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Surgical Management of Peritoneal Carcinosis: Diagnosis, Prevention and Treatment

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Summary. Gastrointestinal and ovarian malignancies frequently recur with metastatic disease limited to the abdominal cavity. Due to full thickness penetration of tumor through bowel wall, spillage of tumor from lymphatic channels by surgical trauma or perforation of the tumor through the ovarian capsule, tumor cells are disseminated throughout the peritoneal surfaces either prior to or at the time of surgical removal of the primary tumor. In the past, diagnosis of recurrent cancer was difficult because no sensitive diagnostic test was available by which to image a small tumor volume present on peritoneal surfaces. Computerized tomography with intraperitoneal infusion of contrast can demonstrate tumor nodules not otherwise detectable. Intraperitoneal installation of I-131 labeled monoclonal antibody has allowed visualization of mucinous tumor on peritoneal surfaces not seen by any other radiologic test. Intraperitoneal chemotherapy has been shown to provide palliation in patients with small volume disease confined to peritoneal surfaces. Because of limited penetration of chemotherapy into large tumor nodules this treatment strategy has not been effective for bulky intraabdominal recurrent cancer. Cytoreductive surgery utilizing high voltage electrocautery and CO_2 laser evaporation of tumor can make patients relatively disease free. These surgical technologies combined with postoperative intraperitoneal chemotherapy have been shown to be of benefit for selected patients with recurrent intraabdominal cancer. The wider application of these intraperitoneal chemotherapy treatments for patients in an adjuvant setting may be of value in preventing the occurrence of peritoneal carcinosis and in improving survival.

Key words: Peritoneal carcinosis – Colon cancer – Ovarian cancer – Gastric cancer – Pancreas cancer – Intraperitoneal chemotherapy – Intraperitoneal immunotherapy – 5-Fluorouracil – Mitomycin-C.

A New Hypothesis Regarding the Mechanism of Gastrointestinal and Ovarian Cancer Recurrence

The natural history of recurrent gastrointestinal and ovarian malignancy is such that a large proportion of patients recur with metastatic disease at the resection site and on peritoneal surfaces. The explanation of this pattern of spread has not been provided in the past. With ovarian cancer tumor penetrates through the capsule, seeds malignant cells throughout the peritoneal surfaces and in the absence of effective chemotherapy eventually results in death from tumor progression. The same phenomenon occurs frequently with gastrointestinal malignancy. Not infrequently, colon cancer will penetrate full thickness through the bowel wall and result in peritoneal implants in the area of the tumor on the serosal surface. The same full thickness tumor penetration of the stomach wall is frequently encountered with gastric cancer. This may not be the only cause for peritoneal carcinosis. At the time of surgical removal of the primary tumor, multiple lymphatic channels must be transected. In a large proportion of patients these lymphatics channels are contaminated by tumor microemboli. These free tumor cells are disseminated at the time of surgery or leak retrograde from severed lymphatic channels in the immediate postopera-

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tive period. The resection site presents to the tumor cells the ideal setting in which to implant and grow. Presumably, this is why local recurrence is so frequent in gastric cancer and in pancreas cancer, especially if lymph nodes are involved by malignancy. In these two diseases a wide resection, as is seen in colon cancer with its long mesentery, is usually not possible. Transection of lymphatics containing viable tumor cells may occur in a majority of patients. The presence of free intraperitoneal tumor cells from the margins of surgical resection is postulated to be the major course for disease recurrence in these malignancies.

Diagnosis of Recurrent Cancer on Peritoneal Surfaces

Traditionally recurrent cancer on peritoneal surfaces has been difficult to confirm. Frequently, before there is radiologic evidence of recurrent cancer a rise in the plasma CEA level is detected. It is not unusual for every radiologic test to be normal even though there is gross intraabdominal disease recurrence. The radiologic test that most clinicians use is the abdominal-pelvic computerized tomogram. A positive CT scan is shown in Fig. 1. Complete opacification of all bowel loops with oral contrast material is of great value when one attempts to discriminate between normal loops of bowel and tumor masses.

The accuracy of the abdominal-pelvic CT scan in detecting intraabdominal malignancy is surprisingly low [11]. Tumor masses that surround the liver may be noted because they indent Glisson's capsule and resemble an intrahepatic filling defect [6]. In other parts of the abdomen tumor masses even 4 cms and above are routinely missed. Tumor within the pelvis is especially difficult to accurately visualize [11].

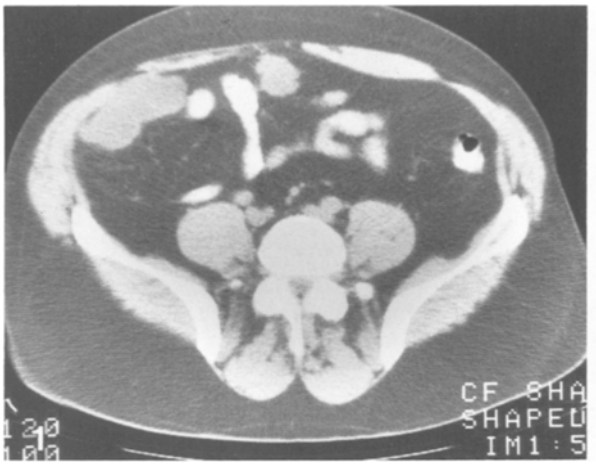
An improvement in the diagnostic accuracy of the abdominal-pelvic CT scan is available. If soluble contrast material is introduced in a large volume of fluid into the peritoneal cavity, the parietal peritoneal surfaces are well-visualized on a CT scan. Even small tumor deposits down to 1 cm in size can be readily demonstrated. Pelvic tumor masses may be seen using this technique but missed by routine CT scan. If oral contrast is used along with the intraperitoneal contrast the thickness of the wall of the large and small bowel loops can be readily determined. Thickened bowel loops often mean that there is a diffuse spread of tumor over the visceral peritoneal surfaces. Figure 2 shows an abdominal cut on a CT scan with intraperitoneal contrast. No abnormalities are noted but the parietal peritoneal surface is clearly visualized. Figure 3 shows a pelvic CT scan with the intraperitoneal infusion of soluble contrast in 2 liters of fluid. Obvious tumor masses are visualized.

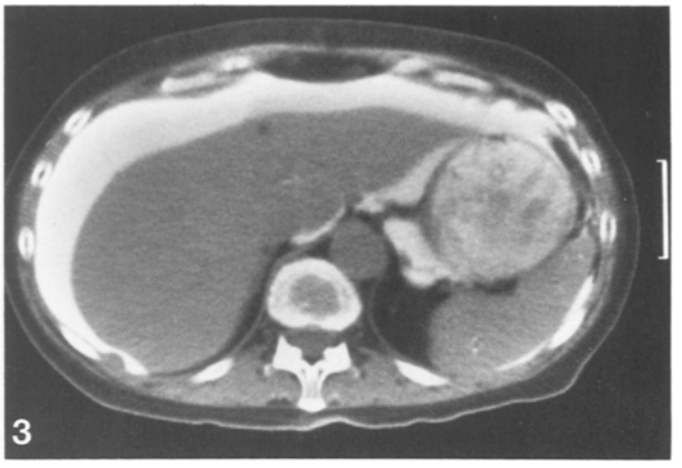
Recently, a new technique has been described to visualize intraperitoneal deposits of mucinous adenocarcinoma. In grade I mucinous adenocarcinoma of colon or ovarian origin, copious amounts of free intraabdominal mucin is frequently present. This will readily bind to the intraperitoneal administration of I-131 labeled monoclonal antibody. Using a whole body gamma camera the deposits of mucinous tumor can be accurately visualized. Figure 4 shows the radionuclide scan obtained after an intraperitoneal installation of I-131 labeled monoclonal antibody B72.3. In this patient all diagnostic tests were negative except for the monoclonal antibody scan. This technology may be of value in the future for accurately detecting and quantitating mucinous tumor present on peritoneal surfaces [2].

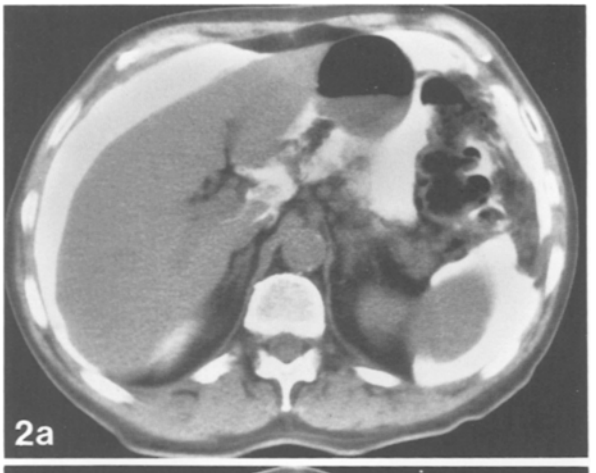
Rationale for Intraperitoneal Chemotherapy

Regional cancer treatments may be more beneficial to patients than systemic therapies if three criteria are met. 1) The systemic benefits of treatment are not sacrificed because adequate doses of drug are administered locally so that therapeutic amounts are present within the peripheral circulation. 2) Higher levels of effective chemotherapeutic agents are present local-regionally so that increased local anticancer effects are present. 3) The local and systemic toxic side effects are no greater than when the drugs are administered by the intravenous route. These criteria are met with several effective anticancer agents used intraperitoneally for the treatment of gastrointestinal malignancy.

The rate at which a drug leaves the peritoneal cavity is, in large part, dependent upon its molecular weight. Table 1 shows the correlation of the absorption of a drug with its molecular weight [7]. The larger the molecular weight the slower the absorbtion. If a drug of the proper size is selected and if that drug is administered in a large volume of fluid into the peritoneal cavity, high concentrations of drug will remain in the peritoneal cavity for an extended time period with a slow release







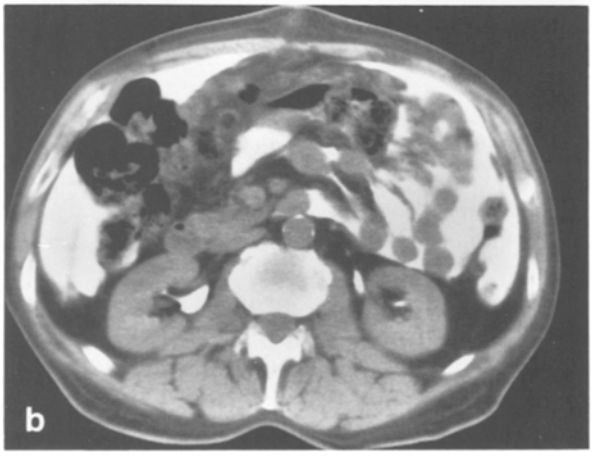


Fig. 1. Computerized tomogram of pelvis in patients with recurrent right colon cancer. Large tumor masses 4–5 cm in diameter were found in the omental fat. Multiple smaller tumor masses 1 mm to 4 cm in diameter were found throughout the abdominal cavity that were not seen on CT scan. In this patient opacification of small bowel loops and a large amount of ascites made the tumor mass obvious

Fig. 2a, b. Computerized tomogram of the abdomen after intraperitoneal instillation of soluble contrast in a larger volume of fluid. This is a normal radiologic study

Fig. 3. Computerized tomogram of the abdomen with intraperitoneal infusion of soluble contrast. An obvious tumor nodule is seen beneath the right liver

into the portal and systemic circulation over approximately 8 h.

A majority of the drug is taken up by visceral peritoneal surfaces and leaves the peritoneal cavity through the portal blood stream. Figure 5 shows a concentration vs time curve for 5-fluorouracil. The distribution of drug in the different body compartments recorded after intraperitoneal 5-fluorouracil instillation is very similar to that reported with a wide variety of drugs given by this route. Levels of chemotherapy in the peritoneal space is 40 to 200 times greater than in the peripheral blood. Notice also that the potential for a high concentrations of drug reaching hepatic

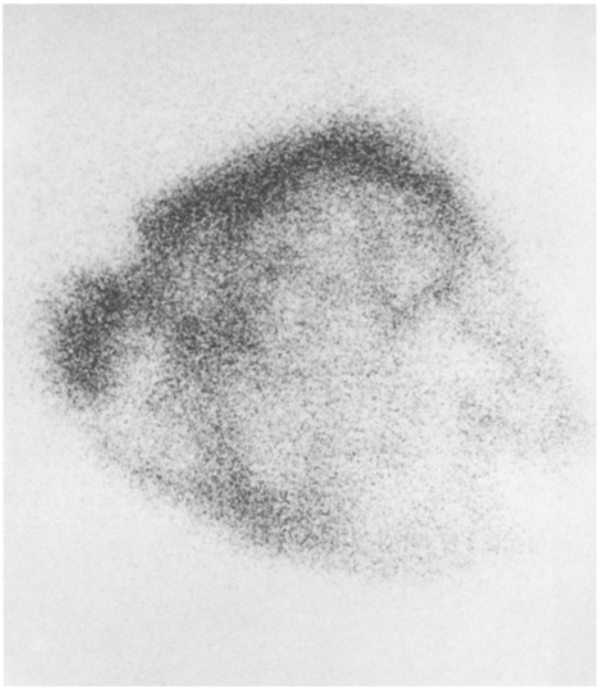


Fig. 4. Radionuclide scan after intraperitoneal instillation of I-131 labeled monoclonal antibody. The mucinous adenocarcinoma in this patient with peritoneal carcinosis from colon cancer has replaced the omental fat. The indentation of the gallbladder on the "omental cake" is readily seen. A tumor mass surrounding the right colon is seen along with tumor accumulations in the right and left abdominal gutters. Photo courtesy of Dr. Jorge Carrasquillo, Department of Nuclear Medicine, NIH, Bethesda

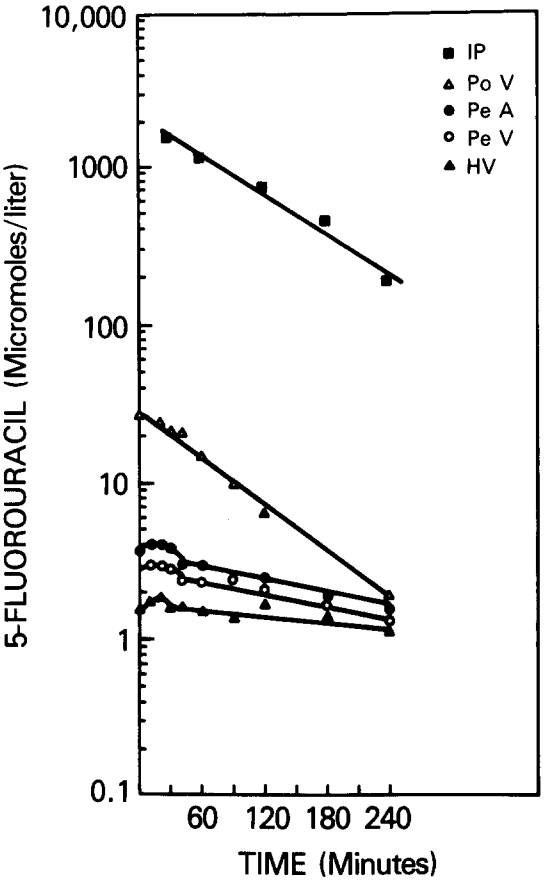


Fig. 5. Concentration versus time for 5-FU after intraperitoneal instillation of 1 gram of drug in 2 liters of dialysis solution

Table 1. Correlation of absorption of intraperitoneal chemotherapy with molecular weight. From [7]

Drug	% Absorbed[a]	MWT
Asparaginase	9	133,000
Doxorubicin[b]	10	544
Bleomycin	12.3	1,400
Methotrexate	15	472
Actinomycin D[b]	21	1,255
Cis-DDP	24.6	300
Melphalan	25.0	323
5-FU	28.4	130
Ara C	29.5	243
Thiotepa[b]	74.4	188
Hexamethylmelamine[b]	91.7	210

[a] % absorbed over 1 h
[b] Drugs whose lipid solubility caused significant increase in % absorbed over 1 h

malignancy also exists; for the concentration of chemotherapy in the portal vein was considerably higher than in the systemic circulation.

One curious feature concerning the physiology of intraperitoneal drug delivery concerns the peritoneal clearance of large biological molecules such as albumin, monoclonal antibody, or interleukin-2. These large molecules all leave the peritoneal cavity at approximately the same rate despite great differences in their molecular size. Flessner and colleagues postulate that large molecules leave the peritoneal cavity by diffusing into the interstitium of soft tissues that constitute the intraabdominal surfaces and then entering lymphatic channels [5]. Therefore these large molecules would be found in high concentration in the mesenteric lymph nodes and thoracic duct. This is in contrast to chemotherapeutic agents which are found in high concentration within the portal vein.

A "diffusion model" by which drugs or biologicals leave the peritoneal cavity may function as follows. Large chemotherapy molecules, such as 5-fluorouracil, adriamycin, mitomycin-C and cis-platin, diffuse out of the abdominal cavity into the surrounding soft tissues. A diffusion gradient occurs in the interstitial tissues. This concentra-

tion gradient would depend upon the rate at which drugs enter the interstitial space and the rate at which they are transported away by the rich capillary network of the bowel, omentum, and abdominal plus diaphragmatic musculature. Because the surface area of the viscera is so much greater than that of the parietal tissues, high drug concentrations within the portal vein are expected.

Biological molecules such as albumin similarly diffuse into the interstitial spaces surrounding the abdominal cavity. However, because of their large size they cannot cross the wall of capillaries and venules. Rather biological materials are taken up by the lymphatics at a constant rate. From lymphatics these biological compounds enter the mesenteric lymph nodes, the thoracic duct and finally enter the venous blood where the thoracic duct joins the subclavian vein. In both situations, marked increases in the concentration of drug over an extended time period occurs within the peritoneal cavity while adequate doses of drug are made available to the systemic circulation for peripheral antitumor effects.

Reported Studies Utilizing Intraperitoneal Chemotherapy

The most notable successes with intraperitoneal chemotherapy have been achieved with tumors that have little or no tendency to spread outside of the abdominal cavity. Colonic tumors and ovarian cancer may be widely disseminated around the abdominal cavity and yet have little or no tendency to metastasize to systemic sites. When mucinous tumor causes peritoneal carcinosis it is referred to as malignant pseudomyxoma peritonei. Sugarbaker and colleagues have reported 70% of patients to be disease free when patients are treated by a combination of cytoreductive surgery and intraperitoneal chemotherapy [9]. In these studies patients are made clinically disease free by surgery and then immediate and delayed intraperitoneal chemotherapy is used to eliminate microscopic disease on peritoneal surfaces. The surgical techniques utilized for cytoreductive surgery are shown in Figs. 6 through 9.

Response rates of more than 60% have been achieved treating small volumes of intraperitoneal ovarian cancer with either cis-platin or mitomycin-C [1, 8]. Our own chemotherapy regimen for immediate, postoperative and delayed chemotherapy for recurrent ovarian or colonic malignancy is shown in Fig. 10. Recent studies have shown that chemotherapy used in the immediate postoperative period has essentially the same pharmacokinetics as chemotherapy given in patients with normal peritoneal surfaces. The studies reported by Cunliffe and colleagues have made the safe use of immediate postoperative intraperitoneal chemotherapy a practical and safe treatment modality [3].

Prevention of Carcinosis with Adjuvant Intraperitoneal Chemotherapy

Sugarbaker and colleagues performed a prospective and randomized clinical study in which patients were treated with either intravenous or intraperitoneal 5-FU following the resection of a poor prognosis colon or rectal cancer [10]. In this study the survival as well as sites of treatment failure of the randomized patients were carefully followed. If patients recurred a second-look surgical procedure was carried out in order to determine the sites of treatment failure. In the patients treated with intraperitoneal 5-FU there was a statistically significant decrease in the proportion of patients who had biospy proven disease on peritoneal surfaces at the time of staging celiotomy. The data is shown in Table 2. Unfortunately because of liver metastases and other distant sites of disease spread there was no statistically significantly difference in survival.

Table 2. Sites of treatment failure for I.V. and I.P. 5-FU. From [10]

No. Patients	No. Recurrence %	Peritoneal surface	Liver	Retro-peritoneal and/or pelvic side wall	Abdominal incision	Lung	Bone marrow
I.P. 5-FU 36	13/(36)	2/10	3/11	7/11	2/11	2/11	2/13
I.V. 5-FU 30	11/(37)	10/11	4/11	3/10	1/11	4/11	0/11
statistical analysis $p^2 =$		0.003	1.0	0.27	1.0	0.64	0.57

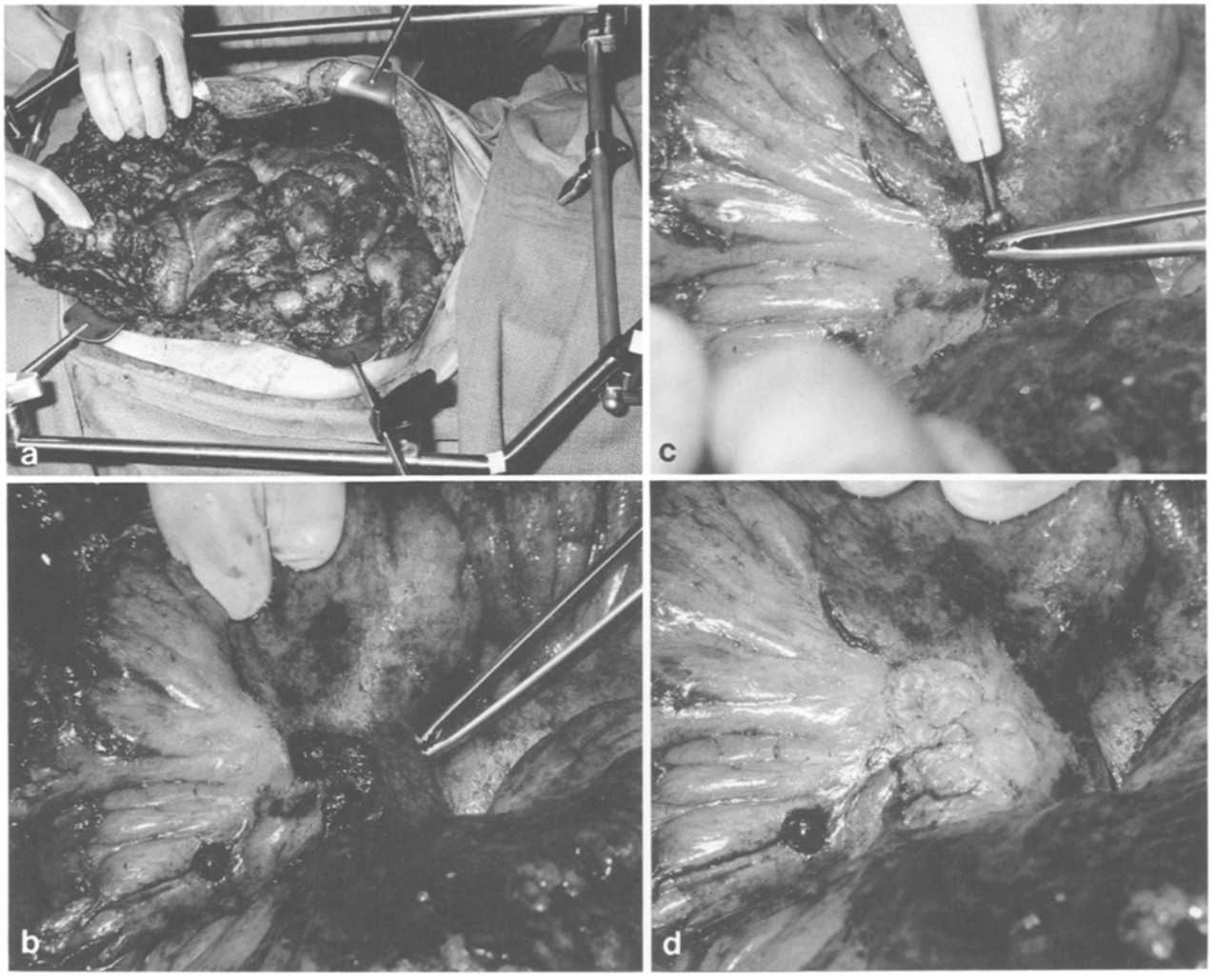


Fig. 6a–d. A long midline abdominal incision is used to provide adequate exposure (**a**). A rectal catheter is used to infuse povidone iodine solution into the colonic lumen. A double lumen foley catheter is placed in the bladder so that the bladder can be distended during the procedure. The legs are placed in stirrups so that the surgeon has a access to the vagina and rectum. Exposure is maintained with a self retaining (Thompson) retractor. The "omental cake" resulting from tumor cells replacing the omental fat is the hallmark of peritoneal carcinosis. **b–d** In cytoreductive surgery for mucinous adenocarcinoma from ovarian or colon cancer, the surgeon attempts to remove all visible tumor. **b** shows nodules of mucinous tumor on the small bowel mesentery. **c** shows gentle traction on the tumor so that the ball tip cautery on "pure cut" electroevaporatic tumor at the tumor-normal tissues interface. **d** shows the clear margin of resection. A laser smoke evacuator is used to remove smoke

Results of these studies led to our adjuvant protocols for studying intraperitoneal chemotherapy. Following the resection of the primary gastrointestinal cancer, a regimen of immediate postoperative intraperitoneal chemotherapy is used. There is a strong rationale for employment of adjuvant chemotherapy in the immediate postoperative period: First, this means that the chemotherapy will have access to the areas at greatest risk for recurrence of cancer before fibrous adhesions form. Micrometastases present at the resection site and on peritoneal surfaces or viable tumor cells leaking out of severed lymphatics should be destroyed with the intraperitoneal chemotherapy. Also, high levels of chemotherapy within the portal vein may help diminish the incidence of hepatic metastases. Second, our studies of drug levels in the postoperative period show much higher doses of drug present within the peritoneal cavity. Therefore increased tumor kill by chemotherapy is expected local-regionally. The concentration of drug within the abdominal cavity is somewhere between 20 and 400 times that which will be found in the systemic blood. Third, tumor cells should be at their lowest number and consequently proliferat-

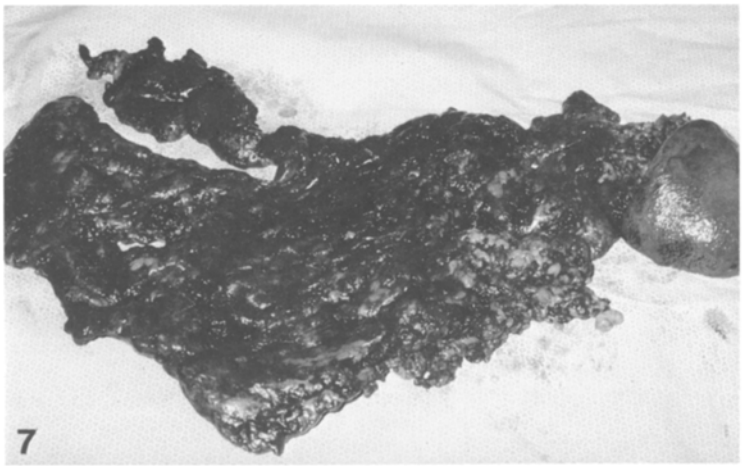


Fig. 7. After electroevaporating tumor on visceral and parietal on peritoneum an *en bloc* resection of greater omentum and spleen is performed. The intact specimens of greater omentum, gastrocolic ligament and spleen are shown. Tumor masses in the pelvis can present a difficult dissection. Complete removal of tumor within the lesser omentum may require sacrifice of the vagus nerve. A gastrojejunostomy or pyloroplasty is then needed

Fig. 8. Tumor on the undersurface or the hemidiaphragm is laser evaporated with the CO_2 or YAG laser. If electrocautery is used, muscular contractions will result in perforation of the diaphragm

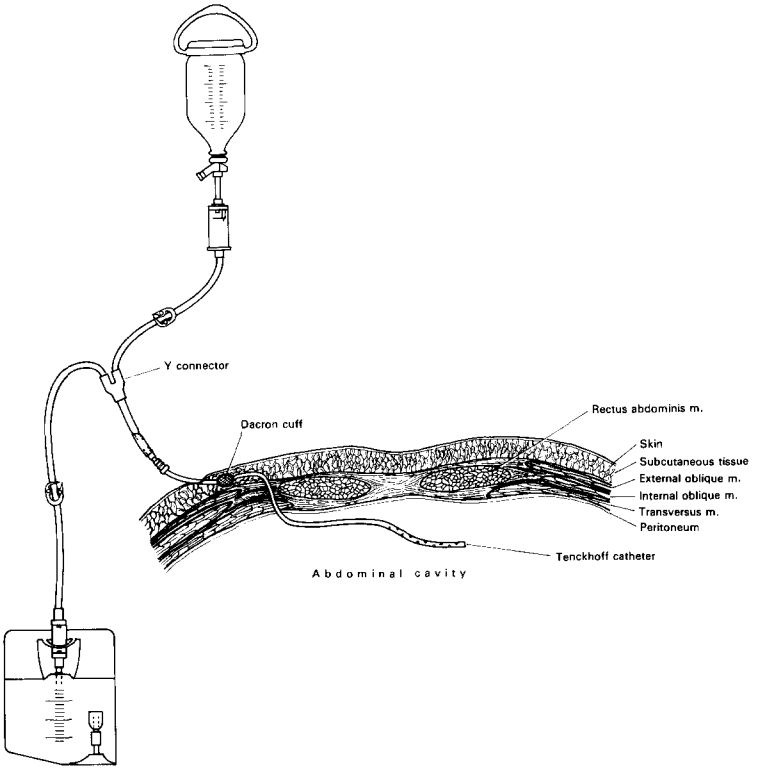


Fig. 9. A Tenckhoff catheter is inserted with the intraabdominal portion directed into the pelvis. A purse string suture is needed at the peritoneal level to prevent leakage of peritoneal lavage fluid. The abdomen is closed with a running # 1 nonabsorbable suture. Lavage of the peritoneal cavity begins in the immediate postoperative period. The intraperitoneal chemotherapy begins on the first postoperative day if the patient's hemodynamic condition has stabilized

ing most rapidly in the immediate postoperative period. They should be most susceptible to the effects of chemotherapy at this time. Fourth, simply removing blood, tissue debris, and fibrinous material from the abdominal cavity by the large volume of dialysis fluid may lavage tumor cells out of the abdominal cavity that would otherwise become entrapped at the resection site, within fibrinous adhesions, or on peritoneal surfaces. Also, removal of cells and biological materials from the abdominal cavity may diminish the tumor stimulating effects of growth

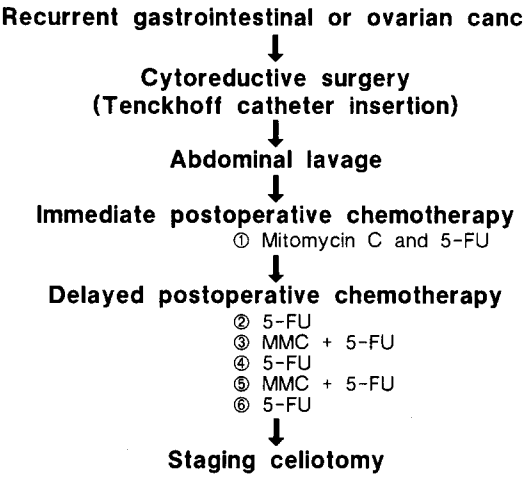


Fig. 10. Peritoneal carcinosis protocol for patients with recurrent gastrointestinal or ovarian cancer. Eligible patients are those with recurrent cancer confined to the peritoneal space. Preoperatively patients receive a single dose of 5-FU. This allows drug levels in tumor tissue to be determined in specimens removed by cytoreductive surgery. Immediately after surgery the abdominal cavity is lavaged to remove blood and tissue debris. On the first postoperative day, mitomycin-c at 12 mg/m² in 1 liter of dialysis fluid is instilled. On postoperative days 2–5, 5-FU at 20 mg/kg in 1 liter of dialysis fluid is instilled. The Tenckhoff catheter is removed at the completion of immediate post-operative chemotherapy and reinserted at 6 weeks to give 5 more cycles of intraperitoneal chemotherapy. After the completion of chemotherapy a staging celiotomy is performed

factors. Finally, host defenses are severely jeopardized by surgical trauma. If there is a time at which the host is in need of an antitumor effect, the immediate postoperative period is this time.

Adjuvant protocols are currently in effect for pancreas cancer, gastric cancer and colon cancer which utilize immediate postoperative intraperitoneal chemotherapy. Multiple agents with proven effectiveness for gastrointestinal malignancy are currently being utilized. The clinical studies now in progress are designed to gradually increase the doses of drugs within the peritoneal cavity until tolerable toxicity is achieved. When an optimal intraperitoneal drug regimen is developed, it will be utilized in the immediate postoperative period as a randomized controlled study through cooperative groups. Through these prospective randomized controlled studies progress in the treatment of cancer patients is possible.

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