoscopic surgery: a critical review. J GI Surg 2008;12:1293–1300. doi:10.1007/s11605-007-0424-4.
5. Marescaux J, Dallemagne B, Peretta S, Wattiez A, Mutter D, Coumaros D. Surgery without scars: report of transluminal cholecystectomy in a human being. Arch Surg 2007;142:823–826. doi:10.1001/archsurg.142.9.823.
6. Zorron R, Maggioni LC, Pombo L, Oliverira AL, Carvalho GL, Filgueiras M. NOTES transvaginal cholecystectomy: preliminary clinical application. Surg Endosc 2008;22:542–547. doi:10.1007/s00464-007-9646-5.
7. Ramos AC, Murakami A, Galvao NM, Galvao MS, Silva AC, Canseco EG, Moyses Y. NOTES transvaginal video-assisted cholecystectomy: first series. Endoscopy 2008;40:572–575. doi:10.1055/s-2008-1077398.
8. Sumiyama K, Gostout CJ, Rajan E, Bakken TA, Knipschield MA, Chung S, Cotton PB, Hawes RH, Kalloo AN, Kantsevoy SV, Pasricha PJ. Transgastric cholecystectomy: transgastric accessibility to the gallbladder improved with the SEMF method and a novel multibending therapeutic endoscope. Gastrointest Endosc 2007;65(7):1028–1034. doi:10.1016/j.gie. 2007.01.010.

J Gastrointest Surg (2009) 13:1151–1154
DOI 10.1007/s11605-008-0780-8

CASE REPORT

Novel Presentation of a Familial Pancreatic Cancer Syndrome

Ajay V. Maker · James A. Warth · Michael J. Zinner

Received: 9 November 2008 / Accepted: 24 November 2008 / Published online: 17 December 2008

Abstract
Introduction Earlier detection of pancreatic cancer may help identify patients for whom surgical intervention could provide cure or prolong life. In this article, we report the occurrence of breast cancer, melanoma, squamous cell carcinoma of the alveolar ridge, colon cancer, a desmoid tumor of the abdominal wall, and pancreatic adenocarcinoma in a 65-year-old woman. She was identified as having the familial atypical multiple mole melanoma–pancreatic cancer syndrome (FAMMM–PC) with a germline p16 mutation at amino acid position 15.
Discussion Patients with this syndrome traditionally present with multiple nevi and melanoma, and a subset also present with other cancers, including pancreatic cancer; however, no FAMMM–PC patient has yet been described with this constellation of cancers, including squamous cell carcinoma of the alveolar ridge and a desmoid tumor. Recognition of the tumors this population of patients is susceptible to developing and their genetic associations can help guide the surgeon in screening, surveillance, and eventually prevention of many of these cancers.

Keywords FAMMM · Pancreatic cancer · Melanoma · p16

Introduction

Pancreatic cancer has an incidence rate nearly identical to its mortality rate. Earlier detection of this disease may help identify patients for whom surgical intervention could provide cure or prolong life; however, it is challenging to identify high risk populations.[1] Five to ten percent of all pancreatic cancer patients have a familial pancreatic cancer syndrome;[2] however, this rate may be underrecognized by surgical oncologists (Table 1). In patients with familial atypical multiple mole melanoma–pancreatic cancer syndrome (FAMMM–PC), up to 17% will develop pancreatic cancer by age 75 and die from the disease.[3]

CDKN2A is a tumor suppressor gene involved in cell cycle inhibition. FAMMM–PC has been mapped to mutations in the p16 gene locus within CDKN2A (Fig. 1). Patients with p16 gene mutations traditionally present with multiple nevi and melanoma, and a subset also present with other cancers, including pancreatic cancer. In particular, the risk of developing malignant disease is increased ten to 40-fold in this population.[3–8] We present a patient with a p16 germline mutation and the novel combination of breast cancer, melanoma, squamous cell carcinoma, colon adenocarcinoma, and a desmoid tumor. Ultimately, she presented with advanced pancreatic cancer and underwent a pancreaticoduodenectomy before succumbing to the disease.

A. V. Maker · M. J. Zinner
Department of Surgery, Brigham and Women's Hospital,
Harvard Medical School,
Boston, MA, USA

J. A. Warth
Department of Medicine,
Brigham and Women's Hospital/Faulkner,
Harvard Medical School,
Boston, MA, USA

A. V. Maker (✉)
303 E. 60th St. #28-H,
New York, NY 10022, USA
e-mail: ajaymaker@gmail.com

Table 1 Hereditary Syndromes Associated with Pancreatic Cancer

Hereditary syndrome	Genetic defect
Familial atypical mole and melanoma syndrome	p16/CDKN2A
Peutz–Jeghers syndrome	serine–threonine kinase
Breast and ovarian cancer	BRCA
Hereditary pancreatitis	Cationic trypsinogen PRSS 1
Familial adenomatous polyposis	APC
Hereditary pancreatic neuroendocrine tumors	Multiple endocrine neoplasia type 1, von Hippel–Lindau, neurofibromatosis type 1, tuberous sclerosis

Materials and Methods

Our patient was a healthy 33-year-old woman when she initially presented with breast cancer. At the time of this writing, she was a 65-year-old woman with a past medical history of gastroesophageal reflux disease, hyperlipidemia, vitamin B-12 deficiency, osteoporosis, and fibromyalgia, who had been diagnosed with seven cancers. Her past social history was significant only for a 20-pack-year smoking history, having quit 37 years ago. She was diagnosed with breast cancer at age 33 years, her first melanoma at age 45, squamous cell carcinoma of the alveolar ridge at age 50, her second melanoma at age 55, colon cancer at age 62, a desmoid tumor of the abdominal wall, and pancreatic adenocarcinoma at age 65. These were all treated with surgical excision and selected adjuvant therapies (Table 2). Her last surgery was a pancreaticoduodenectomy.

In regard to her family history, she had four children including a son who died at age 24 of a nonmalignant cause and three daughters who were 38, 42, and 43 years old. She had two brothers, one of whom was 68 years old and the other died at age 24 of melanoma. She had one nephew and one niece who were diagnosed with dysplastic nevi. Her other two nieces and nephews were otherwise healthy.

Her mother was diagnosed and died with pancreatic cancer at age 89. Her mother had five sisters, one of whom had breast cancer at age 35 and died with Alzheimer's disease at age 85. Another of her maternal aunts died at age 92 with Parkinson's syndrome, and one is still living at the age of 75. Two died of childhood illnesses. She had three maternal uncles, two of whom are living, and one of whom died at age 85 with Alzheimer's disease. Of her living uncles, one was diagnosed with melanoma and has a daughter who was also diagnosed with melanoma. The other is age 94 and has no history of cancer. She has 19 first cousins, none of whom have been diagnosed with cancer. Her maternal grandmother died at age 65 of colon cancer and her maternal grandfather died at age 65 of stomach cancer.

On the paternal side, her father died at age 64 of lung cancer diagnosed at age 63. Her paternal grandmother died at age 65 of heart related issues and her paternal grandfather died at age 58 of lung cancer. Her ethnicity was English and Irish. There was no known Ashkenazi Jewish ancestry.

After recovering from surgery for pancreatic adenocarcinoma, the patient underwent genetic screening and gene analysis. She was identified as having a germline p16 mutation (chromosome 9) on exon 1-alpha, with a nucleotide change at base pair 44 from guanine to adenosine, resulting in premature truncation of the p16 protein at amino acid position 15 (Fig. 1). The mutation W15X corresponded with the codon sequence for tryptophan being replaced with a stop codon. BRCA I and BRCA II were negative. None of her family members have yet been tested.

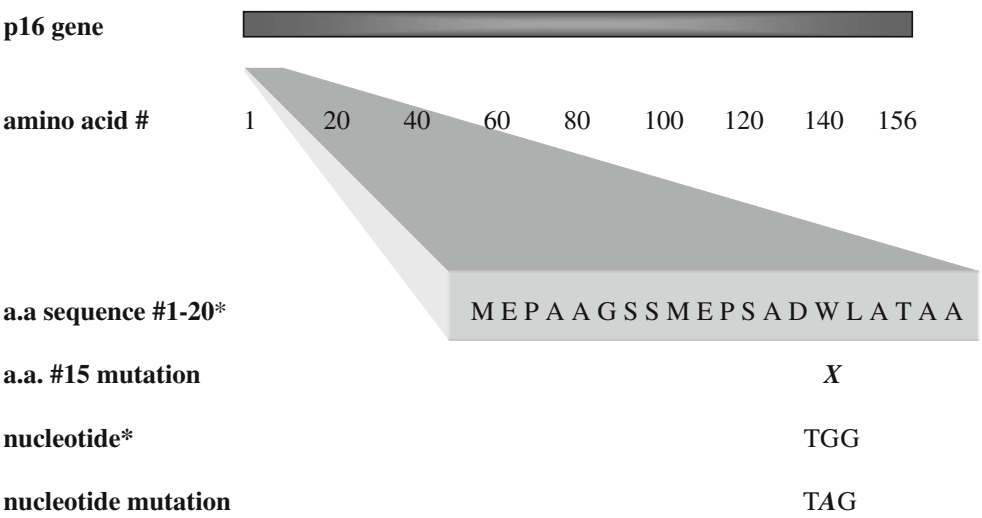

Figure 1 The p16 protein is a splice product of exons 1, 2, and 3 of the CDKN2A gene. It acts as a tumor suppressor gene, and inactivation of p16 can promote uncontrolled cell proliferation. The protein consists of 156 amino acids, designated by single-letter codes in the wild-type (*asterisk*) sequence. A single base-pair mutation in the nucleotide sequence from guanine to adenosine causes premature truncation of the p16 protein at amino acid 15 and predisposes the patient to multiple cancers, including pancreatic cancer.

Table 2 Novel Combination of Cancers in a Patient with a p16 Mutation

Cancer	Age at diagnosis	Location	Description	Treatment	Family history	Status
Breast	33	R breast/Liver	n/a	Mastectomy, chemotherapy	Maternal aunt	NED
Melanoma	45, 55	L forearm, R ankle	0.75 mm, 0.28 mm	Simple excision	Maternal uncle, cousin, brother, nephew, and niece with DN	NED
Squamous cell	50	R maxilla, hard/soft palatte	T4	Maxillectomy, radiation		NED
Colon	62	R colon	T1b, N0	Hemicolectomy	Maternal grandmother	NED
Desmoid	65	Abdominal wall	2.1 cm	Excision		NED
Pancreas	65	Pancreas	T3N1	Pancreaticoduodenectomy	Mother	Deceased

NED no evidence of disease, *n/a* not applicable, *DN* dysplastic nevi

Discussion

Cyclin-dependent kinases (CDKs) 4 and 6 normally interact with cyclin D during the G1 phase of the cell cycle to phosphorylate the retinoblastoma (Rb) protein. Phosphorylation of Rb allows elongation factors to activate genes required for DNA synthesis and forward progression through the cell cycle.[9] p16 is a specific inhibitor of CDKs 4 and 6 at the G1 checkpoint and thus acts as a tumor suppressor gene. In some cancers, inactivation of p16 upregulates CDK4 and promotes early and uncontrolled cell proliferation.[10] p16 has been mapped to chromosome 9q21, an area strongly associated with familial cases of malignant melanoma by linkage, cytogenetics, and loss of heterozygosity studies.[6,11,12]

In addition to melanoma, the most common malignancy associated with p16 gene mutations, patients may also present with other cancers, the next most common being pancreatic cancer. In their study of 19 families with FAMMM cutaneous phenotypes, Lynch et al. described patients with associated melanoma, pancreatic cancer, breast cancer, esophageal cancer, and sarcoma. With these associations, the authors first suggested a "new" putative hereditary carcinoma syndrome they referred to as FAMMM–PC in 2002.[13] Here, we describe a new combination of cancers and new malignancies associated with this syndrome.

Lung, colon, esophageal, cervical, breast, endometrial, parotid, and prostatic cancers, as well as sarcoma and lymphoma, have been described in a large published series of p16 and FAMMM kindreds in eight families and 135 individuals; however, there has not been any one patient with the constellation of cancers present in our patient.[14] Furthermore, although p16 mutations have been identified in head and neck squamous cell carcinoma cell lines in Korean patients,[15] alterations of the p16-retinoblastoma gene pathway have been associated with invasive breast cancer,[16] and loss of p16 protein expression has been seen in murine fibrosarcoma models,[17] no FAMMM–PC patient has yet been described with a squamous cell carcinoma of the alveolar ridge or a desmoid tumor.

In addition, in the largest familial melanoma data set of mutations in the major known high-risk melanoma susceptibility genes, GenoMEL identified 466 melanoma-prone families with 2,137 malignant melanoma patients with 66 different mutations in 190 families. Thirty-eight percent of families ($n=178$) had CDKN2A mutations that involved the p16 protein.[18] Only one GenoMEL family had the same W15X mutation as our patient; thus, this is apparently only the second reported incidence of this mutation in the literature.

There is evidence that surveillance of FAMMM families leads to early detection of melanoma.[3] It is our hope that the new malignancies described here and their novel association as part of a familial pancreatic cancer syndrome may make it possible for these and other cancers to be detected earlier in patients with genetic susceptibility.

Identification of patients with any constellation of these malignancies, or a family history of these cancers, may have FAMMM–PC and should be actively screened for these tumors by their surgeon or oncologist and potentially referred to a genetic counselor for genetic testing. Twenty-three percent of FAMMM–PC offspring of parents with pancreatic cancer developed pancreatic cancer themselves, underscoring the potential role of genetic screening.[14] In this population of patients who are susceptible to developing the tumors, recognition of these tumors and their genetic associations can help guide the surgeon in screening, surveillance, and eventually prevention of many of these cancers. Studies of additional familial pancreatic cancer kindreds as well as patients with apparently sporadic pancreatic cancer are needed. Ideally, p16 mutation status may help identify patients at high risk for pancreatic cancer who should be enrolled in already established early detection programs.[19]

References

1. Bullock GJ, Green JL, Baron PL. Impact of p16 expression on surgical management of malignant melanoma and pancreatic carcinoma. Am J Surg 1999;177(1):15–18. doi:10.1016/S0002-9610(98)00297-9.
2. Lynch HT, Smyrk T, Kern SE, et al. Familial pancreatic cancer: a review. Semin Oncol 1996;23(2):251–275.
3. Vasen HF, Gruis NA, Frants RR, et al. Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). Int J Cancer 2000;87(6):809–811. doi:10.1002/1097-0215(20000915)87:6<809::AID-IJC8>3.0.CO;2-U.
4. Bartsch DK, Sina-Frey M, Lang S, et al. CDKN2A germline mutations in familial pancreatic cancer. Ann Surg 2002;236 (6):730–737. doi:10.1097/00000658-200212000-00005.
5. Borg A, Sandberg T, Nilsson K, et al. High frequency of multiple melanomas and breast and pancreas carcinomas in CDKN2A mutation-positive melanoma families. J Natl Cancer Inst 2000;92 (15):1260–1266. doi:10.1093/jnci/92.15.1260.
6. Goldstein AM, Fraser MC, Struewing JP, et al. Increased risk of pancreatic cancer in melanoma-prone kindreds with p16INK4 mutations. N Engl J Med 1995;333(15):970–974. doi:10.1056/NEJM199510123331504.
7. Goldstein AM, Tucker MA. Screening for CDKN2A mutations in hereditary melanoma. J Natl Cancer Inst 1997;89(10):676–678. doi:10.1093/jnci/89.10.676.
8. Lynch HT, Fusaro RM, Kimberling WJ, et al. Familial atypical multiple mole-melanoma (FAMMM) syndrome: segregation analysis. J Med Genet 1983;20(5):342–344.
9. Serrano M, Hannon GJ, Beach D. A new regulatory motif in cell-cycle control causing specific inhibition of cyclin D/CDK4. Nature 1993;366(6456):704–707. doi:10.1038/366704a0.
10. Kamb A, Gruis NA, Weaver-Feldhaus J, et al. A cell cycle regulator potentially involved in genesis of many tumor types. Science 1994;264(5157):436–440. doi:10.1126/science.8153634.
11. Fountain JW, Karayiorgou M, Ernstoff MS, et al. Homozygous deletions within human chromosome band 9p21 in melanoma. Proc Natl Acad Sci U S A 1992;89(21):10557–10561. doi:10.1073/pnas.89.21.10557.
12. Hussussian CJ, Struewing JP, Goldstein AM, et al. Germline p16 mutations in familial melanoma. Nat Genet 1994;8(1):15–21. doi:10.1038/ng0994-15.
13. Lynch HT, Brand RE, Hogg D, et al. Phenotypic variation in eight extended CDKN2A germline mutation familial atypical multiple mole melanoma–pancreatic carcinoma-prone families: the familial atypical mole melanoma–pancreatic carcinoma syndrome. Cancer 2002;94(1):84–96. doi:10.1002/cncr.10159.
14. Rulyak SJ, Brentnall TA, Lynch HT, Austin MA. Characterization of the neoplastic phenotype in the familial atypical multiple-mole melanoma–pancreatic carcinoma syndrome. Cancer 2003;98 (4):798–804. doi:10.1002/cncr.11562.
15. Park HW, Song SY, Lee TJ, et al. Abrogation of the p16-retinoblastoma-cyclin D1 pathway in head and neck squamous cell carcinomas. Oncol Rep 2007;18(1):267–272.
16. Gorgoulis VG, Koutroumbi EN, Kotsinas A, et al. Alterations of p16–pRb pathway and chromosome locus 9p21–22 in sporadic invasive breast carcinomas. Mol Med 1998;4(12):807–822.
17. Roca R, Kypta RM, Vivanco MM. Loss of p16INK4a results in increased glucocorticoid receptor activity during fibrosarcoma development. Proc Natl Acad Sci U S A 2003;100(6):3113–3118. doi:10.1073/pnas.0634912100.
18. Goldstein AM, Chan M, Harland M, et al. High-risk melanoma susceptibility genes and pancreatic cancer, neural system tumors, and uveal melanoma across GenoMEL. Cancer Res 2006;66 (20):9818–9828. doi:10.1158/0008-5472.CAN-06-0494.
19. Rulyak SJ, Brentnall TA. Inherited pancreatic cancer: surveillance and treatment strategies for affected families. Pancreatology 2001;1(5):477–485. doi:10.1159/000055851.

J Gastrointest Surg (2009) 13:1155–1159
DOI 10.1007/s11605-008-0795-1

CASE REPORT

Liver Recurrence of a Subcutaneous Temporal Hemangiopericytoma: The Index Case

Stéphane Zalinski · Claire Goumard · Olivier Scatton · Benoit Terris · Francoise Plantier · Nicolas Dupin · Olivier Soubrane

Received: 16 October 2008 / Accepted: 11 December 2008 / Published online: 16 January 2009

Abstract
Introduction Hemangiopericytoma is an uncommon soft tissue vascular neoplasm. Intraperitoneal hemangiopericytomas such as primary or secondary liver location have been exceptionally described. Its natural history is mostly benign, but recurrences may occur and determining if these late-discovered tumors are distant metastases or synchronous slow and silent-growing locations is sometimes challenging. The histopathological diagnosis and definition of hemangiopericytoma is based on its distinction with solitary fibrous tumors. Liver resection to treat liver hemangiopericytoma seems to be supported by various published experiences.
Case presentation We herein report the first case of liver metastases from a subcutaneous temporal hemangiopericytoma. The patient was treated by a liver resection. CD34 Immunostaining was negative, but strong expression of Bcl2 and CD99 was found in the neoplastic cells. After 1 year of follow-up, the patient is alive without recurrence.
Conclusion To date, published data, including the case herein reported, support the need for a prolonged follow-up and the role of liver resection to treat liver metastases of hemangiopericytomas. Complete resection of all gross disease appears to be the most significant prognostic factor.

Keywords Subcutaneous hemangiopericytoma · Liver metastases · Hepatic resection

S. Zalinski · C. Goumard · O. Scatton · O. Soubrane (✉)
Department of Hepatobiliary Surgery and Liver Transplantation,
Hôpital Cochin, Assistance Publique-Hôpitaux de Paris,
27 rue du Faubourg Saint Jacques,
75014 Paris, France
e-mail: Olivier.soubrane@cch.aphp.fr

B. Terris
Department of Pathology, Hôpital Cochin,
Assistance Publique-Hôpitaux de Paris,
27 rue du Faubourg Saint Jacques,
75014 Paris, France

F. Plantier · N. Dupin
Department of Dermatology, Hôpital Cochin,
Assistance Publique-Hôpitaux de Paris,
27 rue du Faubourg Saint Jacques,
75014 Paris, France

S. Zalinski · C. Goumard · O. Scatton · B. Terris · F. Plantier · N. Dupin · O. Soubrane
University Paris Descartes,
Paris, France

Introduction

Hemangiopericytoma is a rare and uncommon vascular neoplasm described in 1942 by Stout and Murray.[1] This is a soft tissue sarcoma thought to develop from the Zimmerman's pericytes, contractile cells found within the capillaries network, whose role is to regulate capillaries and post capillaries venules' lumen. As a consequence, hemangiopericytoma may arise anywhere capillaries are found. Yet, it has been mainly reported to arise in the retroperitoneum, extremities, head, neck, and meninges. The evolution of this neoplasm is the most frequently benign, but local and distant recurrences may occur, even after a prolonged disease-free interval.[2] The most frequent sites of metastases are lung, bones, and liver, but many sites can be involved. Retroperitoneal and meningeal tumors are associated with

higher local recurrence rates.[3] Although liver parenchyma is rarely affected, few cases of either primary or metastatic location have been reported.[4–11] We herein report the first case of a subcutaneous temporal hemangiopericytoma that presented three consecutive local recurrences and, 14 years after the initial diagnosis and 3 years after the last local recurrence, a liver recurrence.

Material and Method

A 56-year-old female with a history of recurrent temporal hemangiopericytoma and left breast cancer was diagnosed with an asymptomatic hepatic mass during a systematic clinical examination. Breast cancer occurred 7 years earlier and was treated by surgery and radiotherapy. On histological examination, it was diagnosed as an intraductal adenocarcinoma with no vascular or lymphatic invasion. A subcutaneous temporal primary hemangiopericytoma was diagnosed 14 years earlier and treated by resection. During the follow-up, she was successively diagnosed with three local recurrences, which were all treated by resection as well. Last local recurrence occurred 3 years before the diagnosis of liver metastases. During follow-up, a tumor in the right liver associated with a nodule in segment II was discovered. On computed tomography (CT), these tumors were hypervascular with areas of necrosis. Magnetic resonance imaging of the liver revealed a 150-mm diameter, heterogeneous mass in the right lobe, with necrotic hyperintense areas on the T2-weighted images, and a 55-mm nodular lesion in the left hepatic lobe with a central area of necrosis (Fig. 1). The decision not to perform a percutaneous biopsy of the liver metastases was taken based on the following tenets: (1) imaging features of these tumors were rather suggesting hypervascular tumors such as hepatocellular carcinoma, adenoma, or sarcoma than breast metastases; (2) we believed the hepatic resection to be still indicated in the presence of a late relapse from breast cancer; and (3) since the biopsy would not have changed our surgical strategy, it was felt unnecessary to expose the patient to the morbidity associated with an invasive procedure such as percutaneous biopsy. There was no other clinical abnormality, and the biological tests, including hepatic markers, were normal. The patient underwent a right hepatectomy (segments V–VIII) and a tumorectomy in the left lobe. Postoperative course was uneventful. Gross and microscopic examination of the resected specimen confirmed that both liver lesions were bilobar metastases of a hemangiopericytoma. Macroscopically, the right lobe tumor appeared to be well circumscribed, white colored with some yellow necrotic areas, measuring 200×150 mm (Fig. 2a). The segment II tumor appeared as a white-colored nodule measuring 55 mm. Microscopically, the right lobe tumor was composed of neoplastic spindle cells with elongated nuclei organized in some bundles or lines and separated by an abundant

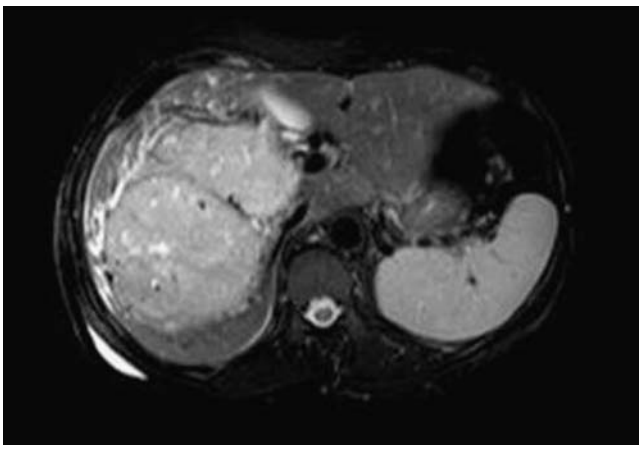

Figure 1 Preoperative Magnetic Resonance Imaging (T2) showing the metastatic hemangiopericytoma developed in the right lobe of the liver.

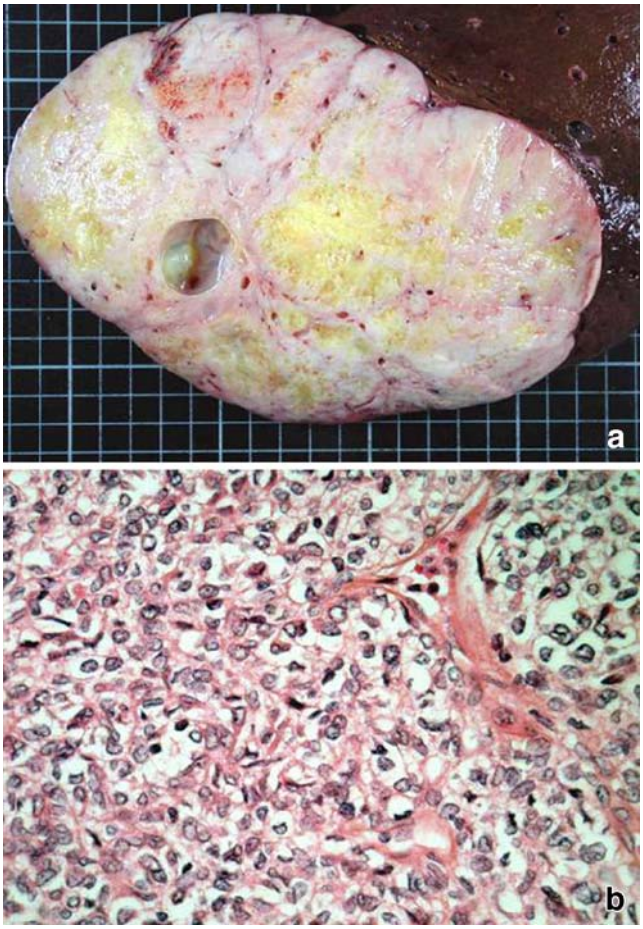

Figure 2 Gross appearance of the right liver tumor. The lesion is well delineated and shows a whitish or yellow appearance with small cystic areas (**a**); Microscopic analysis demonstrates a densely and homogeneous cellular proliferation with thin walled branching vessels (**b**).

ramified vascular network (Fig. 2b). The tumor was mainly composed of highly cellular areas with a mitotic rate of five mitosis per ten HPF detected. Few areas with important fibro-myxoid removals were observed. Immunohistochemistry revealed a strong expression of Bcl-2 and a focal expression of CD99; no immunoreactivity was shown with CD34 and desmin. The segment II nodule had similar histological features. Furthermore, a retrospective comparative analysis showed that histological and immunohistochemical features of the primary and liver tumors to be similar. After a follow-up of 1-year clinical examination was normal and a full body CT scan was normal as well. However, in March 2008, a fourth temporal recurrence was diagnosed and surgically treated.

Discussion

Hemangiopericytoma is a rare soft tissue sarcoma described in 1942 by Stout and Murray.[1] It has been reported in several anatomic locations (retroperitoneum,[12] extremities,[3] head and neck[13] and meninges[14]), but hemangiopericytomas in the peritoneal cavity have been exceptionally described, especially primary and secondary liver locations.[15] The evolution of this neoplasm is the most frequently benign, but local and distant recurrences may occur, even after a prolonged disease-free interval.[2] Although published series are too small to draw strong conclusion regarding clinicopathological markers of poor prognosis, it appears that recurrence rates may vary depending on the primaries location. Retroperitoneal and meningeal primaries are associated with higher recurrence rates,[2,3] whereas recurrence in patients with extremity primaries is uncommon. Although liver parenchyma is rarely affected, few cases of either primary[4] or metastatic[5–11] location have been reported. To the best of our knowledge, most of the reported cases of hepatic metastases were late distant recurrences from primary meningeal hemangiopericytomas. The case herein reported is the first case of liver metastases from a primary subcutaneous location. In all reviewed cases, hepatic recurrences occurred more than 5 years after primary site diagnosis; in one case reported by a Japanese group, hepatic recurrences were even discovered 20 years after the diagnosis of meningeal hemangiopericytoma.[7]

Various clinical presentation have been reported: some patients are asymptomatic[7,16] or present a palpable mass,[17] but inaugural symptoms such as pain or upper abdominal quadrant discomforts have also been described.[18] Severe hypoglycemia has been described as an inaugural symptom in few reports and attributed to an anarchic secretion of insulin-like growth factor II by the tumor. This latter symptom is life threatening for the patients, and it fully justifies the surgical treatment; resection and liver transplantation have been successfully reported.[5,9] Preoperative diagnosis may be suspected preoperatively on the basis of radiological features[16,18] and fine-needle aspiration cytology.[19] Radiologic features are those of a hypervascular tumor, which may be confusing and suggest the differential diagnosis of hepatocellular carcinoma or liver adenoma. When the differential diagnosis is uncertain, a cytologic assessment can be attempted. Fine-needle aspiration cytology for hemangiopericytoma has been sparsely addressed in the literature and whether or not it is worthy and may impact on the surgical strategy is unknown. It has been reported to be an accurate tool to diagnose a recurrent hemangiopericytoma but does not provide any information on biological behavior and aggressiveness of the tumor.[20] Besides, the risk of needle track seeding for these tumors is unknown but may not be nil. In the case herein described, even though the diagnosis is uncertain due to the history of breast cancer and the radiological features of the liver metastases, a biopsy was not performed preoperatively as it was thought to not change our surgical strategy. Indeed, even in the presence of a late relapse from breast cancer, a liver resection was still indicated.[21]

Histological diagnosis of hemangiopericytoma may be challenging because cells are spindle-shaped and hardly distinguished from neoplastic cells of endothelial, fibro-

Table 1 Experiences of Liver Resection for Liver Hemangiopericytoma

Authors	Primary	Metastases	Time to liver metastases (years)	Resection type	Follow-up (months)	Status
Hukill et al.[10]	Meningeal	Liver	11	n/a	2	Dead
Yoshida et al.[11]	Meningeal	Liver	n/a	ERH	31	Alive
Adams et al.[5]	Retroperitoneal	Liver	8	OLT	48	Alive
Kaneko et al.[7]	Meningeal	Liver	19	RH	9	Alive
Chakravarty et al.[8]	Meningeal	Liver	6	n/a	7	Alive
Grunenberger et al.[9]	Meningeal	Liver + Lung	12	TACE + RH + LM	31	Alive
Soares et al.[6]	Meningeal	Liver + kidney	9	RH + RN	24	Alive

TACE hepatic transarterial chemoembolization, *RH* right hepatectomy, *ERH* extended right hepatectomy, *RN* right nephrectomy, *LM* lung metastasectomy, *OLT* orthotopic liver transplantation, *n/a* not available

blastic, or histiocytic origin.[20,22] Also, distinction with solitary fibrous tumors is uncertain[23] and is based on immunostaining features. Both lesions share structural similarities, displaying features of pericytic, fibroblastic and/or myofibroblastic differentiation. Immunohistochemically, they both variably express CD34, CD99, and bcl-2 antigens. Hemangiopericytoma was initially described as a distinctive soft tissue neoplasm, presumably of pericytic origin, commonly characterized by a well-developed branching vascular "staghorn" pattern.[24] Immunohistochemistry shows not only in most of the cases positive staining for CD34 and vimentin[24] but also a strong expression of CD99 and Bcl2.[25,26] In the case herein reported, CD34 immunoreactivity was not observed in the neoplastic cells whereas expression of Bcl2 and CD99 were strongly positives.

Due to the low prevalence rate of this neoplasm, the malignant potential and recurrence rate cannot be determined with precision. Although long-term prognosis is good, local and distant recurrences are frequent.[2] According to Spitz et al.,[2] 5 and 10 years actuarial survival rates of 71% and 54% can be expected, respectively. In their series, 32% of the patients treated with a curative intent developed a local recurrence within a median time of 29 months (range 2 to 225 months), and the 5-year actuarial local recurrence-free survival rate was 72%. Considering distant recurrences, 36% patients had at least one distant metastasis within a median time of 36.5 months (range 13 to 230 months) and the 5-year actuarial local recurrence-free survival rate was 72% as well. Authors concluded that prolonged survival could be achieved in patients with hemangiopericytoma, regardless of its location, providing that complete removal of the gross disease could be achieved.

Few reports have highlighted the good results following chemotherapy alone[27] or in addition to surgery[28] in the treatment of hemangiopericytoma. Experiences of liver resection for metastases of hemangiopericytoma are depicted in Table 1. There is no sufficient data regarding the use of chemotherapy in the setting of hemangiopericytoma liver metastases to transpose lessons learned from other solid tumor liver metastases treatment. There is no evidence to legitimize the role of chemotherapy in multimodal strategy for hepatic recurrence to either better select patient the most likely to benefit from resection, downsize the liver metastases in view of a function sparing resection, or, to the most, render unresectable patients resectable. As mentioned earlier, fine-needle aspiration does not provide information on biological behavior of the tumor and cannot be used as a selection tool for adjuvant therapy. Finally, the role of radiotherapy has been addressed in the literature and is debated. Whereas some authors have suggested its use for a better local control of the disease, others argued against it due to its relative radioresistance. Although there are no guidelines, Spitz et al.[2] agreed to consider it at sites where local recurrences were common. In the setting of liver surgery, it may be considered postoperatively in case of positive margin.

Conclusion

The case herein reported adds further support to previous reported cases of hemangiopericytoma liver metastases; delayed relapses are not uncommon, and patients may benefit from a regular and long-term follow-up that includes cross-sectional imaging of the abdomen. During follow-up, resectability of liver recurrences should be assessed by a multidisciplinary committee which include surgeons specialized in hepatobiliary surgery. Finally, in the era of modern hepatobiliary surgery, liver resection for hemangiopericytoma metastases appears to be a valid strategy as it may offer a prolonged survival with a <5% postoperative mortality.

Acknowledgements The authors would like to acknowledge Mrs. Ami Howard for her assistance in editing this manuscript.

References

1. Stout AP, Murray MR. Hemangiopericytoma: a Vascular Tumor Featuring Zimmermann's Pericytes. Ann Surg 1942;116(1):26–33. doi:10.1097/00000658-194207000-00004.
2. Spitz FR, Bouvet M, Pisters PW, et al. Hemangiopericytoma: a 20-year single-institution experience. Ann Surg Oncol 1998;5 (4):350–355. doi:10.1007/BF02303499.
3. McMaster MJ, Soule EH, Ivins JC. Hemangiopericytoma. A clinicopathologic study and long-term followup of 60 patients. Cancer 1975;36(6):2232–2244.
4. Sano T, Terada T, Hayashi F, et al. Malignant hemangiopericytoma of the liver: report of a case. Jpn J Surg 1991;21(4):462–465. doi:10.1007/BF02470977.
5. Adams J, Lodge JP, Parker D. Liver transplantation for metastatic hemangiopericytoma associated with hypoglycemia. Transplantation 1999;67(3):488–489. doi:10.1097/00007890-199902150-00027.
6. Soares P, Ferlicot S, Laasou K, et al. Renal and hepatic metastasis from meningeal hemangiopericytoma. Prog Urol 2003;13(3):498–501.
7. Kaneko T, Harada A, Isshiki K, et al. Hemangiopericytomatous meningioma metastasized to the liver: report of a case and review of the literature. Surg Today 1993;23(7):644–648. doi:10.1007/BF00311916.
8. Chakravarty BJ, Munn S, Lane MR. Hepatic metastasis from a meningeal haemangiopericytoma. Aust N Z J Med 1991;21 (6):884–885.
9. Grunenberger F, Bachellier P, Chenard MP, et al. Hepatic and pulmonary metastases from a meningeal hemangiopericytoma and severe hypoglycemia due to abnormal secretion of insulin-like growth factor: a case report. Cancer 1999;85(10):2245–2248. doi:10.1002/(SICI)1097-0142(19990515)85:10<2245::AID-CNCR20>3.0.CO;2-K.
10. Hukill PB, Lowman RM. Visceral metastasis from a meningioma: report of a case. Ann Surg 1960;152:804–808.

11. Yoshida K, Tamazaki S, Ota K, et al. A case report of meningioma with multiple liver metastases (in Japanese with English abstract). Acta Hepatica 1988;29:1528–1534.
12. Arnoletti P, Jhala N. Retroperitoneal hemangiopericytoma. J Am Coll Surg 2003;197(4):687–688. doi:10.1016/S1072-7515(03)00592-1.
13. Billings KR, Fu YS, Calcaterra TC, Sercarz JA. Hemangiopericytoma of the head and neck. Am J Otolaryngol 2000;21(4):238–243. doi:10.1053/ajot.2000.8378.
14. Guthrie BL, Ebersold MJ, Scheithauer BW, Shaw EG. Meningeal hemangiopericytoma: histopathological features, treatment, and long-term follow-up of 44 cases. Neurosurgery 1989;25(4):514–522. doi:10.1097/00006123-198910000-00003.
15. Enzinger FM, Smith BH. Hemangiopericytoma. An analysis of 106 cases. Hum Pathol 1976;7(1):61–82. doi:10.1016/S0046-8177(76)80006-8.
16. Cheng NY, Chen RC, Chen TY, Tu HY. Contrast-enhanced ultrasonography of hepatic metastasis of hemangiopericytoma. J Ultrasound Med 2008;27(4):667–671.
17. Kim BW, Wang HJ, Jeong IH, et al. Metastatic liver cancer: a rare case. World J Gastroenterol 2005;11(27):4281–4284.
18. Aliberti C, Benea G, Kopf B, De Giorgi U. Hepatic metastases of hemangiopericytoma: contrast-enhanced MRI, contrast-enhanced ultrasonography and angiography findings. Cancer Imaging 2006;6:56–59. doi:10.1102/1470-7330.2006.0011.
19. Ghaffar H, Parwani A, Rosenthal DL. Fine needle aspiration cytology of hepatic metastasis from a meningeal hemangiopericytoma. A case report. Acta Cytol 2003;47(2):281–286.
20. Chhieng D, Cohen JM, Waisman J, et al. Fine-needle aspiration cytology of hemangiopericytoma: A report of five cases. Cancer 1999;87(4):190–195. doi:10.1002/(SICI)1097-0142(19990825)87:4<190::AID-CNCR5>3.0.CO;2-Y.
21. Adam R, Aloia T, Krissat J, et al. Is liver resection justified for patients with hepatic metastases from breast cancer? Ann Surg 2006;244(6):897–907. discussion 907-8. doi:10.1097/01.sla.0000246847.02058.1b.
22. Nappi O, Ritter JH, Pettinato G, Wick MR. Hemangiopericytoma: histopathological pattern or clinicopathologic entity? Semin Diagn Pathol 1995;12(3):221–232.
23. Gengler C, Guillou L. Solitary fibrous tumour and haemangiopericytoma: evolution of a concept. Histopathology 2006;48(1):63–74. doi:10.1111/j.1365-2559.2005.02290.x.
24. Middleton LP, Duray PH, Merino MJ. The histological spectrum of hemangiopericytoma: application of immunohistochemical analysis including proliferative markers to facilitate diagnosis and predict prognosis. Hum Pathol 1998;29(6):636–640. doi:10.1016/S0046-8177(98)80015-4.
25. Hasegawa T, Matsuno Y, Shimoda T, et al. Frequent expression of bcl-2 protein in solitary fibrous tumors. Jpn J Clin Oncol 1998;28(2):86–91. doi:10.1093/jjco/28.2.86.
26. Rajaram V, Brat DJ, Perry A. Anaplastic meningioma versus meningeal hemangiopericytoma: immunohistochemical and genetic markers. Hum Pathol 2004;35(11):1413–1418. doi:10.1016/j.humpath.2004.07.017.
27. Gowans LK, Bentz ML, DeSantes KB, Thompson KJ. Successful treatment of an infant with constitutional chromosomal abnormality and hemangiopericytoma with chemotherapy alone. J Pediatr Hematol Oncol 2007;29(6):409–411. doi:10.1097/MPH.0b013e31806210da.
28. Ferigo N, Cottalorda J, Allard D, et al. Successful treatment via chemotherapy and surgical resection of a femoral hemangiopericytoma with pulmonary metastasis. J Pediatr Hematol Oncol 2006;28(4):237–240. doi:10.1097/01.mph.0000212903.61276.4b.

J Gastrointest Surg (2009) 13:1160–1162
DOI 10.1007/s11605-008-0595-7

GI IMAGE

Abdominal Cocoon: Clinical Presentation, Diagnosis, and Management

Debajyoti Mohanty · Bhupendra Kumar Jain · Juhi Agrawal · Arun Gupta · Vivek Agrawal

Received: 20 May 2008 / Accepted: 25 June 2008 / Published online: 23 July 2008

Abstract A 15-year-old girl presented with features suggestive of sub-acute intestinal obstruction (SAIO) with a palpable abdominal lump. Contrast-enhanced computed tomogram (CECT) abdomen revealed congregated small gut loops confined to a single area and encased in a thick membrane suggestive of abdominal cocoon. On laparotomy, a thick white membrane was found encasing most of the small gut. The cocoon was excised releasing the encased small bowel. The patient was relieved of her symptoms following surgery. Histopathology of excised cocoon membrane revealed granulomatous inflammation consistent with tuberculosis. The patient was discharged on ninth postoperative day with advice to take anti-tuberculosis drugs for 6 months. The possibility of abdominal cocoon should be considered in patients with SAIO and abdominal lump. Abdominal cocoon being a rare condition, CECT is useful in clinching the diagnosis and planning elective surgery in experienced hands.

Keywords Abdominal cocoon · Sclerosing encapsulating peritonitis · Intestinal obstruction · Low-grade peritonitis · CECT abdomen

Introduction

Small-bowel obstruction (SBO) is a common surgical emergency encountered in our institution. Adhesions account for about 60% of patients with SBO; the other common causes are intestinal stricture, hernia, and neoplasm. Unusual causes are encountered in only 6% of patients.[1] Abdominal cocoon (AC) or sclerosing encapsulating peritonitis is one such unusual cause of SBO. We, herein, report our experience in the diagnosis and treatment of AC.

D. Mohanty · B. K. Jain · J. Agrawal · A. Gupta · V. Agrawal
Department of Surgery, Guru Teg Bahadur Hospital,
University College of Medical Sciences,
Delhi 110 095, India

B. K. Jain (✉)
KE-92, Kavi Nagar,
Ghaziabad 201002, India
e-mail: bhupendrakjain@gmail.com

Case Report

A 15-year-old girl presented with intermittent colicky central abdominal pain and bilious vomiting for duration of 24 months. There was no history of constipation. She had neither prior abdominal surgery nor had history of exposure to tuberculosis. There was central abdominal distension with a tender, firm lump palpable in the central abdomen. Plain upright abdominal X-ray showed absence of multiple air fluid levels. Ultra sonogram (USG) abdomen showed hypo-peristaltic, thickened small gut loops. Contrast-enhanced computed tomogram (CECT) of the abdomen revealed congregated small gut loops confined to a single area and encased in a thick membrane suggestive of abdominal cocoon (Fig. 1a, b). Decision for laparotomy was taken on the basis of clinical and radiological findings. On laparotomy, a thick white membrane was found encasing most of the small gut (Fig. 2a) with dense adhesions in the pelvis. Greater omentum was not identified. Excision of the cocoon membrane was undertaken with care to avoid injury to intestine (Fig. 2b, c). The pelvic adhesions were released. Histopathology of the cocoon wall revealed granulomatous inflammation consistent with tuberculosis. She was prescribed anti-tuberculous treatment postoperatively and was discharged on the ninth postoper-

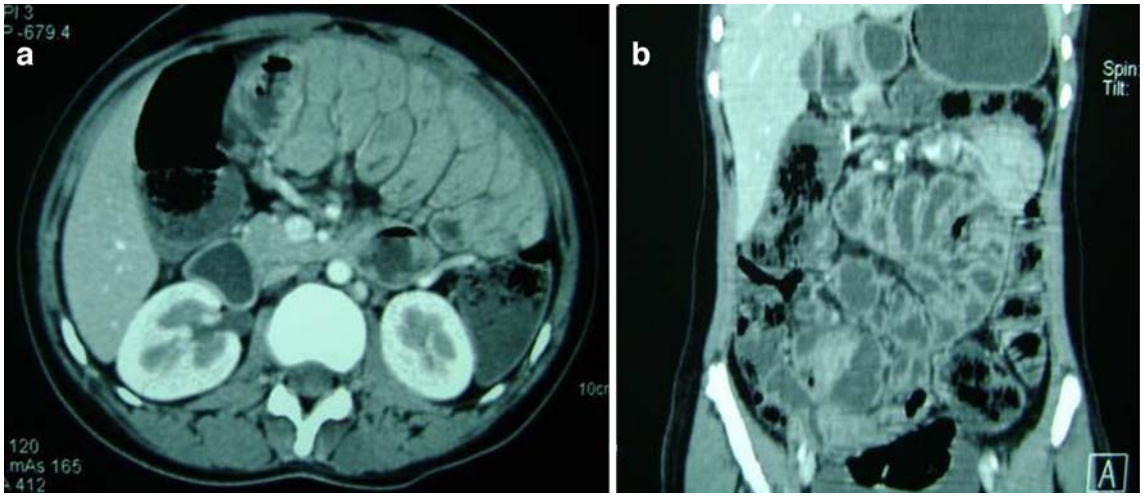

Figure 1 **a**, **b** Contrast-enhanced CT images show congregated small gut loops confined to a single area and encased in a thick membrane.

ative day. The patient was symptom-free on follow-up over a period of 6 months.

Discussion

AC is characterized by partial or total encasement of the small gut by a fibrocollagenous sac that looks like a cocoon.[2] The primary or the idiopathic form is seen characteristically in young adolescent girls of 4–18 year age group from the tropical or subtropical countries.[3] The more common secondary form is associated with prolonged beta blocker therapy, local irritation of the peritoneum by trauma, peritoneal dialysis, peritoneal–venous shunting, and ventriculoperitoneal shunt.[4] The plausible hypothesis for pathogenesis of AC is recurrent low grade or subclinical peritonitis, during which the patients had no significant abdominal signs, leading to sclerosis and membrane formation with subsequent development of a cocoon.[5] Histopathology of the excised membrane suggested tuberculous infection in our patient. Tuberculosis is highly prevalent in this part of the world and is likely to have a role in the formation of AC due to retrograde infection via fallopian tubes from subclinical pelvic inflammatory disease/genito urinary tuberculosis.[3,6]

During the last 3 years, we have managed another three patients with abdominal cocoon. The patients had two distinct clinical presentations. Two patients, having partial encasement involving distal ileum, had more acute presentation with abdominal distension, due to dilatation of bowel proximal to encasement, as a prominent sign. Abdominal X-ray revealed multiple air fluid levels, and patients required emergency laparotomy. The other two patients had a palpable abdominal lump due to encasement of the

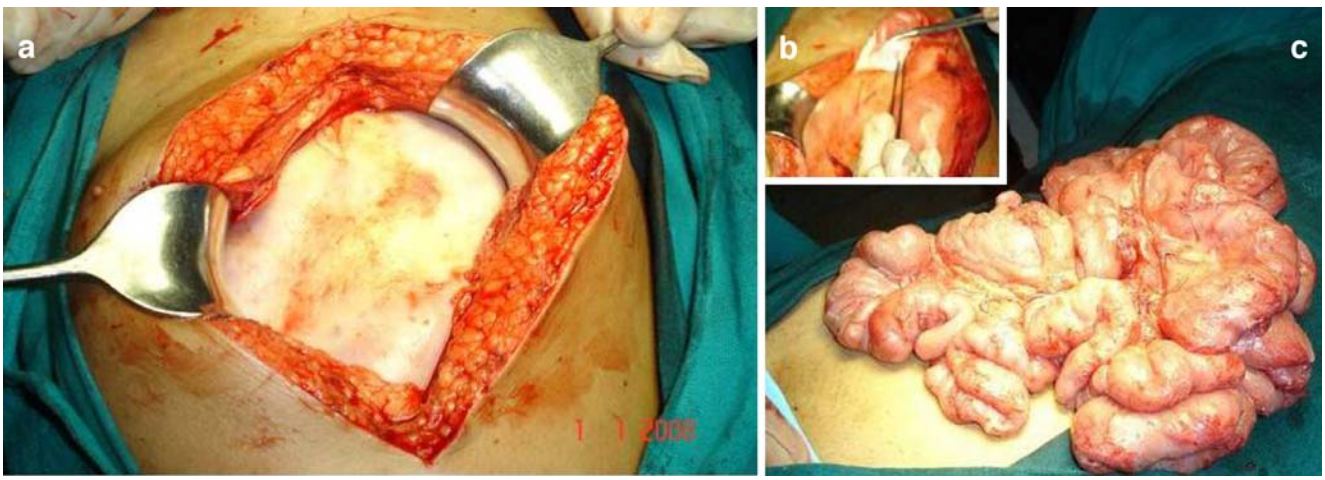

Figure 2 **a** Abdominal cocoon at laparotomy, **b** dissection of cocoon releasing the encased bowel, and **c** thick edematous bowel loops after completion of dissection.

whole edematous and matted small gut within the cocoon. Kinking and extrinsic compression of the small gut by the cocoon resulted in partial obstruction of the bowel accounting for SAIO. The symptoms in this group were less pronounced; there was absence of multiple air fluid levels in abdominal X-ray. The features allowed elective operation after further evaluation with CECT.

Presence of an abdominal lump was found to have a correlation with the total encasement of the small bowel in our study. While the plain X-ray abdomen and USG were non-contributory, the CECT abdomen provided the definitive diagnosis of abdominal cocoon by revealing congregated small gut loops confined to a single area and encased in a thick membrane.

The possibility of AC should be considered in patients presenting with SAIO and abdominal lump. Abdominal cocoon being a rare condition, CECT is useful in clinching the diagnosis and planning elective surgery in experienced hands. Meticulous dissection of the cocoon membrane from the gut to release the entrapped intestine and separation of the inter loop adhesions is the treatment of choice. Iatrogenic injury to bowel and consequent bowel resections are associated with high morbidity and are to be avoided.

References

1. Jones PF. Intraoperative techniques in small bowel obstruction without associated vascular impairment. In Fielding LP, Welch JP, eds. Intestinal Obstruction. Edinburgh: Churchill Livingstone, 1987.
2. Okamoto N, Maeda K, Fujisaki M, Sato H. Abdominal cocoon in a aged man: report of a case. Surg Today 2007;37:258–60. doi:10.1007/s00595-006-3343-1.
3. Foo KT, Ng KC, Rauff A, Foong WC, Sinniah R. Unusual small intestinal obstruction in girls: the abdominal cocoon. Br J Surg 1978;65:427–30. doi:10.1002/bjs.1800650617.
4. Cohen O, Abrahamson J, Ben-ari J, Frajewicky V, Eldar S. Sclerosing encapsulating peritonitis primary and secondary forms. J Clin Gastroenterol 1996;22(1):54–7. doi:10.1097/00004836-199601000-00016.
5. Maguire D, Srinivasan P, O'Grady J, Rela M, Heaton ND. Sclerosing encapsulating peritonitis after orthotopic liver transplantation. Am J Surg 2001;182:151–4. doi:10.1016/S0002-9610(01)00685-7.
6. Lalloo S, Krishna D, Maharajh J. Abdominal cocoon associated with tuberculous pelvic inflammatory disease. Br J Radiol 2002;75:174–6.

J Gastrointest Surg (2009) 13:1163–1165
DOI 10.1007/s11605-009-0846-2

LETTER TO THE EDITORS

Early Enteral Nutrition Within 24 h of Intestinal Surgery Versus Later Commencement of Feeding: A Systematic Review and Meta-analysis

Emma Osland · Rossita Yunus · Shahjahan Khan · Muhammed Ashraf Memon

Received: 20 November 2008 / Accepted: 18 February 2009 / Published online: 6 March 2009

Dear Dr Lewis, Andersen, and Thomas:

It was with great interest that we read your most recent systematic review and meta-analysis addressing the important issue of early versus later commencement of enteral feeding in gastrointestinal surgery patients.[1] While your 2006 Cochrane review[2] has clear merit in that it expands on the number of studies and thus the power of your earlier analysis,[3] we feel that the present study is essentially a duplication of your Cochrane effort, although with slightly different conclusions.

While we concur with your overall conclusions about "nil by mouth" (NBM) conveying no benefit over early enteral feeding in terms of postsurgical outcomes in gastrointestinal surgery, there are several aspects of your analysis that, in our opinion, threaten to undermine your otherwise valid conclusions. Firstly, your inclusion of the study by Helslin et al.[4] utilizing the immune-enhancing enteral feed product Impact® (Sandoz Nutrition) in 8% (n=97) of your pooled sample potentially confounds your results and limits the conclusions that can be made about benefits to postoperative infections and length of hospital stay conferred by early feeding. This is because nutritional products fortified with arginine, glutamine, nucleic acids, antioxidants, and/or omega-3 fatty acids may be independently associated with a reduced risk of postoperative complications, wound infections, and length of hospital stay[5–7] in elective surgical oncology patients. We acknowledge, however, recent clinical studies investigating such products have not supported the conclusions of these earlier studies.[8,9]

Secondly, a total of 10% (n=118) of your pooled sample are reported to have received nutrition distal to the anastomosis.[4,10–12] Given that fear of anastomotic dehiscence has been purported as a primary reason for avoidance of early feeding, we feel that any meta-analysis attempting to refute these concerns regarding anastomotic dehiscence must include studies providing nutrition proximal to anastomosis and not distal. It is therefore our expectation that studies where a substantial number of subjects are fed distal to the surgical site would be excluded. Failure to do so invalidates your ability to make comments on the benefit or harm posed by early feeding with regard to anastomotic breakdown.

Thirdly, as you have rightly stated, malnutrition is a common finding in patients undergoing elective gastrointestinal surgery[13,14] and has been shown to be independently associated with poor outcomes such as delayed wound healing, development of postoperative complications, and mortality in surgical patients.[13–17] For this reason, we feel it is of vital importance that a balanced, nutritionally complete intake be provided within the early feeding period. Consequently, we question the benefit of including studies that provide only clear fluids within 24 h postoperatively[18] as it is impossible to meet nutritional requirements on this type of diet irrespective of the quantity

E. Osland · M. A. Memon (✉)
Department of Surgery and Nutrition, Ipswich Hospital,
Chelmsford Avenue,
Ipswich, Queensland 4305, Australia
e-mail: mmemon@yahoo.com

R. Yunus · S. Khan
Department of Mathematics and Computing,
Australian Centre for Sustainable Catchments,
University of Southern Queensland,
Toowoomba, Queensland, Australia

M. A. Memon
Department of Surgery, University of Queensland,
Brisbane, Queensland, Australia

M. A. Memon
Faculty of Health Sciences and Medicine, Bond University,
Gold Coast, Queensland, Australia

consumed due to the absence or grossly inadequate provision of protein, lipids, and many micronutrients.[19]

Fourthly, we draw attention to a number of studies that appear to us to meet your inclusion criteria that have been omitted from your analysis. The study by Feo et al.[20] was excluded in all your meta-analyses[1–3] as you state "both treatment groups were allowed liquid diet, therefore [there was] not control group to early feeding."[2] The cited paper, however, clearly states liquid diet in the NBM group was only provided after passage of flatus,[20] thereby meeting your inclusion criteria. Furthermore, there are at least four eligible studies[21–25] we have located that do not appear to have been identified in your searches in which all or subgroups from the study population may provide additional numbers for your study.

Fifthly, from a statistical point of view, we note that you report on both fixed and random effects models in the most recent paper,[1] while only the former is reported in your earlier publications.[2,3] The relative appropriateness of fixed versus random effects model has received increasing attention with relation to meta-analyses. The fixed effect meta-analysis assumes that there is one identical true treatment effect common to every study: This is not the case in your (or indeed any) meta-analysis. The random effects model of meta-analysis is an alternative approach that does not assume that a common ("fixed") treatment effect exists. The random effects model assumes that the true treatment effects in the individual studies may be different from each other, and thus no single number to estimate in the meta-analysis exists but rather a distribution of numbers. The most common random effects model also assumes that these different true effects are normally distributed. The random effect model allows for the possibility that populations vary from study to study and therefore estimates the *mean* and *standard deviation* of the different effects. As described above, there are several important differences among the interventions provided within the studies included in your meta-analysis that potentially impacts on treatment effects, and therefore, a random effects model is the most appropriate model in this setting, and fixed effect model should be discarded. We were also disappointed to see that the figures reported in your latest paper were solely that of the fixed effects model rather than the random effects outcomes unique to your latest paper.

Furthermore, we note an error between the "tabulated data" (Fig. 1) and "outcomes" reported within the text with regards to "wound infections." Under outcome, the absolute risk for wound infection in the treatment group has been reported incorrectly from 0% (zero out of 16) to 33% (ten out of 30). The correct figures should read 1.23% (one over 81) to 33% (ten out of 30). It appears that the value of zero out of 16 is from the pneumonia dataset.

Finally, we agree that the mounting body of evidence showing no demonstrable harm from early enteral nutrition provision postoperatively justifies a large adequately powered clinical trial that places a primary focus on linking nutritional intake to postoperative outcomes. This latter aspect has largely been omitted from investigations on this topic to date, to the detriment of our more informed understanding of this topic. While our clinical experience concurs with your comments closing your Cochrane review that "patients only take a small proportion of required energy in the first few days post operation,"[2] as the objective data to verify this is currently absent from the literature, we feel the omission of this statement from the current paper appropriate.

References

1. Lewis SJ, Andersen HK, Thomas S. Early Enteral Nutrition Within 24 h of Intestinal Surgery Versus Later Commencement of Feeding: A Systematic review and Meta-analysis. J Gastrointest Surg 2008;(Jul):16.
2. Andersen HK, Lewis SJ, Thomas S. Early enteral nutrition within 24 h of colorectal surgery versus later commencement of feeding for postoperative complications. Cochrane Database Syst Rev 2006;(4):CD004080.
3. 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(7316):773–776. doi:10.1136/bmj.323.7316.773.
4. Heslin MJ, Latkany L, Leung D, et al. A prospective, randomized trial of early enteral feeding after resection of upper gastrointestinal malignancy. Ann Surg 1997;226(4):567–577. doi:10.1097/00000658-199710000-00016, discussion 577–580.
5. Braga M, Gianotti L, Nespoli L, Radaelli G, Di Carlo V. Nutritional approach in malnourished surgical patients: a prospective randomized study. Arch Surg 2002;137(2):174–180. doi:10.1001/archsurg.137.2.174.
6. Braga M, Gianotti L, Radaelli G. Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial. Arch Surg 1999;134(4):428–433. doi:10.1001/archsurg.134.4.428.
7. Zheng Y, Li F, Qi B. Application of perioperative immunonutrition for gastrointestinal surgery: a meta-analysis of randomized controlled trials. Asia Pac J Clin Nutr 2007;16(Suppl 1):253–257.
8. Lobo DN, Williams RN, Welch NT. Early postoperative jejunostomy feeding with an immune modulating diet in patients undergoing resectional surgery for upper gastrointestinal cancer: a prospective, randomized, controlled, double-blind study. Clin Nutr 2006;25(5):716–726. doi:10.1016/j.clnu.2006.04.007.
9. Klek S, Kulig J, Sierzega M. Standard and immunomodulating enteral nutrition in patients after extended gastrointestinal surgery—a prospective, randomized, controlled clinical trial. Clin Nutr 2008;27(4):504–512. doi:10.1016/j.clnu.2008.04.010.
10. Sagar S, Harland P, Shields R. Early postoperative feeding with elemental diet. BMJ 1979;1(6159):293–295.
11. Beier-Holgersen R, Boesby S. Influence of postoperative enteral nutrition on postsurgical infections. Gut 1996;39(6):833–835. doi:10.1136/gut.39.6.833.
12. Watters JM, Kirkpatrick SM, Norris SB, Shamji FM, Wells GA. Immediate postoperative enteral feeding results in impaired respira-

tory mechanics and decreased mobility. Ann Surg 1997;226(3):369–377. doi:10.1097/00000658-199709000-00016, discussion 377–380.
13. Windsor JA, Hill GL. Weight loss with physiologic impairment. A basic indicator of surgical risk. Ann Surg 1988;207(3):290–296. doi:10.1097/00000658-198803000-00011.
14. Ward N. Nutrition support to patients undergoing gastrointestinal surgery. Nutr J 2003;2:18. doi:10.1186/1475-2891-2-18.
15. Clark MA, Plank LD, Hill GL. Wound healing associated with severe surgical illness. World J Surg 2000;24(6):648–654. doi:10.1007/s002689910106.
16. Huckleberry Y. Nutritional support and the surgical patient. Am J Health Syst Pharm 2004;61(7):671–682. quiz 683–674.
17. Gallagher-Allred CR, Voss AC, Finn SC, McCamish MA. Malnutrition and clinical outcomes: the case for medical nutrition therapy. J Am Diet Assoc 1996;96(4):361–366, 369. quiz 367–368 . doi:10.1016/S0002-8223(96)00099-5.
18. Reissman P, Teoh TA, Cohen SM, Weiss EG, Nogueras JJ, Wexner SD. Is early oral feeding safe after elective colorectal surgery? A prospective randomized trial. Ann Surg 1995;222 (1):73–77. doi:10.1097/00000658-199507000-00012.
19. Hancock S, Cresci G, Martindale R. The clear liquid diet: when is it appropriate? Curr Gastroenterol Rep 2002;4(4):324–331. doi:10.1007/s11894-002-0083-2.
20. Feo CV, Romanini B, Sortini D. Early oral feeding after colorectal resection: a randomized controlled study. ANZ J Surg 2004;74 (5):298–301. doi:10.1111/j.1445-1433.2004.02985.x.
21. Nessim A, Wexner SD, Agachan F. Is bowel confinement necessary after anorectal reconstructive surgery? A prospective, randomized, surgeon-blinded trial. Dis Colon Rectum 1999;42 (1):16–23. doi:10.1007/BF02235177.
22. Zhou T, Wu XT, Zhou YJ, Huang X, Fan W, Li YC. Early removing gastrointestinal decompression and early oral feeding improve patients' rehabilitation after colorectostomy. World J Gastroenterol 2006;12(15):2459–2463.
23. Han-Geurts IJ, Hop WC, Kok NF, Lim A, Brouwer KJ, Jeekel J. Randomized clinical trial of the impact of early enteral feeding on postoperative ileus and recovery. Br J Surg 2007;94(5):555–561. doi:10.1002/bjs.5753.
24. Han-Geurts IJ, Jeekel J, Tilanus HW, Brouwer KJ. Randomized clinical trial of patient-controlled versus fixed regimen feeding after elective abdominal surgery. Br J Surg 2001;88(12):1578–1582. doi:10.1046/j.0007-1323.2001.01934.x.
25. Lucha PA, Butler R, Plichta J, Francis M. The economic impact of early enteral feeding in gastrointestinal surgery: a prospective survey of 51 consecutive patients. Am Surg 2005;71(3):187–190.

J Gastrointest Surg (2009) 13:1166–1167
DOI 10.1007/s11605-009-0848-0

LETTER TO THE EDITORS

Reply to Letter to the Editor: Osland et al.

S. J. Lewis

Received: 5 January 2009 / Accepted: 18 February 2009 / Published online: 13 March 2009

Dear Editor:

Thank you for the opportunity to reply to the comments of Osland et al. We are pleased that they concur with our overall conclusions. As with all meta-analysis, there are confounding variables between studies, and the use of immunutrition may well be one. However, as pointed out in the comments, there is little evidence of improved outcome with immunutrition. We set out to do a pragmatic analysis with a relatively limited number of studies, of the benefit of early enteral nutrition. We found no indication from the small study by Heslin et al.[1] that immunutrition improved outcomes when compared with the other studies; indeed an increase in wound infection rate was seen in the interventional group.

Osland et al. hypothesise that only nutrition delivered proximally to an anastomosis can be of benefit. Unlike colonocytes, which derive most of their energy supply from the lumen contents, in the proximal colon and small intestine, there is a greater reliance on vascular nutrition.[2] Mucosal proliferation is also dependent on the availability of growth factors and neuronal control mechanisms as characterised by trophic effects of nutrition on isolated intestines in animal models.[3] Nutrition and even "sham feeding" stimulates the release of intestinal hormones such as gastrin, GIP, and GLP, which have local and systemic influences. Only 10% of patients within our analysis received distal feeding, and we found the direction of effect to be similar to those receiving proximal feeding. This leads us on to the next point, relating to the amount of nutrition given. It is quite clear that the clinical benefits achieved by providing early nutrition occur with patients receiving only a small percentage of their requirements. The reason for this is complex, as mentioned above the release of intestinal polypeptides may have a role in improving the metabolic recovery. Animal models suggest that as little as 15–30% of energy requirements may lead to improved outcomes.[4,5] Indeed, the return of intestinal function through diet may also be relevant to improved outcomes, as recent studies have shown faster patient recovery is achieved with the postoperative use of chewing gum.

The comments by Osland et al. are confused with regard to wound infections. We have rechecked the papers for wound infections in both groups and the data presented in our analysis are correct.

In a random effect model, there is less weight on study size, therefore small studies, which are more likely to be of lower quality, have disproportionate weight. The issue with the fixed effect model is the underlying assumption that the study populations are the same—when in fact they may not be. Either way, the best solution is to present both.

With regard to the other studies mentioned: (1) Feo et al.[6]: patients were randomly allocated to have either a naso-gastric tube and be nil-by-mouth until the passage of flatus or no naso-gastric tube, water (not explicit in the paper, but we had contacted the authors) then diet from the second postoperative day onward. (2) Nessim et al.[7]: this is a study examining the benefits of bowel confinement where the interventional group received clear liquids with high-dose loperamide and codeine, while with the control group of patients started a regular dietary intake on the day of surgery. (3) Zhou et al.[8]: this is a study of early vs late removal of naso-gastric tubes after colorectal surgery. The early removal group were also offered a "liquid fibreless" diet from the second postoperative day. (4) and (5) Han-

S. J. Lewis (✉)
Department of Gastroenterology,
Consultant Physician and Gastroenterologist, Derriford Hospital,
Plymouth PL6 8DH, UK
e-mail: sjl@doctors.org.uk

Geurts et al.: in both studies (it is not clear if some or all patients are common to both studies), patients undergoing colonic and vascular surgery were randomly allocated to choose when they wanted to start an oral diet (patient controlled group) or a fixed feeding regime where diet was introduced on postoperative day 4. No data were presented as to whether oral dietary intake was started within 24 h of surgery in the patient-controlled group or not.[9] In the second study,[10] patients in the patient controlled group tolerated food at a median of 2 days after surgery. (6) The small study (n=51) by Lucha et al.[11] was designed to examine the economic impact of early feeding and should have been included in our analysis. Patients undergoing colorectal surgery were randomly allocated to receive feeding from 8 h after surgery vs later feeding. Only one complication was reported in each arm. No other useful data was extractable. The study has no impact on our statistics.

Stephen Lewis
Henning K Andersen
Steve Thomas

References

1. Heslin MJ, Latkany L, Leung D, et al. A prospective, randomized trial of early enteral feeding after resection of upper gastrointestinal malignancy. Ann Surg 1997;226:567–680. doi:10.1097/00000658-199710000-00016.
2. Roediger WE. W Role of anaerobic bacteria in the metabolic welfare of the colonic mucosa in man. Gut 1980;21:793–798. doi:10.1136/gut.21.9.793.
3. Sakata T. Effects of indigestable dietary bulk and short chain fatty acids on the tissue weight and epithelial cell proliferation rate of the digestive tract in rats. J Nutr Sci Vitaminol (Tokyo) 1986;32:355–362.
4. Omura K, Hirano K, Kanehira E, et al. Small amount of low-residue diet with parenteral nutrition can prevent decreases in intestinal mucosal integrity. Ann Surg 2000;231:112–118. doi:10.1097/00000658-200001000-00016.
5. Sax HC, Illig KA, Ryan CK, et al. Low-dose enteral feeding is beneficial during total parenteral nutrition. Am J Surg 1996;171:687–590. doi:10.1016/S0002-9610(96)00039-6.
6. Feo CV, Romanini B, Sortini D, et al. Early oral feeding after colorectal resection: a randomized controlled study. ANZ J Surg 2004;74:298–301. doi:10.1111/j.1445-1433.2004.02985.x.
7. Nessim A, Wexner SD, Agachan F, et al. Is bowel confinement necessary after anorectal reconstructive surgery? A prospective, randomized, surgeon-blinded trial. Dis Colon Rectum 1999;42:16–23. doi:10.1007/BF02235177.
8. Zhou T, Wu XT, Zhou YJ, et al. Early removing gastrointestinal decompression and early oral feeding improve patients' rehabilitation after colorectostomy. World J Gastroenterol 2006;12:2459–2463.
9. Han-Geurts IJ, Jeekel J, Tilanus HW, et al. Randomized clinical trial of patient-controlled versus fixed regimen feeding after elective abdominal surgery. Br J Surg 2001;88:1578–1582. doi:10.1046/j.0007-1323.2001.01934.x.
10. Han-Geurts IJ, Hop WC, Kok NF, et al. Randomized clinical trial of the impact of early enteral feeding on postoperative ileus and recovery. Br J Surg 2007;94:555–561. doi:10.1002/bjs.5753.
11. Lucha PA Jr, Butler R, Plichta J, et al. The economic impact of early enteral feeding in gastrointestinal surgery: a prospective survey of 51 consecutive patients. Am Surg 2005;71:187–190.