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Successful management of microscopic residual disease in large bowel cancer

Abstract Although cancer surgery has been of great benefit to patients with large bowel cancer, a flaw that has caused the death of countless patients has gone unrecognized. Although surgeons have dealt successfully with the primary tumor, they have neglected to treat microscopic residual disease. Persistent cancer cells within the abdomen and pelvis are responsible for the death of 30–50% of the patients who die with this disease and for quality of life consequences that result from intestinal obstruction caused by cancer recurrence at the resected site and on peritoneal surfaces. New surgical techniques for large bowel cancer resection minimize the surgery-induced microscopic residual disease that may result from surgical trauma. New developments in exposure, hemostasis, adequate lymphadenectomy, and qualitatively superior margins of excision have occurred. Clinical data show that a 40% improvement in survival with an optimization of surgical technique is possible. Not only should the surgical event for primary colon and rectal cancer be optimized, but also the successful treatment of peritoneal carcinomatosis should be pursued. Resected site disease and peritoneal carcinomatosis can be prevented through the use of perioperative intraperitoneal chemotherapy in patients at high risk of persistent microscopic residual disease. These are patients with perforated cancer, positive peritoneal cytology, ovarian involvement, tumor spill during surgery, and adjacent organ involvement. Patients with established peritoneal carcinomatosis can be salvaged with an approximate 50% long-term survival rate if the timely use of peritonectomy procedures, intraperitoneal chemotherapy, and knowledgeable patient selection are utilized. Peritonectomy procedures allow the removal of all visible peritoneal carcinomatosis with acceptable surgical morbidity (25%) and mortality (1.5%) rates. Heated intraoperative intraperitoneal chemotherapy using mitomycin C, in addition to early postoperative intraperitoneal 5-fluorouracil, can eradicate microscopic residual disease in the majority of patients. The peritoneal cancer index, which quantitates colon cancer peritoneal carcinomatosis by distribution and by lesion size, must be used in the selection of patients who may benefit from these advanced oncologic surgical treatment strategies. The completeness of the cytoreduction score is the most powerful prognostic indicator in this group of patients. The surgeon must be aware that there are no long-term survivors unless complete cytoreduction occurs. With a combination of proper techniques for the resection of primary disease, peritonectomy procedures for the removal of all visible peritoneal implants, intraoperative and early postoperative chemotherapy for the eradication of microscopic residual disease, and quantitative tools for proper patient selection, one can optimize the surgical treatment of patients with large bowel cancer.

Key words Colorectal cancer · Hyperthermia · Intra-peritoneal chemotherapy · Peritoneal carcinomatosis · Mitomycin C · 5-Fluorouracil

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Introduction

The surgical reality that accompanies colorectal cancer resection suggests that although approximately 50% of patients come to the surgeon with a contained malignancy, as a result of surgery this cancer is converted into a disseminated disease process. Improper concepts and flawed technology lead to a surgery-induced dissemination of microscopic residual disease in a large percentage

of patients. Inadequate exposure, imperfect hemostasis, inadequate lymphadenectomy, and qualitatively poor margins of excision lead to the spillage of cancer cells in 30–50% of patients. Many minor technical changes in the surgical approach to this disease can make a great difference in survival. The goal of cancer surgery for large bowel cancer is containment. This can be achieved, but surgeons must believe that they are the most important prognostic variable before finding the commitment required to modify the current surgical approach.

The skill of the surgeon as a prognostic variable

The surgical literature contains several early pleas for modifications in surgical technology. Turnbull and associates [25] emphasized the "no touch isolation technique." Although the statistical support for these concepts may not be acceptable by modern-day standards, one cannot overlook the successful results achieved by Turnbull.

Phillips et al. (1984) published a report on local recurrence after curative surgery for large bowel cancer [12]. They called attention to the intersurgeon variability in local recurrence after colorectal cancer resection. The incidence of local recurrence was determined for surgeons performing more than 30 resections. Three surgeons had a local recurrence rate of $< 5\%$, seven of 5–10%, three 10–15%, six 15–20%, and one $> 20\%$ ($P < 0.05$). After stratification by sex and Dukes' classification, the statistical significance remained.

McArdle and Hole in 1991 showed a variability among surgeons in terms of patients' postoperative morbidity and mortality and ultimate survival [11]. The proportion of patients undergoing apparently curative resection varied among surgeons from 40–76%. The intensity of the surgical effort that was exerted in an attempt to achieve a "curative approach" varied greatly within the surgical community. The short-term consequences of surgery, i.e., morbidity and mortality, also varied greatly when individual surgeons rather than institutions were assessed. Most striking was the fact that survival at 10 years in patients who underwent curative resection varied from 20–63% between the consultant surgeons responsible for managing colorectal patients.

Hermanek and colleagues presented data in 1995 to show that locoregional recurrence varied from $> 50\%$ to approximately 5% among German surgeons [8]. There was also a marked correlation between locoregional recurrence and 5-year survival rates. As might be expected, a rate of locoregional recurrence of $\leq 5\%$ was associated with a nearly 80% 5-year survival rate. A local recurrence rate of $> 50\%$ was associated with a low, approximately 40% 5-year survival rate. A difference in 5-year survival rate of 40% occurred between the groups of patients operated on by individual surgeons. Surgeons with a low local recurrence rate have high survival rates and vice versa ($P < 0.005$). Thus although the TNM status was the predominant prognosticator, the surgeon was an independent prognostic factor by which to determine locoregional recurrence and thus survival.

In 1997 Holm and colleagues reviewed the influence of preoperative radiation therapy and other variables on the outcome of patients with rectal cancer. They found that patients operated on by surgeons who had been certified specialists for at least 10 years had a lower risk of local recurrence and death from rectal cancer [9]. Patients operated on in university hospitals also had a lower risk of death related to technical factors. They concluded that there was a significant surgeon-related variation in patient outcome which was probably related to surgical technique.

In 1998 Porter and colleagues compared the outcome of patients treated by trained colorectal surgeons who operated frequently for rectal cancer with surgeons lacking specialized training and performing < 21 procedures over the 8 years of the study [14]. The risk of local recurrence was increased in patients whose surgery was performed by surgeons without colorectal training and by those performing fewer resections. Similarly, a decreased disease-specific survival rate was found to be independently associated with surgeons lacking specialized colorectal training ($P = 0.03$) and surgeons performing occasional rectal resections ($P = 0.005$). The 5-year survival rate with trained and frequently operating surgeons was 67.3% and that with untrained and infrequently operating surgeons was 39.2%.

Anthone et al. [1] asked the question: "Does designated surgical interest improve the surgical management of colorectal cancer?" These authors compared survival in patients operated on by members of the American Society of Colon and Rectal Surgery to that for surgeons who were not members. The database comprised 11,677 patients with colon and rectal cancer. Of the total operations performed by society members, 38% of patients died; of all operations performed by nonmembers of the society, 46% of patients died. Patients operated on by members of the society were more likely to be alive at the time of follow-up than patients operated on by other surgeons (odds ratio 1.39, 95% confidence interval 1.15–1.68).

The mechanisms causing differences in surgeon-related survival statistics was reviewed by Averbach et al. in 1995 [2]. They concluded that the surgeon's efforts to contain a malignant process during cancer resection varied greatly. In their view, local recurrence correlated directly with reduced survival. Scott and colleagues suggested that respect for the mesorectum could reduce the local recurrence rates following surgery for rectal cancer to the 5% level [15]. They concluded that incomplete excision of the mesorectum contributes to local recurrence in a large proportion of patients with rectal cancer, particularly those with tumors in the middle and lower third of the rectum. Heald and colleagues [7] have presented clinical data that strongly suggest that the surgeon's technique is far superior to radiation therapy or chemotherapy in reducing the incidence of local and regional recurrence following a rectal cancer excision.

Why do primary colorectal cancer operations fail (metastases vs spread)?

The reoperative data provided by Gunderson and Sosin provide information regarding anatomic sites of first recurrence of large bowel cancer [6]. These sites of first recurrence are of great value in establishing the technical flaws in surgery that allow cancer spread. However, even though cancer spread on abdominal or pelvic surfaces is related to faulty surgical technique, surgeons cannot be held responsible for dissemination via portal blood or in distant lymph nodes, lungs, or other systemic spread. Liver metastases will occur prior to death in approximately 30% of patients according to Pickren and colleagues [13]. Systemic sites of disease progression may also occur. Most likely, systemic disease results from metastases from metastases. This dissemination of cancer throughout the body occurs due to metastases located within the liver or from lymph node metastases that seed via the thoracic duct. Surgery cannot reduce the incidence of cancer metastases but should reduce the incidence of spread to near zero.

If colorectal cancer fails within abdominal lymph nodes, on peritoneal surfaces, or at the resection site, one must interpret this as "iatrogenic recurrence" [3]. These sites of recurrence testify to the fact that the surgeon's resection did not provide adequate containment of the primary malignancy. The surgeon should take full responsibility for all locoregional failures in large bowel cancer (Fig. 1).

The incidence of failure with liver metastases, metastases at systemic sites, or locoregional spread on the peritoneal surfaces will be observed in direct proportion to the aggressive nature of the malignancy. The most aggressive tumors may show surgical treatment failure within the liver and systemic sites as well as locoregional failure. The least aggressive tumors would be expected to show isolated locoregional failures. The causes of iatrogenic recurrence are related to faulty surgical technique in a majority of patients. However, advanced treatment strategies are necessary to eradicate locoregional recurrence in some patients, especially those whose malignancy demonstrates aggressive behavior. The causes of iatrogenic recurrence involve:

1) insufficient lymphadenectomy;
2) traumatized narrow margins of excision resulting in microscopic residual disease;
3) blood loss from the cancer specimen which allows tumor-contaminated blood to remain within the peritoneal cavity; and
4) lymph leak from transected lymphatic channels which allows viable cancer cells to remain within the peritoneal cavity.

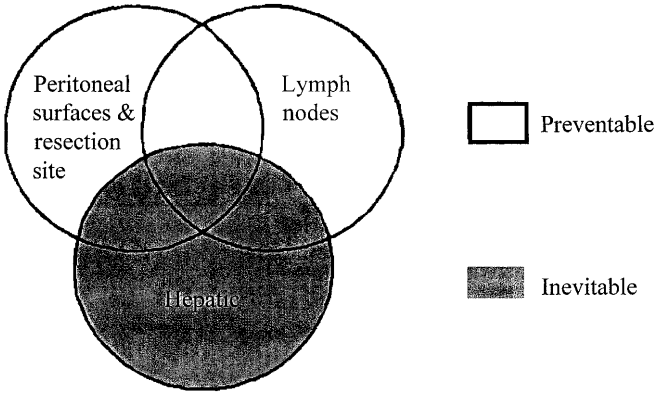

Fig. 1 Sites of treatment failure for large bowel cancer. The surgeon should accept responsibility for recurrence at the anatomic sites represented in the shaded areas. Modified, with permission, from Sugarbaker PH et al. [23]

An optimization of surgical technology to contain the malignant process can prevent iatrogenic recurrence in a majority of patients. First, adequate exposure is required so that the cancer specimen can be handled gently with minimal traction, and thereby prevent disruption of the malignant tissue. Second, optimal containment requires complete hemostasis. No blood loss from the transection of blood vessels should be allowed. Laser-mode electrosurgery should be used to transect tissue [18], which gives an additional margin of heat necrosis that will minimize microscopic residual disease at the margins of resection. Third, conglomerate suture ligatures in continuity should be used to transect major vascular and lymphatic channels. Fourth, adequate lateral margins of dissection are required to prevent the disruption of soft tissues that are in immediate contact with the primary malignancy. Generous utilization of peritonectomy procedures will provide the most adequate lateral margins [17]. These procedures allow surgeons to maintain a biological covering of the tumor as it is being resected. Finally, there must be adequate lymph node dissection. The lymphadenectomy should be sufficiently complete that persistence or progression of disease within the abdominal or pelvic lymph node chains is prevented. For left colorectal cancer, a complete lymphadenectomy means resection of paracolic, intermediate, and inferior mesenteric nodes that are at the junction of the inferior mesenteric artery and aorta. In other parts of the colon, one must dissect lymph nodes away from the middle colic, right colic, or ileocolic artery that are immediately adjacent to the superior mesenteric artery and vein.

The surgeon should not ligate any lymphatic or venous structures prior to the ligation of the relevant arterial structures. No venous hypertension should be elicited while the dissection is proceeding. Also, tissues surrounding large vascular structures should be ligated as a conglomerate of artery, vein, and lymphatic channels to prevent leakage of blood and lymph from the "specimen side of the dissection." On the patient side of the dissection, large blood vessels should be ligated in continuity and then suture ligated. Again, conglomerate ligation of blood vessels and lymphatic channels follows the principle of containment.

Optimal exposure is a necessary requirement of colorectal cancer surgery. Optimal exposure requires a midline incision, a self-retaining retractor to allow complete visualization of the operative field, and a second tier of retractors to remove viscera and other organs from the operative field (Fig. 2). Frequent irrigation of the operative field will remove blood from the tissues to be dissected so that they maintain a transparent quality. Blood-stained tissues promote further blood loss because blood vessels cannot be seen prior to their transection in a bloody operative field. Finally, sometimes surgeons need better help than can be provided by resident assistance. Very difficult cases require expert assistance, such as that provided by a second experienced surgeon.

Optimal hemostasis is essential not only to preserve the translucent nature of the tissues and thereby facilitate exposure but also to prevent the dissemination of cancer cells contained within blood. The most dangerous bleeding, in terms of cancer dissemination, is that from transected veins and venules on the cancer specimen. Hemostasis is facilitated by using peritonectomy procedures, laser-mode electrosurgery, ligatures in continuity proximally and distally on all vessels, and morsilization of fatty tissue surrounding small- and medium-sized blood vessels prior to ligation (Fig. 3).

A thorough knowledge of anatomy and the preservation of mesodermal planes is required within the abdomen and pelvis and within the retroperitoneal portion of the abdomen and pelvis. A prominent mesodermal layer exists posterior to the right colon. This layer must be respected when performing a right colectomy.

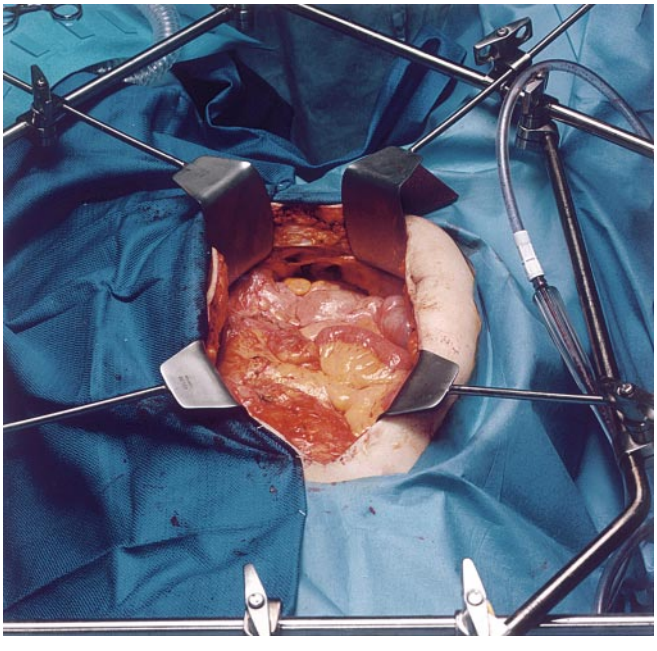

Fig. 2 Optimal exposure requires a midline incision, a self-retaining retractor to allow complete visualization of the operative field, and a second tier of retractors to remove viscera and other organs from the operative field

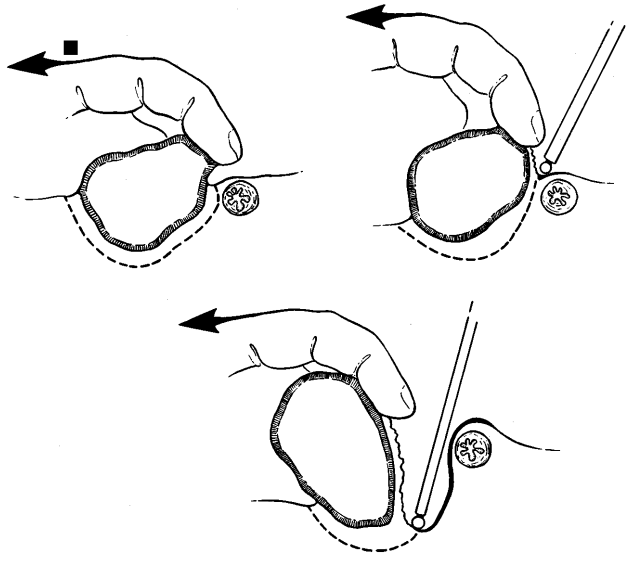

Fig. 3 Laser-mode electrosurgery has replaced dissection with scissors or knife in gastrointestinal cancer surgery. A lens-shaped (lenticular) defect is created by dissection with a ball-tip when high-voltage electrosurgery on pure cut is used. Strong traction on the specimen will optimize the skeletonization of vital structures using ball-tip dissection. A 0.5–1.0-mm layer of heat necrosis remains at the furthest extent of the dissection. This heat necrosis is an adequate tumor-free margin of resection

A prominent mesodermal layer also exists between the left colon and lower border of the pancreas, perirenal fat, the left paracolic gutter, and left side of the pelvis. In addition, as the rectum becomes a retroperitoneal structure, the mesorectum persists and can guide the surgeon to the proper tissue plane that will allow not only optimal containment of the cancerous process but also preservation of function.

To summarize, optimal containment of primary colon and rectal cancer involves optimal exposure, complete hemostasis, adequate lymph node dissection, and adequate margins of resection. The technical requirements include but may not be limited to gentle handling of the cancer specimen, peritonectomy procedures to provide a biological dressing that will shroud the malignant process, respect for the mesodermal envelope that contains tumors in the portions of bowel associated with the retroperitoneum or pelvis, refusal to lyse potentially cancer-containing adhesions, laser-mode electrosurgery to eliminate bleeding and provide a more adequate margin through heat necrosis, and conglomerate ligation of artery, veins, and lymphatic channels on the specimen side of the dissection.

Prevention of peritoneal carcinomatosis in high-risk groups

In some patients, there is a high likelihood of subsequent peritoneal carcinomatosis determined at the time of the colorectal cancer exploration. Positive peritoneal cytol-

ogy, cancerous involvement of the ovaries, visible evidence of peritoneal seeding on the surface of the specimen, blood loss from the surface of a necrotic tumor mass, adjacent organ involvement, intraoperative cancer spill from a disruption of the specimen, and perforation of the malignancy through the primary cancer can be assumed to cause cancerous seeding of peritoneal surfaces. Even though a complete lymphadenectomy has been performed, lymph nodes at the most distal margin of resection may be involved. This situation results in a high likelihood of cancerous lymph leak. It is unreasonable to expect cancer cells to be progressing within regional lymph nodes and for cancer cells to be absent from within the adjacent lymphatic channels. These lymphatic channels are inevitably transected as a result of the removal of the primary tumor. All of these conditions place the patient at high risk for subsequent progression of peritoneal carcinomatosis.

Whenever there is a high likelihood of peritoneal dissemination, the fact should be documented. In this instance, surgeons should use an intraoperative intraperitoneal chemotherapy wash as an essential part of the cancer surgery. The concept of eradicating the last cancer cell demands not only maximal containment of the primary tumor but also the selective treatment of patients who are at high risk for microscopic residual disease with perioperative intraperitoneal chemotherapy. In summary, clean-up of microscopic residual disease is a responsibility of the competent colorectal cancer surgeon.

Treatment of peritoneal carcinomatosis from colorectal cancer

In patients who have carcinomatosis at the time of colon or rectal cancer resection, surgeons must accept a loss of containment of the primary tumor. However, in a selected group of patients locoregional containment can still be exploited. The successful treatment of peritoneal surface spread of large bowel cancer requires a combined approach that utilizes peritonectomy procedures and perioperative intraperitoneal chemotherapy. In addition, knowledgeable patient selection is mandatory. Both visceral and parietal peritonectomy procedures must be utilized in an attempt to resect all visible evidence of disease [17]. Complete cytoreduction is essential for the treatment of peritoneal surface malignancy to result in long-term survival. Peritonectomy procedures are utilized only in areas of visible implants. Small tumor nodules on the peritoneal surface are removed using electroevaporation. Involvement of the visceral peritoneum requires resection of that portion of the bowel [21]. A complete stripping of all the peritoneum including normal tissue is unnecessary and can result in a high incidence of postoperative complications. If all visible cancer can be removed, then the residual disease can be routinely eradicated by adequate perioperative intraperitoneal chemotherapy.

Laser-mode electrosurgery is necessary for adequate peritonectomy [18]. Removal of peritoneal surface disease using the traditional scissor or knife dissection will unnecessarily disseminate tumor emboli further. Laser-mode electrosurgery leaves a margin of heat necrosis devoid of viable malignant cells. Also, in the absence of laser-mode electrosurgery, profuse bleeding from stripped peritoneal surfaces may occur during the intraperitoneal wash with chemotherapy.

Conceptual changes with the use of chemotherapy for peritoneal carcinomatosis

Changes in the use of chemotherapy in patients with peritoneal carcinomatosis have shown favorable results [22, 24]. A change in the route of drug administration has occurred: chemotherapy is given intraperitoneally rather than intravenously. In this new strategy, intravenous chemotherapy alone is rarely indicated. Also, a change in timing has occurred because chemotherapy begins in the operating room and will continue for the first 5 postoperative days. There has been a change in selection criteria for the treatment of patients with peritoneal carcinomatosis. The lesion size of the peritoneal implant is of crucial importance. Small lesions indicate that treatment has been instituted at an early phase of the intraperitoneal dissemination process. The initiation of these treatments for peritoneal surface malignancy must occur as early as possible in the natural history of the disease to achieve the greatest benefits. A major change now needs to occur in the attitude of oncologists toward this manifestation of large bowel cancer. Peritoneal carcinomatosis may be cured with early application of combined treatments.

Peritoneal-plasma barrier

Intraperitoneal chemotherapy provides a high response at the peritoneal surface of the abdomen and pelvis as a result of the ''peritoneal-plasma barrier.'' Large molecular weight substances such as mitomycin C are confined to the abdominal cavity for long time periods and provide dose-intensive therapy. The area-under-the-curve ratios of intraperitoneal to intravenous exposure are favorable. Table 1 presents the area under the curve (intraperitoneal/intravenous) for the drugs in routine clinical use in patients with peritoneal seeding. In our experience, these include 5-fluorouracil, mitomycin C, doxorubicin, cisplatin, Taxol, and gemcitabine.

Tumor cell entrapment

The author and colleagues have advanced the ''tumor cell entrapment'' hypothesis to explain the rapid progression of peritoneal surface malignancy in patients with microscopic or gross residual disease [19]. This

Table 1 Area-under-the-curve ratios of peritoneal surface exposure to systemic exposure for drugs used to treat intraabdominal cancer

Drug	Molecular weight	Area-under-the-curve ratio
5-Fluorouracil	130	250
Mitomycin C	334	75
Doxorubicin	544	500
Cisplatin	300	20
Taxol	808	1000
Gemcitabine	263	50

theory relates a high incidence and rapid progression of peritoneal implants to entrapment of these tumor cells on traumatized peritoneal surfaces and a progression of the cells fixed at a particular anatomic site through growth factors that are involved in the wound healing process. Reimplantation of malignant cells in patients with peritoneal carcinomatosis into peritonectomized surfaces must be expected unless intraperitoneal chemotherapy is used.

Patient selection for treatment of peritoneal carcinomatosis

The greatest impediment to lasting benefits from peritonectomy procedures and intraperitoneal chemotherapy is improper patient selection. In the past, numerous patients with advanced intraabdominal disease have been treated with minimal benefit. Even with extensive cytoreduction and aggressive intraperitoneal chemotherapy, the patient with gross disease is not likely to receive lasting benefit. Patients who benefit must have minimal disease isolated to peritoneal surfaces so that following peritonectomy, the chemotherapy is only required to eradicate microscopic residual disease. Partial responses are not of great benefit in peritoneal surface malignancies. Complete and lasting responses are reasonable goals. In the natural history of peritoneal carcinomatosis from large bowel cancer, the time for the initiation of treatment has a significant impact on the benefits achieved. Asymptomatic patients with small-volume peritoneal surface malignancy must be selected for treatment.

Quantitative clinical assessments of peritoneal carcinomatosis

The clinically most accurate quantitative assessment of peritoneal carcinomatosis is the peritoneal cancer index [5, 10]. This assessment is a clinical integration of both peritoneal implant size and distribution of peritoneal surface malignancy (Fig. 4). It should be used in the decision-making process as the abdomen is explored. Patients who have a low peritoneal cancer index should undergo cytoreductive surgery with curative intent. Those patients with a high peritoneal cancer index only receive debulking surgery with palliative intent. To arrive at a score, the size of intraperitoneal tumor nodules must be assessed in all of the 13 abdominal and pelvic regions. The lesion size (LS) score should be used. An LS-0 score means that no malignant deposits are visualized; an LS-1 score signifies the presence of tumor nodules less than 0.5 cm (the number of tumor nodules is not scored, only the size of the largest nodule); an LS-2 score signifies the presence of tumor nodules between 0.5 and 5.0 cm. An LS-3 score signifies tumor nodules >5.0 cm in any dimension. In addition, confluence or layering of tumor within an abdominal or pelvic region indicates an LS-3 score. An LS score is determined for each of the 13 regions. The summation of the lesion size scores in each of the 13 abdomino-pelvic regions is the peritoneal cancer index for that patient. A maximum score is 39 or 13×3.

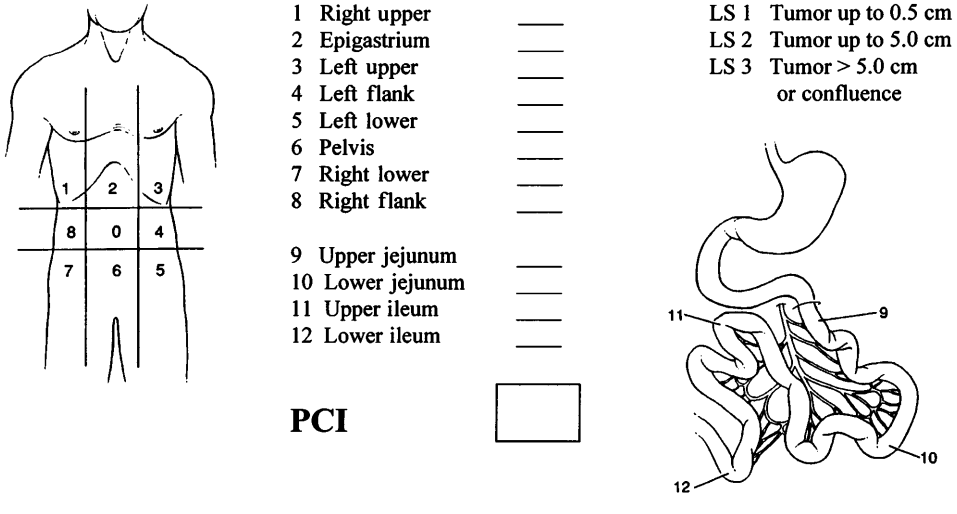

Fig. 4 Peritoneal cancer index is determined after the abdominal exploration is complete. It assists in making a surgical judgement to proceed or not with an attempt at complete cytoreduction

One caveat concerning scoring of the peritoneal cancer index should be mentioned. If cancer is found at a crucial anatomic site in which cytoreduction is impossible, then the patient will have a poor prognosis despite a low peritoneal cancer index. Invasion of the base of the bladder or unresectable disease on a pelvic side wall may by itself result in residual invasive cancer even after maximal cytoreduction. Unresectable cancer at numerous sites along the surface of the small bowel will also confer a poor prognosis. Thus invasive cancer at a crucial anatomic site may function as a systemic disease equivalent in assessing prognosis. Since long-term survival can only be achieved in patients in whom complete cytoreduction is carried out, residual disease at crucial anatomic sites may cause the surgeon to select palliative debulking rather than potentially curative cytoreduction despite a favorable peritoneal cancer index score.

Completeness of cytoreduction score

The second assessment used to measure prognosis with peritoneal carcinomatosis from large bowel cancer is the completeness of cytoreduction (CC) score. This information is of less value to the surgeon in planning treatment than the peritoneal cancer index. The CC score is not available until after cytoreduction is complete rather than as the abdomen is being explored. However, if during exploration it becomes obvious that cytoreduction will not be complete, surgeons may decide that palliative debulking will provide symptomatic relief and less surgical risk. In other words, it would be inappropriate to continue with an aggressive cytoreduction. The CC score is the major prognostic indicator in treating large bowel cancer dissemination to peritoneal surfaces.

In scoring the CC, the likelihood of effective chemotherapy must be considered. A CC-0 score indicates that no peritoneal seeding was exposed during the complete exploration. A CC-1 score indicates that the tumor nodules persisting after cytoreduction are <2.5 mm. This is the nodule size thought to be penetrable by intraperitoneal chemotherapy. Therefore a CC-0 or CC-1 cytoreduction is designated as a complete cytoreduction. A CC-2 score indicates tumor nodules between 2.5 mm and 2.5 cm. A CC-3 score indicates tumor nodules >2.5 cm or confluence of unresectable tumor nodules at any site within the abdomen or pelvis. CC-2 and CC-3 cytoreduction scores are considered incomplete cytoreduction (Fig. 5).

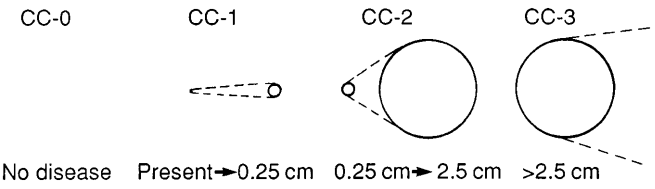

Fig. 5 Completeness of cytoreduction assessment is performed after the maximal surgical effort has been completed

Current methodology for delivery of heated intraoperative intraperitoneal chemotherapy

In the operating room, heated intraoperative, intraperitoneal mitomycin C chemotherapy is used for patients with peritoneal carcinomatosis from colorectal cancer. Heat is part of the optimizing process and is used to bring as much dose intensity to the abdominal and pelvic surfaces as possible. Hyperthermia with intraperitoneal mitomycin C chemotherapy has several advantages. First, heat has more toxicity for cancerous tissue than it does for normal tissue. Temperatures $>43°C$ can be directly cytotoxic to cancerous tissue. This predominant effect on cancer increases as the vascularity of the malignancy decreases. Second, hyperthermia increases the penetration of chemotherapy into tissues. As tissues soften in response to heat, the elevated interstitial pressure of a tumor mass decreases and allows improved drug penetration. Third, and probably most important, heat increases the cytotoxicity of mitomycin C chemotherapy. This synergism occurs only at the interface of heat and body tissue at the peritoneal surface. The synergy is not produced at systemic sites within the body. The rationale for using heated intraperitoneal mitomycin C chemotherapy as a surgically directed modality in the operating room is presented in Table 2.

After the cancer resection is complete, the Tenckhoff catheter and closed-suction drains are placed through the abdominal wall and made watertight with a purse string suture at the skin. Temperature probes are directed into the abdomen and pelvis and are secured to the skin edge. Using a running no. 2 monofilament suture, the skin edges are secured to the self-retaining retractor. A plastic sheet is incorporated into these sutures to create a covering for the abdominal cavity. A slit in the plastic cover is made to allow the surgeon's double-gloved hand access to the abdomen and pelvis (Fig. 6). During the 90 min of perfusion, all the anatomic structures within the peritoneal cavity are uniformly exposed to heat and chemotherapy. The surgeon vigorously manipulates all the viscera to keep adherence of peritoneal surfaces to a minimum. Roller pumps force

Table 2 Rationale for the use of heated intraoperative intraperitoneal chemotherapy

Heat increases drug penetration into tissue
Heat increases the cytotoxicity of selected chemotherapy agents
Heat has an antitumor effect by itself
Intraoperative chemotherapy allows manual distribution of drug and heat uniformly to all surfaces of the abdomen and pelvis
Renal toxicities of chemotherapy given in the operating room can be avoided by careful monitoring of urine output during chemotherapy perfusion
The time that elapses during the heated perfusion allows a normalization of many parameters (temperature, blood clotting, hemodynamics, etc.)

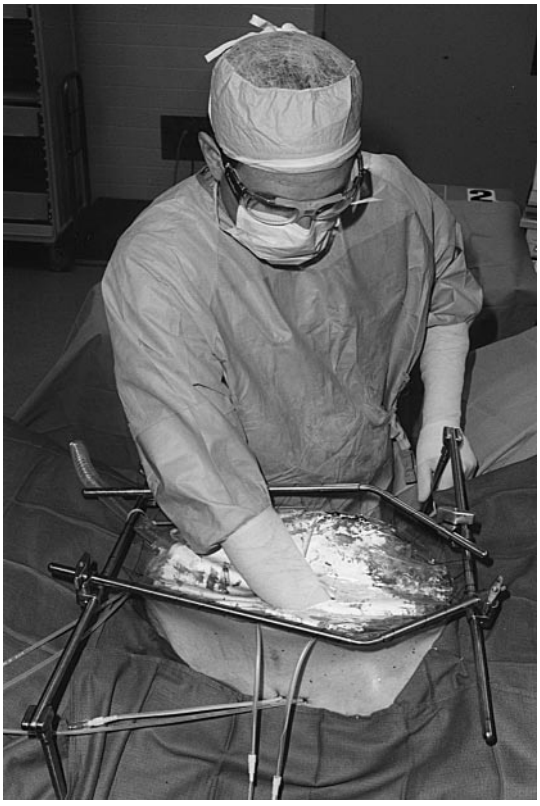

Fig. 6 Coliseum technique for the delivery of heated intraoperative intraperitoneal chemotherapy. The surgeon manually separates all surfaces to maintain uniformity of heat and chemotherapy throughout the abdomen and pelvis and is required to "scrub" all surfaces to eliminate all adherent fibrin and blood clot

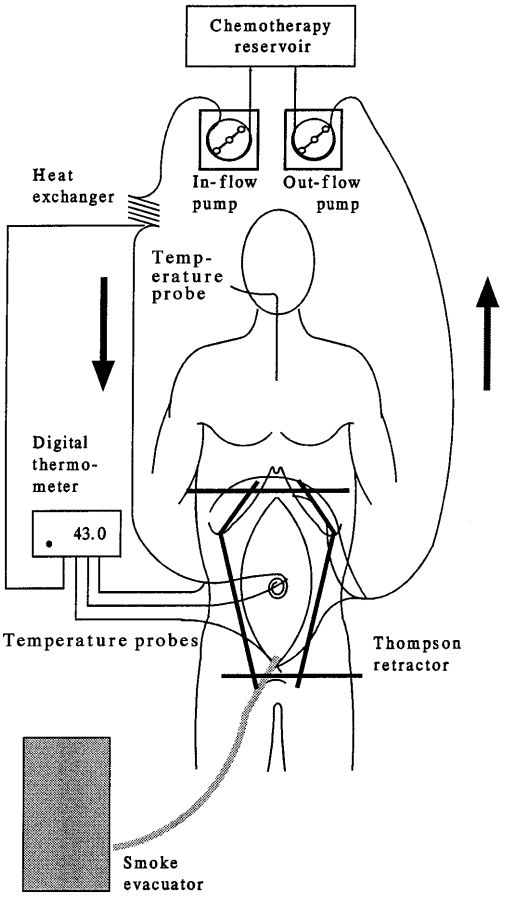

Fig. 7 Apparatus required for heated intraoperative intraperitoneal chemotherapy

the chemotherapy solution into the abdomen through the Tenckhoff catheter and pull it out through the drains. The heat exchanger keeps the fluid infused at 44°C to 46°C so that the intraperitoneal fluid is maintained at 42°C to 43°C. The apparatus used for administering the heated intraoperative intraperitoneal chemotherapy is diagrammed in Fig. 7. The smoke evacuator is used to pull air from beneath the plastic cover through activated charcoal, preventing contamination of air in the operating room by chemotherapy aerosols.

After the intraabdominal heated chemotherapy with mitomycin C is complete, the abdomen is suctioned dry of fluid. The abdominal wall is then reopened and the retractors repositioned prior to reconstructive surgery. It should be reemphasized that no suture lines are constructed until after the chemotherapy perfusion is complete. The standardized orders for heated intraoperative, intraperitoneal mitomycin C chemotherapy are given in Table 3.

Immediate postoperative abdominal lavage

In patients with peritoneal carcinomatosis from large bowel cancer, early postoperative intraperitoneal 5-fluorouracil is always recommended. The catheters that were positioned for intraoperative chemotherapy for drug instillation and abdominal drainage must be kept clear of blood clots and tissue debris. To accomplish this, an abdominal lavage is started in the operating room. This lavage utilizes the same tubes and drains that were positioned for heated intraoperative, intraperitoneal chemotherapy. Large volumes of fluid are rapidly

Table 3 Standardized orders for heated intraoperative intraperitoneal chemotherapy

Mitomycin Orders	
1.	For adenocarcinoma from appendiceal, colonic, rectal, gastric, and pancreatic cancer add mitomycin C _____ mg to 2 L of 1.5% peritoneal dialysis solution
2.	Dose of mitomycin C for men 12.5 mg/m^2, for women 10 mg/m^2
3.	Use a 33% dose reduction for heavy prior chemotherapy, marginal renal function, age >60 years, extensive intraoperative trauma to small bowel surfaces, or prior radiotherapy
4.	Send 1 L of 1.5% peritoneal dialysis solution to test the perfusion circuit
5.	Send 1 L of 1.5% peritoneal dialysis solution for immediate postoperative lavage
6.	Send the above to operating room _____ at _____AM/PM

infused and then drained from the abdomen after a short dwell time. The standardized orders for immediate postoperative abdominal lavage are given in Table 4. All intraabdominal catheters are withdrawn before the patient is discharged from the hospital.

Early postoperative intraperitoneal 5-fluorouracil

The standardized orders for early postoperative intraperitoneal 5-fluorouracil are presented in Table 5. After the patient stabilizes postoperatively and after the drainage from the immediate postoperative abdominal lavage is no longer bloodstained, the 5-fluorouracil instillation begins. In some patients who have extensive small bowel trauma from lysis of adhesions, the early postoperative 5-fluorouracil is withheld for fear of fistula formation. During the first 6 h of intraperitoneal 5-fluorouracil administration, the patient turns every 30 min from the right to left side to maximize drug distribution through gravitational effects.

Table 4 Immediate postoperative abdominal lavage

Day of operation:
1. Run in 1000 mL 1.5% dextrose peritoneal dialysis solution as rapidly as possible Warm to body temperature prior to instillation; clamp all abdominal drains during infusion
2. No dwell time
3. Drain as rapidly as possible through the Tenckhoff catheter and abdominal drains
4. Repeat irrigations every 1 h for 4 h, then every 4 h until returns are clear; then every 8 h until chemotherapy begins
5. Change dressing at Tenckhoff catheter and abdominal drain skin sites using sterile technique once daily and as necessary
6. Standardized precautions must be used for all body fluids from this patient

Table 5 Early postoperative intraperitoneal chemotherapy with 5-fluorouracil

Postoperative days 1–5
1. Add to _____ mL of 1.5% dextrose peritoneal dialysis solution: (a) _____ mg 5-fluorouracil (650 mg/m^2, maximal dose 1300 mg) (b) 50 mEq sodium bicarbonate
2. Intraperitoneal fluid volume: 1 L for patients < 2.0 m^2, 1.5 L for > 2.0 m^2
3. Drain all fluid from the abdominal cavity prior to instillation, then clamp abdominal drains
4. Run the chemotherapy solution into the abdominal cavity through the Tenckhoff catheter as rapidly as possible; dwell for 23 h and drain for 1 h prior to next instillation
5. Use gravity to maximize intraperitoneal distribution of the 5-fluorouracil; instill the chemotherapy with the patient in a full right lateral position; after 1/2 h, direct the patient to turn to the full left lateral position; change position right to left every 1/2 h; if tolerated, use 10 degrees of Trendelenburg position; continue turning for the first 6 h after instillation of chemotherapy solution
6. Continue to drain abdominal cavity after final dwell until Tenckhoff catheter is removed
7. Use 33% dose reduction for heavy prior chemotherapy, age > 60 years, or prior radiotherapy

Reoperative surgery after cytoreduction with intraperitoneal chemotherapy

Patients who have not had prior 5-fluorouracil treatments are maintained on systemic chemotherapy after discharge from the hospital. After approximately 6 months of systemic 5-fluorouracil chemotherapy, the patient is recommended for a second-look procedure [4]. At the time of second-look surgery, the abdomen is widely opened and all the peritoneal surfaces are visualized with a complete takedown of all adhesions. Additional cytoreduction is performed and additional visceral peritonectomies may be required. If a CC-0 or CC-1 cytoreduction can be achieved, then heated intraoperative, intraperitoneal chemotherapy is used again. Early postoperative intraperitoneal 5-fluorouracil is also recommended after the reoperation. In some patients, the disease may suggest a "chemotherapy failure." In this situation, a change in the drugs used for intraperitoneal chemotherapy is recommended. Usually a regimen of intraperitoneal cisplatin and doxorubicin is utilized.

Clinical tesults of treatment of colorectal carcinomatosis

To date, approximately 100 patients with peritoneal carcinomatosis from colon cancer have been treated using the above-described methods. The clinical pathway currently utilized to treat these patients is shown in Fig. 8 [4]. In patients with peritoneal carcinomatosis from colon cancer, a peritoneal cancer index must be determined after complete exploration of the abdomen and pelvis. In clinical studies of peritoneal carcinomatosis from colon cancer, a peritoneal cancer index of ≤ 10 was associated with a 5-year survival rate of 50%, an index of 11–20 with a 5-year survival rate of 20%, and an index of > 20 with a 5-year survival rate of 0%. Figure 9 shows the Kaplan-Meier survival curves for these three groups of patients. The P value for the low peritoneal cancer index scores versus high peritoneal cancer index scores is $P < 0.0001$. The value of the peritoneal cancer index as a selection tool in this patient population is obvious.

In patients who had complete cytoreduction, there was a marked improvement in survival. Patients with residual disease showed the expected short survival of patients with peritoneal carcinomatosis (Fig. 10). These data suggest an early aggressive approach to peritoneal surface spread of adenocarcinoma of the colon and rectum in selected patients. Patients with positive lymph nodes at the time of resection of the primary cancer have a less favorable prognosis but 15% may enjoy prolonged survival [20].

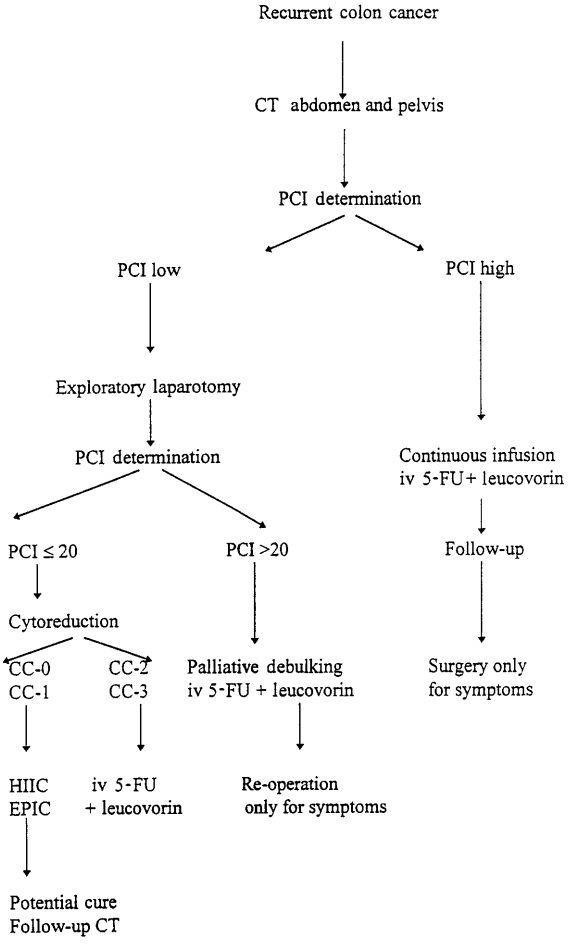

Fig. 8 Clinical pathway used to treat patients with peritoneal carcinomatosis from colon cancer

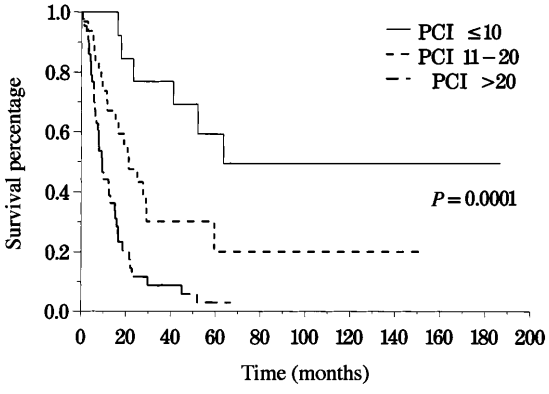

Fig. 9 Survival of patients with peritoneal carcinomatosis from colon or rectal cancer by peritoneal cancer index

Patient care considerations

The major detrimental side effect of combined cytoreductive surgery and intraperitoneal chemotherapy is prolonged ileus. Patients may have a nasogastric tube in place with large volumes of secretions being aspirated from the stomach for 2–4 weeks postoperatively. For this reason, parenteral feeding is recommended for all of these patients. The length of time required for nasogastric suctioning is dependent upon the extent of peritonectomy and the extent of prior abdominal adhesions that required lysis.

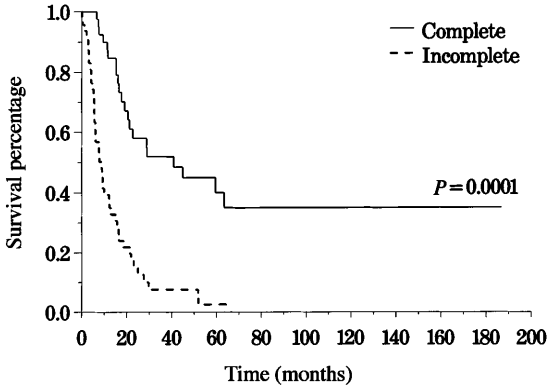

Fig. 10 Survival of patients by complete (CC-0 and CC-1) versus incomplete (CC-2 and CC-3) cytoreduction

The most life-threatening postoperative complication is small bowel fistula. Usually, these are sidewall perforations of the small bowel but occasionally a colon or stomach perforation occurs. Patients need to be aware of the possibility of fistula formation before cytoreductive surgery and intraperitoneal chemotherapy are contemplated. The incidence of anastomotic leak is very low.

The morbidity rate of cytoreductive surgery and intraperitoneal chemotherapy for colon cancer is approximately 25%, and the mortality rate is 1.5%. Mortality is usually related to neutropenia which can occur from overly aggressive use of intraperitoneal 5-fluorouracil. In some patients who are aged >60 years old and have received heavy prior systemic chemotherapy and prior radiation therapy a dose reduction of the intraperitoneal 5-fluorouracil must be made [16].

Ethical considerations in treating peritoneal carcinomatosis from colon and rectal cancer

Currently, the phase II studies that show benefit in the prevention or treatment of peritoneal carcinomatosis demand that patients be treated. Patients recommended

Table 6 Patients with colorectal cancer recommended for perioperative intraperitoneal chemotherapy

Positive peritoneal cytology
Ovarian involvement
Peritoneal seeding on the serosal surface of the colon
Rupture of a necrotic tumor mass
Adjacent organ involvement
Intraoperative tumor spill
Perforation of the primary tumor
Involved lymph nodes at the margin of excision
Limited peritoneal seeding with a peritoneal cancer index of <20
Limited peritoneal seeding so that complete cytoreduction can be achieved

for treatment are those identified in Table 6. Until clinical trials have been initiated, we also recommend that patients with bulky lymph node metastases or lymphatic dissemination that continues to the superior mesenteric vein or aorta should be treated. The likelihood of tumor spill as a result of cancer cells leaking from lymphatic channels is so great that these low-morbidity/mortality treatments need to be initiated.

In patients with potentially curable large bowel cancer, intraperitoneal chemotherapy treatments should only be initiated as Institutional Review Board-approved, randomized, controlled studies. There is a strong rationale for treatment of patients with advanced malignancy, especially those in whom major surgical trauma is required for resection, i.e., have large tumors at the hepatic flexure, splenic flexure, or within the pelvis.

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