Special Article

Review of a Personal Experience in the Management of Carcinomatosis and Sarcomatosis

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Background: Peritoneal surface malignancy can result from seeding of gastrointestinal cancer or abdomino-pelvic sarcoma; it can also occur as a primary disease, such as peritoneal mesothelioma. In the past, this clinical situation was treated only with palliative intent.

Methods: An aggressive approach to peritoneal surface malignancy involves peritonectomy procedures, perioperative intraperitoneal chemotherapy and knowledgeable patient selection. The clinical assessments necessary for valid clinical judgements include the cancer histopathology (invasive vs expansive progression), the preoperative abdominal and pelvic CT, the peritoneal cancer index and the completeness of cytoreduction score. Proper patient selection is mandatory for optimizing the results of treatment.

Results: In a series of phase II studies, appendiceal tumors with peritoneal seeding became the paradigm for success with an 85% long-term survival in selected patients. Carcinomatosis from colon cancer had an overall 5-year survival of 50% with selected patients. Also, sarcomatosis patients overall had a 40% 5-year survival in selected patients. Peritoneal mesothelioma showed a 36% 5-year survival. In all malignancies, early aggressive treatment of minimal peritoneal surface dissemination showed the greatest benefit.

Conclusions: Oncologists must accept responsibility for knowledgeable management of peritoneal surface dissemination of cancer because a curative approach has been demonstrated in large phase II studies and all historical controls show 0% long-term survival. Adjuvant phase III studies with perioperative intraperitoneal chemotherapy in diseases where peritoneal surface spread occurs are indicated.

Key words: carcinomatosis – sarcomatosis – intraperitoneal chemotherapy – peritonectomy procedures – peritoneal mesothelioma

INTRODUCTION

Oncology has evolved from the treatment of primary cancer to include the management of metastatic disease. For gastrointestinal cancer, early success with this new concept occurred with reoperative surgery of locally recurrent colon and rectal cancer (1,2). Next, the resection of liver metastases from colon cancer proved to be of benefit in a selected group of patients (3). Extension of the concept of complete surgical eradication of metastatic disease to bring about long-term survival to patients with peritoneal surface malignancy has been pioneered by our group (4,5). This review presents the background, the standardized treatments currently in use and the selection factors leading to long-term survival with acceptable morbidity and mortality. It discusses the treatment of peritoneal surface dissemination of appendix cancer and pseudomyxoma peritonei, colon cancer, gastric cancer and abdomino-pelvic sarcoma (6). A brief presentation of the palliation of debilitating ascites is included.

PRINCIPLES OF MANAGEMENT

The successful treatment of peritoneal surface malignancy requires a combined approach that utilizes peritonectomy procedures and perioperative intraperitoneal chemotherapy. To balance properly the risks and benefits, knowledgeable patient selection is mandatory. Both visceral and parietal peri-

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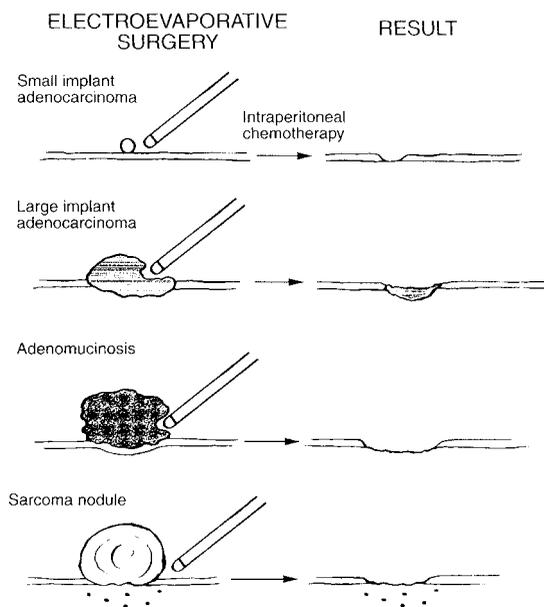
Figure 1. Electroevaporative surgery is used to remove visible evidence of cancerous implants from peritoneal surfaces. Success depends on the invasive character and size of the implant.

tonectomies are necessary for complete cytoreduction, which is essential for treatment to result in long-term survival. Between one and six peritonectomy procedures may be required (7,8). Their utilization depends on the distribution, volume and depth of invasion of the malignancy disseminated within the peritoneal space. The question of when to pursue potentially curative cytoreduction and when to accept palliative debulking as the proper strategy may present difficult judgements.

RATIONALE FOR PERITONECTOMY PROCEDURES

Peritonectomy procedures are necessary if one is to successfully treat peritoneal surface malignancies with curative intent. Peritonectomy procedures are used in the areas of visible cancer nodules in an attempt to leave the patient with only microscopic residual disease (Fig. 1). Small tumor nodules are removed using electroevaporation (9). Invasion of visceral peritoneum by larger tumor nodules requires resection of a portion of the stomach, small intestine or colorectum.

INTRAPERITONEAL CHEMOTHERAPY

CONCEPTUAL CHANGES WITH INTRAPERITONEAL CHEMOTHERAPY

Changes in the use of chemotherapy in patients with peritoneal carcinomatosis and peritoneal sarcomatosis have occurred and improved the results of treatment. A change in route of drug administration has occurred. Chemotherapy is given intraperitoneally or by combined intraperitoneal and intravenous routes. Also, a change in timing has occurred in that chemotherapy begins in the operating room and may be continued for the first five postoperative days. Third, a change in selection criteria for treatment of abdominal and pelvic malignancies has occurred. With the non-aggressive peritoneal surface malignancies as an exception, the extent of peritoneal surface disease is of crucial importance. Patients with small-size peritoneal tumor nodules that have a limited distribution within the abdomen and pelvis are most likely to receive prolonged benefit. Complete cytoreductive surgery is necessary prior to the intraperitoneal chemotherapy instillation and this is unlikely for advanced carcinomatosis or sarcomatosis. Aggressive treatment strategies for an advanced and invasive intraperitoneal malignancy will not produce long-term benefits and are often the cause of excessive morbidity and mortality. Treatments to eradicate established seeding must be initiated as early as is possible in the natural history of these diseases in order to achieve the greatest benefits. Optimally, cytoreduction and intraperitoneal chemotherapy should be considered in the management of the primary cancer.

PERITONEAL PLASMA BARRIER

Intraperitoneal chemotherapy gives high response rates with microscopic residual disease within the abdomen and pelvis because the 'peritoneal plasma barrier' provides dose-intensive therapy (10). High molecular weight cytotoxic drugs, such as mitomycin C, are confined to the abdominal cavity for long time periods (11). This means that the exposure of peritoneal surfaces to pharmacologically active molecules can be increased considerably by giving the drugs via the intraperitoneal route rather than the intravenous route.

For the chemotherapy solutions used to treat peritoneal carcinomatosis, 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 studies, these include 5-fluorouracil, mitomycin C, doxorubicin, cisplatin, paclitaxel and gemcitabine.

One should not assume that the intraperitoneal administration of chemotherapy eliminates their systemic toxicities. Although the drugs are sequestered within the peritoneal space, they eventually are cleared into the systemic circulation. For this reason, the safe doses of most drugs instilled into the peritoneal cavity are similar to the intravenous dose. The exceptions are drugs with hepatic metabolism, such as 5-fluorouracil. An increased dose of ~50% is usually possible

Table 1. 'Area under the curve' (AUC) ratios of peritoneal surface exposure to systemic exposure for drugs used to treat intra-abdominal cancer

Drug	Molecular weight (Da)	AUC ratio
5-Fluorouracil	130	250
Mitomycin C	334	75
Doxorubicin	544	500
Cisplatin	300	20
Paclitaxel	808	1000
Gemcitabine	263	50

with 5-fluorouracil. The dose for a 5-day course of intravenous 5-fluorouracil is ~500 mg/m^2; for intraperitoneal 5-fluorouracil, the dose is 750 mg/m^2 per day. This considerable (50%) increase in the dose of 5-fluorouracil is of great advantage in an attempt to eradicate peritoneal carcinomatosis in patients with colorectal cancer.

TUMOR CELL ENTRAPMENT

The 'tumor cell entrapment' hypothesis explains the inevitable progression of malignancy in patients who undergo treatment of peritoneal surface cancer using surgery alone. This theory relates the high incidence and rapid progression of peritoneal surface implantation to (1) free intraperitoneal tumor emboli, (2) fibrin entrapment of intra-abdominal tumor emboli on traumatized peritoneal surfaces and (3) progression of entrapped tumor cells through growth factors involved in the wound healing process. These phenomena may cause a high incidence of surgical treatment failure in patients treated for primary gastrointestinal cancer (11). The reimplantation of malignant cells into peritonectomized surfaces in a reoperative setting must be expected unless perioperative intraperitoneal chemotherapy is used.

Chemotherapy employed in the perioperative period not only directly destroys tumor cells but also eliminates viable platelets, white blood cells and monocytes from the peritoneal cavity. This diminishes the promotion of tumor growth associated with the wound-healing process. Intraperitoneal chemotherapy should eliminate local recurrence and peritoneal surface recurrence. Removal of the leukocytes and monocytes also decreases the ability of the abdomen to resist an infectious process. For this reason, strict aseptic technique is imperative when administering the chemotherapy or handling abdominal tubes and drains.

PRIOR LIMITED BENEFITS WITH INTRAPERITONEAL CHEMOTHERAPY

In the past, the use of intraperitoneal chemotherapy had limited success and infrequent use by oncologists. There have been two major impediments to greater benefits. Intracavitary instillation allows very limited penetration of drug into tumor nodules. Only the outermost layer (~1 mm) of a cancer nodule is

penetrated by the chemotherapy. This means that only minute tumor nodules can be definitively treated. In prior work oncologists attempted to treat patients with established disease, a group of patients which caused disappointment in results with intraperitoneal drug use. Microscopic residual disease is the ideal target for intraperitoneal chemotherapy protocols.

A second cause for limited success with intraperitoneal chemotherapy was a non-uniform drug distribution. A majority of patients treated by drug instillation into the abdomen or pelvis had prior surgery, which invariably causes scarring between peritoneal surfaces. The adhesions create multiple barriers to the free access of fluid. Although the instillation of a large volume of fluid will partially overcome the problems created by adhesions, some surface areas will have no access to chemotherapy. Limited access from adhesions was impossible to predict and increased with repeated instillations of chemotherapy solutions.

Non-uniform drug distribution after surgery may result from fibrin entrapment. Surgery causes fibrin deposits on surfaces that have been traumatized by the cancer resection. Free intraperitoneal cancer cells become trapped within the fibrin. The fibrin is infiltrated by platelets, neutrophils and monocytes as part of the wound healing process. As collagen is laid down, the tumor cells are entrapped within scar tissue. The scar tissue is dense and poorly penetrated by intraperitoneal chemotherapy.

Finally, non-uniform distribution was caused by gravity. In a supine patient intraperitoneal fluid does not uniformly distribute itself to anterior and lateral peritoneal surfaces. Gravity pulls the fluid to dependent portions of the abdomen, especially the pelvis, paracolic gutters and the right retrohepatic space. Unless the patient actively pursues frequent changes in position or the surgeon manually distributes the chemotherapy solution intraoperatively, the surfaces between bowel loops and the anterior abdominal wall will remain relatively untreated.

PATIENT SELECTION FOR TREATMENT

The greatest impediment to lasting benefits from intraperitoneal chemotherapy should be attributed to improper patient selection. A great number of patients with advanced intra-abdominal disease have been treated with minimal benefit. Even with extensive cytoreductive surgery and aggressive intraperitoneal chemotherapy, the patient with advanced disease is not likely to experience a lasting benefit. Rapid recurrence of intraperitoneal cancer combined with progression of lymph nodal or systemic disease are likely to interfere with long-term survival in these patients. Patients that benefit must have minimal residual disease isolated to peritoneal surfaces that have access to chemotherapy so that complete eradication of disease can occur. In the natural history of carcinomatosis and sarcomatosis the time of the initiation of treatment has a great bearing on the benefits achieved. Patients need to be definitively treated when the diagnosis of peritoneal surface malignancy is first made. Small-volume peritoneal surface

malignancy must be selected for intraperitoneal chemotherapy protocols.

CLINICAL ASSESSMENTS OF PERITONEAL SURFACE MALIGNANCY

In the past, peritoneal surface cancer was considered to be a fatal disease process. For example, with adenocarcinoma the only assessment used was either carcinomatosis present (with a presumed fatal outcome) or carcinomatosis absent (with curative treatment options available). Currently, there are four important clinical assessments of peritoneal surface malignancy that need to be used to select patients who will benefit from treatment protocols: (1) histopathology to assess the invasive character of the malignancy; (2) preoperative CT scan of chest, abdomen and pelvis; (3) the peritoneal cancer index; and (4) the completeness of cytoreduction score.

HISTOPATHOLOGY TO ASSESS INVASIVE CHARACTER

The biological aggressiveness of a peritoneal surface malignancy will have a profound influence on its treatment options. Non-invasive tumors may have a large volume of disease extensively distributed on peritoneal surfaces and yet be completely resectable by peritonectomy procedures. Also, these non-invasive malignancies are unlikely to metastasize by lymphatics to lymph nodes and by the blood to liver and other systemic sites. Therefore, treatment by cytoreductive surgery and intraperitoneal chemotherapy may have a curative intent in patients with a large mass of widely disseminated pseudomyxoma peritonei and cystic peritoneal mesothelioma (12). Pathology review and an assessment of the invasive vs non-aggressive nature of a colonic malignancy are essential to treatment planning.

PREOPERATIVE CT SCAN

A preoperative CT scan of the chest, abdomen and pelvis with maximal oral and intravenous contrast is of great value in planning treatments for peritoneal surface malignancy. Systemic metastases can be clinically excluded and pleural surface spread ruled out. Unfortunately, the CT scan should be regarded as an inaccurate test by which to quantify the intestinal type of peritoneal carcinomatosis from adenocarcinoma. The malignant tissue progresses on the peritoneal surfaces and its shape conforms to the normal contours of the abdomino-pelvic structures. This is different from the metastatic process in the liver or lung, which progresses as three-dimensional tumor nodules and can be accurately assessed by CT (13).

However, the CT scan has been of great help in quantifying mucinous adenocarcinoma within the peritoneal cavity (14). These tumors produce copious colloid material that is readily distinguished from normal structures by shape and by density. Using two distinctive radiological criteria, those patients with resectable mucinous peritoneal carcinomatosis can be distinguished from those with non-resectable malignancy. This keeps patients who are unlikely to benefit from reoperative

surgery from undergoing cytoreductive surgical procedures. The two radiological criteria found to be most useful are (1) segmental obstruction of small bowel and (2) the presence of tumor nodules >5 cm in diameter on small bowel surfaces or directly adjacent to small bowel mesentery.

These criteria reflect radiologically the biology of the mucinous adenocarcinoma. Obstructed segments of bowel signal an invasive character of malignancy on small bowel surfaces that would be surgically impossible to be completely cytoreduced. Mucinous cancer on small bowel or small bowel mesentery indicates that the mucinous cancer is no longer redistributed.

PERITONEAL CANCER INDEX

The third assessment of peritoneal surface malignancy is the peritoneal cancer index. This is a clinical integration of both peritoneal implant size and distribution of peritoneal surface malignancy (Fig. 2). It should be used in the decision-making process as the abdomen is explored. To arrive at a score, the size of intraperitoneal nodules must be assessed. The lesion size (LS) score should be used. An LS-0 score means that no malignant deposits are visualized in a particular abdomino-pelvic region. An LS-1 score signifies tumor nodules <0.5 cm present. The number of nodules is not scored; only the size of the largest nodules is scored. An LS-2 score signifies tumor nodules between 0.5 and 5.0 cm present. LS-3 signifies tumor nodules >5.0 cm in any dimension present. If there is a confluence or layering of tumor, the lesion size is scored as 3.

In order to assess the distribution of peritoneal surface disease, the abdomino-pelvic regions are utilized. For each of these 13 regions, an LS score is determined. The summation of the LS score in each of the 13 abdomino-pelvic regions is the peritoneal cancer index for that patient. A maximum score is 39 (13×3).

The peritoneal cancer index has been validated to date in several clinical situations. Gomez-Portilla et al. showed that the peritoneal cancer index could be used to predict long-term survival in patients with peritoneal carcinomatosis from colon cancer having a second cytoreduction (15). Berthet et al. showed that the peritoneal cancer index predicted benefits for treatment of peritoneal sarcomatosis from recurrent visceral or parietal sarcoma (16). In both clinical studies, the patients with a favorable prognosis had a score of <12. Sugarbaker reported a survival of 50% in colon cancer patients with carcinomatosis and a peritoneal cancer index of ≤10 (17). Sebbag et al. showed that the peritoneal cancer index predicted treatment benefits in patients with peritoneal mesothelioma (18).

There are some caveats in the use of the peritoneal cancer index. First, non-invasive malignancy on peritoneal surfaces, even though great masses of tumor have occurred, may be completely cytoreduced. Diseases such as pseudomxyoma peritonei, grade I sarcoma and minimally invasive peritoneal mesothelioma are in this category. With these tumors the status of the abdomen and pelvis after cytoreduction may have no relationship to the status at the time of abdominal exploration. In other words, even though the surgeons may find an abdo-
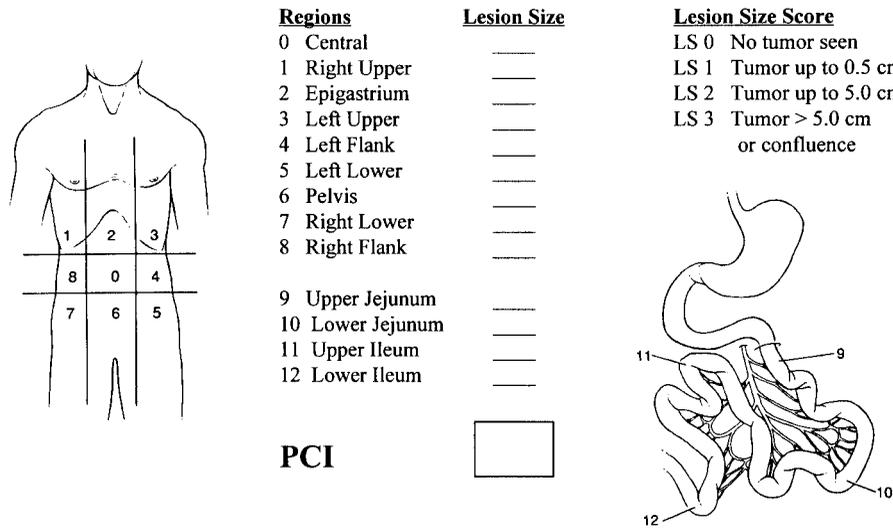
Peritoneal Cancer Index

Figure 2. Peritoneal cancer index is a composite score of lesion size 0–3 in abdomino-pelvic regions 0–12.

men with a peritoneal cancer index of 39, it can be converted to an index of 0 by cytoreduction. In these diseases, the prognosis will only be related to the condition of the abdomen after the cytoreduction.

A second caveat for the peritoneal cancer index is invasive cancer at crucial anatomical sites. For example, invasive cancer not resectable from the common bile duct will cause a poor prognosis despite a low peritoneal cancer index. Also, invasive cancer implants at numerous sites along the small bowel will confer a poor prognosis. Invasive cancer at crucial anatomical sites may function as systemic disease in assessing prognosis with invasive cancer. Long-term survival cannot occur in patients with an incomplete cytoreduction, even if there was favorable score with the peritoneal cancer index.

COMPLETENESS OF CYTOREDUCTION SCORE

The final assessment to be used to assess prognosis with peritoneal surface malignancy is the completeness of cytoreduction (CC) score. This information is of less value to the surgeon in planning treatments than the peritoneal cancer index. The CC score is not available until after the cytoreduction is complete, rather than as the abdomen is being explored. If, during exploration while determining the peritoneal cancer index, it becomes obvious that cytoreduction will be incomplete, the surgeon may decide that a palliative debulking that will provide symptomatic relief is appropriate and may discontinue plans for an aggressive cytoreduction with intraperitoneal chemotherapy. In both non-invasive and invasive peritoneal surface malignancy, the CC score is a major prognostic indicator. It has been shown to function with accuracy in pseudomyxoma peritonei, colon cancer with peritoneal

carcinomatosis, sarcomatosis and peritoneal mesothelioma (15–18).

The size of peritoneal implants used to determine the CC score may vary with the histology of the peritoneal surface malignancy. Chemotherapy-responsive malignancies, such as ovarian cancer, may be eradicated even though visible tumor nodules remain after cytoreduction. For gastrointestinal cancer, the CC score has been defined as follows. A CC-0 score indicates that no peritoneal seeding was exposed during the complete exploration. A CC-1 score indicates that tumor nodules persisting after cytoreduction are <2.5 mm in diameter. This is a nodule size thought to be penetrable by intracavity chemotherapy and would, therefore, be designated a complete cytoreduction. A CC-2 score indicates tumor nodules between 2.5 mm and 2.5 cm in diameter. A CC-3 score indicates tumor nodules >2.5 cm in diameter or a confluence of unresectable tumor nodules at any site within the abdomen or pelvis. CC-2 and CC-3 cytoreductions are considered incomplete cytoreduction.

PATIENT SELECTION FOR PALLIATIVE SURGERY

Although some patients with peritoneal surface spread of invasive abdominal and pelvic cancer can be treated with a curative approach using cytoreductive surgery and intraperitoneal chemotherapy, others have incurable recurrent malignancy. These patients will often have life-threatening complications prior to a terminal event. The cause of great suffering and eventual death is often intestinal obstruction and the complications that this condition may initiate (starvation, fistula formation, abscess and intestinal perforation). The options available to the surgeon to help alleviate adverse symptoms are many.

Table 2. Stop signals for surgical palliation (debulking) of advanced primary or recurrent gastrointestinal cancer

1	Poor operative risk so that the patient is unlikely to survive the operation
2	Liver metastasis or clinical evidence of distant disease
3	Inability to clear the primary tumor mass
4	Inability to re-establish gastrointestinal function because of extensive peritoneal seeding

Stop signals 1 and 2 are established preoperatively. Stop signals 3 and 4 are determined after the abdomen has been explored.

Table 3. Clinical features that suggest selection of aggressive vs conservative surgical approach

	Aggressive resection indicated	Conservative approach favored
Histological grade	Low	High
History of peritoneal seeding	Absent	Present
CT shows shortening of the bowel mesentery	Unlikely	Likely
CT shows multiple sites of segmental intestinal obstruction	Unlikely	Likely
CT shows tumor nodules >5 cm associated with small bowel	Unlikely	Likely
Large localized cancer recurrence	Likely	Unlikely
Operative risk	Low	High
Short interval between surgeries	Unlikely	Likely
Mucinous ascites	Likely	Unlikely
Serous or bloody ascites	Unlikely	Likely

CT = computed tomography.

Selection of the treatment that offers the proper risks and benefits can be one of the most difficult of all surgical judgements. For example, some 10–30% of patients with progressive colorectal cancer who develop intestinal obstruction will have adhesions rather than cancer as the cause of obstruction (19). If the surgeon elects not to operate, months and even years of good-quality life may be lost. At the other extreme, patients with multiple sites of small bowel obstruction from cancer may have a major exploratory surgery, develop multiple complications that result in an expensive and long hospitalization and experience little or no benefit. Are there guidelines for proper patient selection? Unfortunately, the clinical information that is available to the surgeon is often inaccurate or even misleading (13). Precise treatment plans may not be possible in all patients. However, some guidelines for knowledgeable selection of treatments may be possible.

Work-up in patients with intestinal obstruction and recurrence of colorectal cancer is directed at a determination of the extent of small bowel involvement, the extent of metastatic disease to liver and systemic sites and the patient's operative risk. Assessment of the extent of small bowel involvement may be the most difficult of these three parameters without an exploratory surgical procedure. A major surgical intervention may be appropriate if nutritional independence can be restored. If there is insufficient small bowel available after the relief of obstruction to maintain adequate nutrition, then surgical interventions should be limited to insertion of tubes (gastrostomy or cervical esophagostomy) and ostomy construction. Major exploratory surgery should be avoided if at all possible for these patients have a limited survival of ~6 months (20–22). Table 2 provides the stop signals for surgical palliation of advanced primary or recurrent gastrointestinal cancer.

Attempts to palliate intestinal obstruction from recurrent gastrointestinal cancer by surgery are related to the pattern of dissemination of carcinomatosis. Even with a large volume of cancer recurrence, the accumulation of cancer-causing obstruction can be found at three specific anatomical sites. These are the gastric outlet, the terminal ileum and ileocecal valve region and the rectosigmoid colon (22). In patients with a good performance status, aggressive resection of localized disease may offer considerable benefit with acceptable risk. The operation often used includes a greater omentectomy, abdominal colectomy and pelvic peritonectomy with end ileostomy. In some patients, the greater omentectomy will not restore adequate stomach drainage, so a gastrojejunostomy is necessary in order to decompress the stomach. Table 3 shows the clinical data used to select patients for abdominal colectomy with end-ileostomy as an approach to intestinal obstruction with recurrent gastrointestinal cancer.

CURRENT METHODOLOGY FOR DELIVERY OF INTRAPERITONEAL CHEMOTHERAPY

HEATED INTRAOPERATIVE INTRAPERITONEAL CHEMOTHERAPY

In the operating room, heated intraoperative intraperitoneal chemotherapy is used. Heat is part of the optimizing process and is used to bring as much dose intensity to the abdominal and pelvic surfaces as is possible. Hyperthermia with intraperitoneal chemotherapy has several advantages. First, heat by itself has more toxicity for cancerous tissue than for normal 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 selected chemotherapy agents. This synergism occurs only at the interface of heat and body tissue at the peritoneal surface.

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 secured to the skin edge. Using a long-running No. 2 monofilament suture, the skin edges are secured
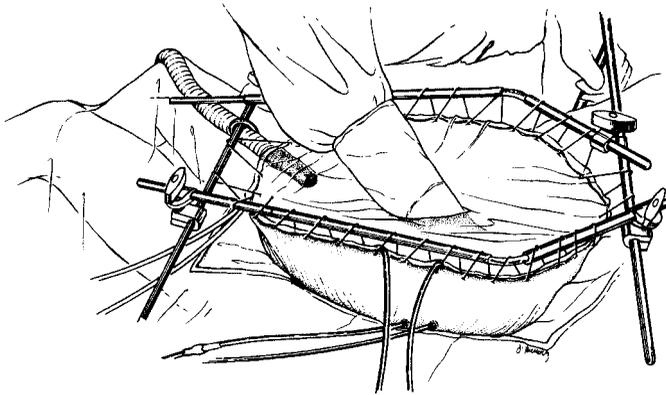
Figure 3. Coliseum technique for heated intraoperative intraperitoneal chemotherapy. Surgical manipulation of the abdominal contents after complete resection of cancer assures uniform distribution of heat and chemotherapy.

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. 3). During the 90 min of perfusion, all the anatomical structures within the peritoneal cavity are uniformly exposed to heat and to chemotherapy. The surgeon continuously manipulates and gauze debrides all viscera. Roller pumps force the chemotherapy solution into the abdomen through the Tenckhoff catheter and pull it out through the drains. A heat exchanger keeps the fluid being infused at 44–46°C so that the intraperitoneal fluid is maintained at 41–42°C. The smoke evacuator is used to pull air from beneath the plastic cover through activated charcoal, preventing contamination (by chemotherapy aerosols) of air in the operating room. The standardized chemotherapy orders for heated intraoperative intraperitoneal chemotherapy are shown in Table 4.

After the intraoperative perfusion is complete, the abdomen is suctioned dry of fluid. The abdomen is then reopened, retractors repositioned and reconstructive surgery is performed. It should be emphasized that no suture lines are constructed until after the chemotherapy perfusion is complete. One exception to this rule is closure of the vaginal cuff to prevent intraperitoneal chemotherapy leakage. The standardized orders for heated intraoperative intraperitoneal chemotherapy are provided in a practice manual (23).

IMMEDIATE POSTOPERATIVE LAVAGE

In order to keep the catheters for drug instillation and the abdominal drainage catheters clear of blood clots and tissue debris, an abdominal lavage is begun in the operating room. The fluid instillation utilizes the same tubes and drains that were positioned for the heated intraoperative intraperitoneal chemotherapy. Large volumes of fluid are rapidly infused and then drained from the abdomen after a short dwell time. The standardized orders for immediate postoperative lavage are given in Table 5.

Table 4. Standardized orders for heated intraoperative intraperitoneal chemotherapy

Standardized Orders for Heated Intraoperative Intraperitoneal Chemotherapy
Mitomycin Orders
Mitomycin C _____ mg to 2 liters of 1.5% dextrose peritoneal dialysis solution. Dose of mitomycin C for males 12.5 mg/m²; dose of mitomycin C for females 10 mg/m².
Use 33% dose reduction for heavy prior chemotherapy, marginal renal function, age greater than 60, extensive intraoperative trauma to small bowel surfaces or prior radiotherapy.
Send 1 liter of 1.5% dextrose peritoneal dialysis solution to test the perfusion circuit.
Send 1 liter of 1.5% dextrose peritoneal dialysis solution for immediate postoperative lavage.
Send the above to operating room _____ at _____ o'clock.
Cisplatin and Doxorubicin Orders
For gastric and ovarian cancer, mesothelioma and sarcoma; add cisplatin _____ mg to 2 liters of 1.5% dextrose peritoneal dialysis solution. Dose of cisplatin 50 mg/m².
Add doxorubicin _____ mg to same 2 liters of 1.5% dextrose peritoneal dialysis solution. Dose of doxorubicin 15 mg/m².
Use 33% dose reduction for heavy prior chemotherapy, marginal renal function, age greater than 60, extensive intraoperative trauma to small bowel surfaces or prior radiotherapy.
Send 1 liter of 1.5% dextrose peritoneal dialysis solution to test the perfusion circuit.
Send the above to operating room _____ at _____ o'clock.

EARLY POSTOPERATIVE INTRAPERITONEAL CHEMOTHERAPY

Using the same tubes and drains as were utilized for the heated intraoperative intraperitoneal chemotherapy, five consecutive days of chemotherapy instillation is recommended. Early postoperative intraperitoneal 5-fluorouracil is used in patients with appendiceal, colonic, rectal and other gastrointestinal cancers excluding gastric cancer. In gastric cancer, ovarian cancer and mesothelioma patients, early postoperative intraperitoneal paclitaxel is utilized. The standardized orders for early postoperative intraperitoneal 5-fluorouracil paclitaxel are given in Table 6.

SECOND-LOOK SURGERY PLUS ADDITIONAL INTRAPERITONEAL CHEMOTHERAPY

As the clinical data regarding treatment of peritoneal surface malignancy become available, the need for additional operative procedures and additional cycles of intraperitoneal chemotherapy becomes clear. This currently seems most evident with the tumors that do not have a tumor marker by which to monitor for recurrent disease. Peritoneal carcinomatosis from colon cancer is now routinely managed with a second-look surgery at 6–9 months. Also, primary peritoneal

Table 5. Standardized orders for immediate postoperative abdominal lavage

Standardized Orders for Immediate Postoperative Abdominal Lavage
Day of Operation: 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. No dwell time. Drain as rapidly as possible through the Tenckhoff catheter and abdominal drains. Repeat irrigations every 1 h for 4 h, then every 4 h until returns are clear; then every 8 h until chemotherapy begins. Change dressing covering Tenckhoff catheter and abdominal drain sites using sterile technique once daily and prn.

Table 6. Standardized orders for early postoperative intraperitoneal chemotherapy

Standardized Orders for Early Postoperative Intraperitoneal Chemotherapy with 5-Fluorouracil
Postoperative Days 1–5: Add to _____ ml 1.5% dextrose peritoneal dialysis solution: (a) _____ mg 5-fluorouracil (650 mg/m^2 × _____ m^2) (maximum dose 1500 mg) and (b) 50 meq. sodium bicarbonate. Intraperitoneal fluid volume: 1 liter for patients ≤2.0 m^2, 1.5 liter for >2.0 m^2. Instill for 5 consecutive days on _____ through _____. Drain all fluid from the abdominal cavity prior to instillation, then clamp abdominal drains. Run into abdominal cavity through Tenckhoff catheter as rapidly as possible the chemotherapy solution. Dwell for 23 h and drain for 1 h prior to next instillation. Continue to drain the abdominal cavity after final dwell until Tenckhoff catheter is removed. Use 33% dose reduction for heavy prior chemotherapy, age greater than 60, extensive intraoperative trauma to small bowel surfaces or prior radiotherapy.

Standardized Orders for Early Postoperative Intraperitoneal Chemotherapy with Paclitaxel
Postoperative Days 1–5: Add to _____ ml 1.5% dextrose peritoneal dialysis solution: _____ mg paclitaxel (20 mg/m^2 × _____ m^2) (maximum dose 40 mg). Intraperitoneal fluid volume: 1 liter for patients ≤2.0 m^2, 1.5 liter for >2.0 m^2. Instill for 5 consecutive days on _____ through _____. Drain all fluid from the abdominal cavity prior to instillation, then clamp abdominal drains. Run into abdominal cavity through Tenckhoff catheter as rapidly as possible the chemotherapy solution. Dwell for 23 h and drain for 1 h prior to next instillation. Continue to drain the abdominal cavity after final dwell until Tenckhoff catheter is removed. Use 33% dose reduction for heavy prior chemotherapy, age greater than 60, extensive intraoperative trauma to small bowel surfaces or prior radiotherapy.

surface malignancy, especially mesothelioma, has a scheduled second-look surgery at 6–9 months.

At the second-look surgery, the abdomen is widely opened and all of the peritoneal surfaces are visualized with a complete take-down of all adhesions. Additional cytoreduction is performed and additional visceral resections may be required. If a CC-1 cytoreduction can again be achieved, then heated intraoperative intraperitoneal chemotherapy and early postoperative intraperitoneal chemotherapy are recommended.

If it appears from the re-operation that the initial heated chemotherapy and early postoperative chemotherapy treatments were successful for the most part, then the same regimen will be employed again. If there is a 'chemotherapy failure' and recurrent disease is seen in areas that have been previously peritonectomized, then a chemotherapy change would be initiated.

CLINICAL RESULTS OF TREATMENT

RELIABLE RELIEF OF DEBILITATING ASCITES

Patients frequently experience a large volume of malignant ascites as a cancerous process moves toward its terminal phase. This may be caused by breast cancer, gastric cancer, mucinous malignancies of the colon or appendix and primary peritoneal surface cancers. Debulking surgery plus intraperitoneal chemotherapy is uniformly successful in eliminating the debilitating ascites. Success usually requires two or three instillations of a systemic dose of appropriate chemotherapy agents into the abdomen. Frequently combinations of both systemic and intraperitoneal chemotherapy are selected (23).

It is important to inform patients that intraperitoneal chemotherapy, as treatment for malignant ascites, is for symptomatic relief and should not be considered curative. The mass of solid tumor seen by CT scan will remain unchanged or will progress during treatment. Only the ascites will disappear. The mechanism of action of intraperitoneal chemotherapy on large-

volume malignant ascites is destruction of surface cancer. This causes a layer of fibrosis over all malignant deposits and also on normal parietal and visceral peritoneal surfaces. This fibrotic layer of tissue prevents formation of both normal peritoneal fluid and malignant fluids. The fluid that had previously accumulated in the abdomen is directed by the layer of fibrosis into the circulation. After a reduction in tumor volume by debulking surgery and three or four intraperitoneal chemother-
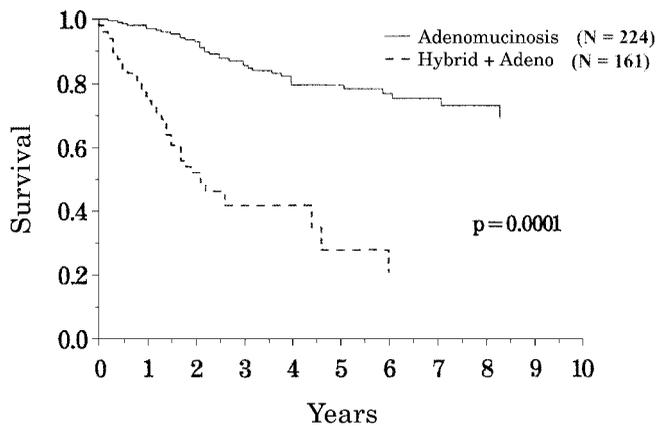
Figure 4. Survival of appendiceal malignancy with established peritoneal surface disease by histologic appearance. Modified from Ref. 6: Sugarbaker PH, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. *Ann Surg Oncol* 1999;6:727–31.

Figure 5. Survival of appendiceal malignancy with established peritoneal surface disease by completeness of cytoreduction. Modified from Ref. 6: Sugarbaker PH, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. *Ann Surg Oncol* 1999;6:727–31.

apy treatments, the abdominal space will cease to produce peritoneal fluid.

TREATMENT OF MUCINOUS ASCITES

One caveat must be mentioned regarding the management of debilitating ascites. If the intraperitoneal fluid is mucinous, it cannot be drained through a tube. Relief of mucinous ascites can only be achieved by laparotomy and manual removal of mucinous tumor. Often a greater omentectomy, abdominal colectomy and end-ileostomy constitute the optimal debulking procedure. Liposuction apparatus may greatly facilitate the complete evacuation of the viscous material. If the tumor mass can be reduced to a low volume, then intraoperative and early postoperative intraperitoneal chemotherapy may slow the reaccumulation of mucinous tumor.

APPENDIX CANCER AND PSEUDOMYXOMA PERITONEI

The earliest success in the treatment of peritoneal carcinomatosis is appendiceal malignancy. The experience with nearly 600 patients treated over a 20-year time span is available. The appendiceal malignancies are characterized by unique clinical features that facilitate the successful treatment documented with this tumor. First, spread from appendiceal tumors usually occurs in the absence of lymph node and liver metastases. The primary tumor occurs within a tiny lumen. Even small tumors early in the natural history of the disease will cause appendix obstruction and cause appendix perforation. This results in a release of tumor cells into the free peritoneal cavity. The seeding of the abdomen occurs in almost every patient before lymph node metastasis or liver metastasis has occurred. Second, there is a wide spectrum of invasion in which these tumors exhibit. The ones that are minimally invasive can be totally resected even though there is a great tumor burden using peritonectomy procedures to achieve a CC-1 cytoreduction. Third, the majority of these tumors are mucinous. The texture of the implants allows greater penetration by chemotherapy than with
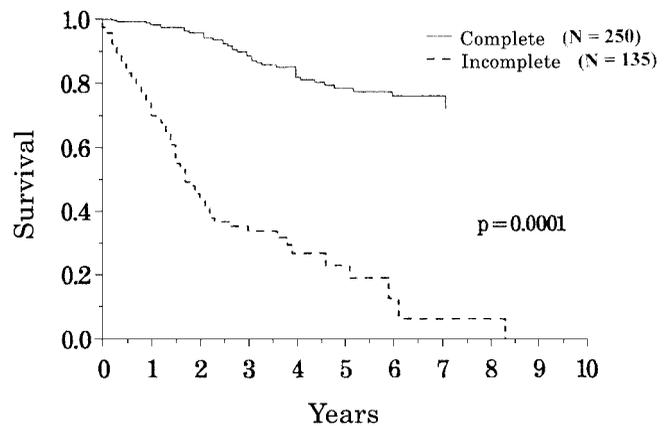
solid tumors. Finally, the malignancy only disseminates intraperitoneally so that all of its components are within the regional chemotherapy field. If the intraperitoneal chemotherapy is successful in eradicating the residual tumor on peritoneal surfaces, the patient will be a long-term survivor. If disease persists after chemotherapy, the peritoneal malignancy will recur. If a CC-1 cytoreduction was achieved in these patients the response achieved by the intraperitoneal chemotherapy determines the outcome.

The treatment strategies used included peritonectomy procedures combined with perioperative intraperitoneal chemotherapy with mitomycin C and 5-fluorouracil. Survival was significantly correlated with the invasive character of the mucinous tumor (Fig. 4) and the completeness of cytoreduction (Fig. 5). In contrast to most other studies with gastrointestinal cancer patients, in appendix tumors the peritoneal cancer index and lymph node involvement were not prognostic factors in patients with peritoneal dissemination of malignancy if intraperitoneal chemotherapy was used.

COLON CANCER WITH PERITONEAL CARCINOMATOSIS

To date, approximately 150 patients have been treated who have peritoneal carcinomatosis from colon cancer (17). The peritoneal carcinomatosis index provided a score valuable in selecting patients for treatment (Fig. 6). In patients who had a complete cytoreduction, there was marked improvement in survival; patients with residual disease show the expected short survival with peritoneal carcinomatosis from colon cancer (Fig. 7). These data suggest an early aggressive approach to peritoneal surface spread of adenocarcinoma of the colon in selected patients.

SARCOMATOSIS

Berthet et al. have reviewed their experience with cytoreductive surgery and intraperitoneal chemotherapy for the treatment of selected patients with sarcomatosis (16). If the
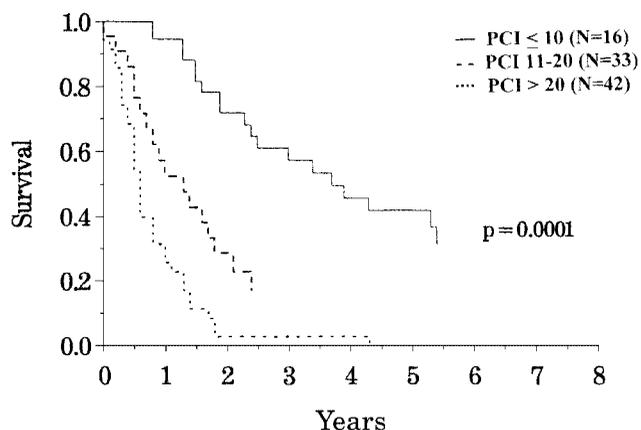
Figure 6. Survival of patients with peritoneal carcinomatosis from colon cancer by peritoneal cancer index. Modified from Ref. 17: Sugarbaker PH. Successful management of microscopic residual disease in large bowel cancer. *Cancer Chemother Pharmacol* 1999;43:S15–S25.
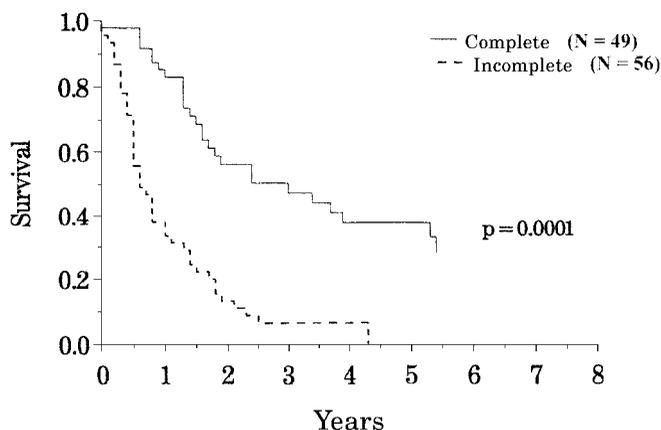

Figure 7. Survival of patients with peritoneal carcinomatosis from colon cancer by completeness of cytoreduction. Modified from Ref. 17: Sugarbaker PH. Successful management of microscopic residual disease in large bowel cancer. *Cancer Chemother Pharmacol* 1999;43:S15–S25.

peritoneal cancer index at the time of abdominal exploration was <13, there was a 75% 5-year survival rate. In those who had a peritoneal cancer index of ≥13, the 5-year survival rate was only 13% (Fig. 8). The completeness of cytoreduction was also statistically significant for an improved prognosis. Twenty-seven patients with a complete cytoreduction had a 5-year survival rate of 39%. Sixteen patients with a CC-2 or CC-3 resection had a survival rate of 14% (Fig. 9).

RECURRENT AND OBSTRUCTING GASTROINTESTINAL CANCER

Averbach and Sugarbaker looked at their experience with an extremely problematic group of patients (19). These are

patients who developed intestinal obstruction after prior treatment for a gastrointestinal malignancy. With aggressive treatments using second-look surgery, peritonectomy procedures and intraperitoneal chemotherapy, a complete cytoreduction resulted in a 5-year survival in 60% of the patients and an incomplete resection resulted in no 5-year survivals. The patients with appendiceal malignancy had a greatly improved survival compared with those with colon cancer or other diagnoses. A free interval of >2 years between primary malignancy and the onset of obstruction also correlated favorably with prolonged survival. Only patients with intraperitoneal chemotherapy used in conjunction with cytoreductive surgery were shown to have prolonged survival.
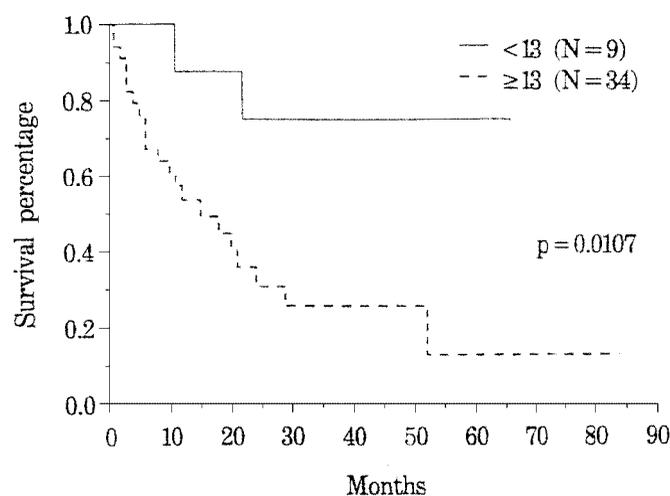

Figure 8. Survival of patients with recurrent abdomino-pelvic sarcoma by peritoneal cancer index. Modified from Ref. 2: Sugarbaker PH. Management of peritoneal surface malignancy: appendix cancer and pseudomyxoma peritonei, colon cancer, gastric cancer, abdominopelvic sarcoma and primary peritoneal surface malignancy. In: Bland K, Daly JM, Karakousis CP, editors. Surgical Oncology Contemporary Principles and Practice. New York: McGraw-Hill 2001;1149–76.

Figure 9. Survival of patients with recurrent abdomino-pelvic sarcoma by completeness of cytoreduction. Modified from Ref. 2: Sugarbaker PH. Management of peritoneal surface malignancy: appendix cancer and pseudomyxoma peritonei, colon cancer, gastric cancer, abdominopelvic sarcoma and primary peritoneal surface malignancy. In: Bland K, Daly JM, Karakousis CP, editors. Surgical Oncology Contemporary Principles and Practice. New York: McGraw-Hill 2001;1149–76.
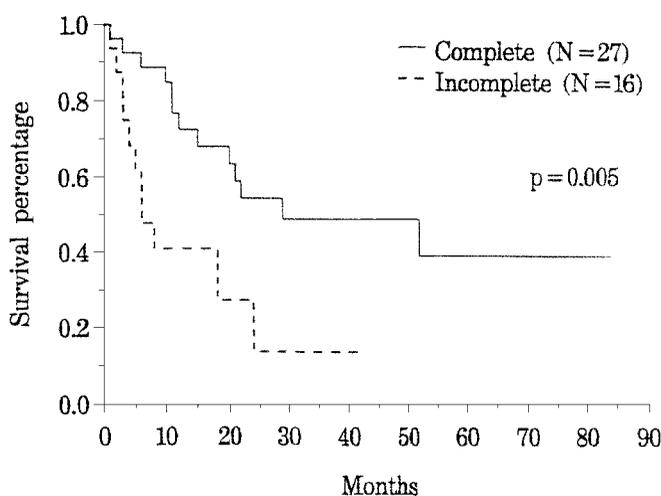
MORBIDITY AND MORTALITY OF PHASE II STUDIES

The morbidity and mortality of 200 consecutive patients who had cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy for peritoneal carcinomatosis have been reported (24). In these patients, there were three treatment-related deaths (1.8%). Peripancreatitis (7.1%) and fistula (4.7%) were the most common major complications. There were 25.3% of patients with grade III or IV complications.

Following these treatments, the patient is maintained on parenteral feeding for 2–4 weeks. Approximately 20% of patients, especially those who have had extensive prior surgery or who have a short bowel, will need parenteral feeding for several weeks after they leave the hospital.

ETHICAL CONSIDERATION IN CLINICAL STUDIES WITH PERITONEAL SURFACE MALIGNANCY

The sequence of events that should accompany a new program in peritoneal surface malignancy has not yet been defined. The requirements for formal institutional review board approval will vary from one institution to another. Guidelines for an evolution of treatment strategies that allows for persistent clinical research may occur as follows.

Without exception, adjuvant intraperitoneal chemotherapy studies in patients with primary colorectal cancer must be randomized and require review by a research board. Also, when a group first attempts to initiate treatment plans with intraperitoneal chemotherapy, the learning curve associated with a new technology is best approached by a start-up protocol approved by an institutional review board. This forces the group to standardize the methods and familiarize themselves with the experience of others. Selection criteria for treatment of patients with a reasonable likelihood of benefit must be evident. An omnibus protocol is suggested, which allows aggressive cytoreduction and perioperative intraperitoneal chemotherapy in patients with no systemic dissemination and small-volume peritoneal seeding from recurrent colorectal cancer, resected primary gastric cancer and resected primary or recurrent abdomino-pelvic sarcoma. This omnibus protocol should be utilized, over a limited time period, to treat 10–20 patients.

Formal protocols should not be required for the treatment of debilitating ascites. Also, the long-term survival of patients with established peritoneal surface malignancy that has a small volume and limited distribution has been established. After completing the start-up protocols, phase II clinical studies on this group of patients by an oncological team that has demonstrated experience should proceed without the need for further institutional review board approval. The peritoneal surface spread of most gastrointestinal cancers that have a low peritoneal cancer index and that, after surgery, have a CC score of 0 or 1 should be routinely treated according to standardized intraperitoneal chemotherapy protocols.

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