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ORIGINAL CONTRIBUTIONS

Peritoneal Carcinomatosis from Appendiceal Cancer: Results in 69 Patients Treated by Cytoreductive Surgery and Intraperitoneal Chemotherapy

Paul H. Sugarbaker, M.D., Bo-Wei Zhu, M.D., Grace Banez Sese, M.D., Barry Shmookler, M.D.

From The Cancer Institute, Washington Hospital Center, Washington, D.C.

Sixty-nine patients presenting over a 10-year period with peritoneal carcinomatosis from appendiceal cancer were treated with cytoreductive surgery combined with intraperitoneal chemotherapy. The three-year survival is 89.5 percent in patients (38/69) with pseudomyxoma peritonei, 34.5 percent in patients (25/69) with cystadenocarcinoma, and 38.1 percent in patients (6/69) with adenocarcinoma ($P < 0.01$). In this study, a classification of residual disease following the cytoreductive surgery was used. The prognosis of the patients with minimal residual disease was better than that of those with moderate or gross disease, showing a 91.6 percent three-year survival compared with 47.8 percent and 20 percent, respectively ($P < 0.01$). The patients without lymphatic or hematogenous metastases had a better three-year survival than those with metastases (75.1 percent *vs.* 28.6 percent; $P < 0.01$). These findings suggest that peritoneal carcinomatosis from appendiceal cancer can be treated with long-term disease-free survival. The patients with low malignant potential cancer, complete cytoreduction, and no metastases showed the most effective disease control.
[Key words: Appendix; Pseudomyxoma; Peritoneum; 5-Fluorouracil; Mitomycin C; Intraperitoneal chemotherapy; Cytoreductive surgery]

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Malignant tumors of the appendix are rare gastrointestinal tumors, accounting for 0.2 to 0.5 percent of all tumors of the gastrointestinal tract.[1–3] Peritoneal carcinomatosis from appendiceal cancer is a clinical entity characterized by peritoneal implants of the tumor in the resection site, on the peritoneal surface, or most commonly at both of these anatomic locations. In 30 percent of these patients, peritoneal carcinomatosis is present at the time of initial surgery.[4] Histopathologically, the most common malignant diseases are cystadenocarcinoma, adenocarcinoma, and carcinoid. In the past, peritoneal carcinomatosis from perforated appendiceal cancer has been considered as a uniformly lethal disease process. In an attempt to improve salvage of patients with peritoneal seeding from appendiceal cancer, we prospectively studied 69 patients. The new surgical treatment strategy combined early postoperative and delayed intraperitoneal chemotherapy. Reported here is our experience with this disease treated by a uniform management plan over a period of 10 years.

Address reprint requests to Dr. Sugarbaker: Medical Director, The Cancer Institute, Washington Hospital Center, 110 Irving Street, N.W., Washington, D.C. 20010.

PATIENTS AND METHODS

Patients

Between September 1981 and January 1992, 69 patients with histologically proven peritoneal carcinomatosis from appendiceal cancer were treated. There were 46 males and 23 females, ranging in age from 28 to 77 years, the median age being 51 years (Table 1). The preoperative workup was aimed at evaluation of the disease and ruling out extra-abdominal disseminated disease. Clinical examination and laboratory tests including carcinoembryonic antigen, lung CT scans, abdominal CT scans, and appropriate gastrointestinal radiologic studies were obtained. Pathology reports and slides from prior surgical procedures were reviewed.

Cytoreductive Surgery

The goal in surgical treatment of the patients with peritoneal carcinomatosis from appendiceal cancer was to removal all clinical evidence of disease. A planned approach to the removal of as much disease as possible is required for best results. Cytoreductive surgery has been described by Sugarbaker.[5-7] This approach with curative intent consists of five peritonectomy procedures: omentectomy-splenectomy, left subdiaphragmatic peritonectomy, right subdiaphragmatic peritonectomy, pelvic peritonectomy-sleeve resection of sigmoid colon, and cholecystectomy-lesser omentectomy.

Table 1.
Clinical Data

Number of patients	69
Male	46 (67%)
Female	23 (33%)
Age (yr)	
Range	28–77
Median	51
Presenting symptoms and signs	
Increasing abdominal girth	18 (26.1%)
Appendicitis	16 (23.2%)
Appendiceal abscess	12 (17.4%)
Abdominal mass	3 (4.3%)
Inguinal hernia	3 (4.3%)
Small bowel obstruction	2 (2.9%)
Acute abdomen	2 (2.9%)
Hydronephrosis	1 (1.5%)
Status	
No evidence of disease (NED)	32 (46.4%)
Alive with disease (AWD)	16 (23.2%)
Died of disease (DOD)	15 (21.7%)
Died of other causes (DOC)	6 (8.7%)

Each has a definite *en bloc* resection that requires an orderly sequence of surgical maneuvers in order to create an optimum cytoreductive surgery.

Briefly, the peritonectomy procedures are performed as follows: first the "omental cake," the bulky tumor mass that infiltrates the omentum and surrounds the spleen, is removed. The dissection usually begins in the middle of the greater curvature of the stomach and proceeds by dividing the gastro-omental vessels first toward the pylorus and then toward the gastroesophageal junction. Only in early cases of mucinous peritoneal carcinomatosis can the spleen be preserved. To perform the left subdiaphragmatic peritonectomy, the peritoneum beneath the diaphragm is stripped laterally and posteriorly. In the right subdiaphragmatic dissection, the peritoneum beneath the right hemidiaphragm is stripped from the underlying diaphragmatic musculature. To separate peritoneum infiltrated by tumor from the normal diaphragmatic muscle beneath, a ball-tipped electrocautery on pure cut is used. The dissection is continued until the specimen is only attached to the bare area of the liver and to Glisson's capsule. Then a partial Glisson's capsulectomy is performed. The envelope of peritoneum and liver capsule are removed *en bloc* so that the right subdiaphragmatic and subhepatic spaces are left tumor free. A complete pelvic peritonectomy includes a resection of all parietal and visceral peritoneum and the cancer contained on these surfaces. Peritoneum is stripped from the preperitoneal fat of the pelvic sidewalls and from the abdominal aspect of the bladder muscle. All internal genitalia are removed in females. Perirectal fat beneath the peritoneal reflection is dissected toward the rectum. All tumor that filled the *cul-de-sac* medially and the pelvis laterally is above this plane of dissection. The rectum is skeletonized so that it can be elevated out of the pelvis totally free of tumor. The lesser omentectomy-cholecystectomy with dissection of the porta hepatis is the last procedure. The dissection proceeds along the lesser curvature of the stomach to the cardioesophageal junction. The cholecystectomy is performed. The tissues of the porta hepatis are delicately dissected from the base of the gallbladder along the lesser omentum. Care is taken to preserve the left gastric artery. As a final cytoreduction, the scattered tumor deposits on the surface of the small bowel, large bowel, and mesentery must be removed.

Reconstruction

With removal of the lesser omentum and multiple branches of the vagus nerve, a pyloroplasty or gastrojejunostomy is required for gastric drainage. A colorectal circular-stapled anastomosis through the stapled rectal stump is performed.

Early Postoperative Intraperitoneal Chemotherapy

A Tenckhoff catheter is placed through the abdominal wall. A closed suction drain is placed within the pelvis and beneath both hemidiaphragms. The gastrointestinal tract must be decompressed by a large-bore nasogastric sump tube. The closed suction drains and Tenckhoff catheter remain in place until the intraperitoneal chemotherapy is complete.

As soon as the abdomen is closed, abdominal lavage with 1.5 percent dextrose dialysate is initiated to remove clotted blood and tissue debris that result from surgery. One liter of fluid is run into the abdominal cavity as rapidly as possible. The fluid is immediately drained by gravity. This procedure is repeated on an hourly basis until the effluent is clear. Abdominal and pelvic lavage is repeated every four hours until the intraperitoneal chemotherapy is begun on the first postoperative day.

On the first postoperative day, mitomycin C at 10 mg/m^2 in 1 liter of dialysis fluid is instilled. On postoperative days two to five, the 5-fluorouracil at 15 mg/kg in 1 liter of dialysis fluid is instilled. Sodium bicarbonate at 50 mEq is added as a buffer to the 5-fluorouracil solution. The drug is allowed to dwell for 23 hours and then removed over one hour by closed suction drains. When drainage ceases, another container of intraperitoneal chemotherapy is infused by gravity as rapidly as possible into the peritoneal cavity. On the sixth postoperative day, all fluid is drained from the peritoneal cavity and the Tenckhoff catheter is withdrawn from the abdomen. The closed suction drains are removed when output is minimal.[7,8]

The completeness of surgery was classified by the operating surgeon. An R-0 resection meant that no tumor was seen free in the peritoneal cavity. An R-1 resection designated no visible evidence of tumor greater than 1 mm in diameter remaining behind in the abdomen. An R-2 resection designated tumor nodules up to 2 cm in diameter, and an R-3 resection designated gross tumor left behind (Table 2).

Delayed intraperitoneal chemotherapy was given after the patients recovered from cytoreductive surgery and early postoperative intraperitoneal chemotherapy. Three additional cycles of delayed intraperitoneal and systemic chemotherapy were given. The 5-fluorouracil was given intraperitoneally at 20 mg/kg for five consecutive days. The mitomycin C was given intravenously at 10 mg/m^2 on the third day of the cycle. Some early patients in the trial had 12 cycles of intraperitoneal 5-fluorouracil and intravenous mitomycin C and did not have early postoperative intraperitoneal chemotherapy.

RESULTS

Male patients accounted for 66.7 percent (46/69), and female patients accounted for 33.3 percent (23/69). The crude three-year survival rate is 66.1 percent in males and 84.2 percent in females. Most patients were concentrated in age groups of 40, 50, and 60 years, as shown in Figure 1.

The most common preoperative presenting symptoms or signs at initial surgery are shown in Table 1. Increasing abdominal girth was the presenting clinical feature in 26.1 percent of cases (18/69), appendicitis in 23.2 percent (16/69), paraappendiceal abscess in 17.4 percent (12/69), abdominal mass in 4.3 percent (3/69), inguinal hernia in 4.3 percent (3/69), small bowel obstruction in 2.9 percent (2/69), acute abdominal pain in 2.9 percent (2/69), and hydronephrosis in 1.5 percent (1/69).

The diagnosis of peritoneal carcinomatosis from appendiceal cancer was confirmed after review of

Table 2.
Classification of Residual Disease

Classification	Description	Number of Patients
R-0	No residual disease, no peritoneal tumor contamination	2
R-1	Microscopic residual disease	43
R-2	Macroscopic residual disease with all tumor nodules <2 cm	19
R-3	Gross residual disease with tumor nodules ≥2 cm	5

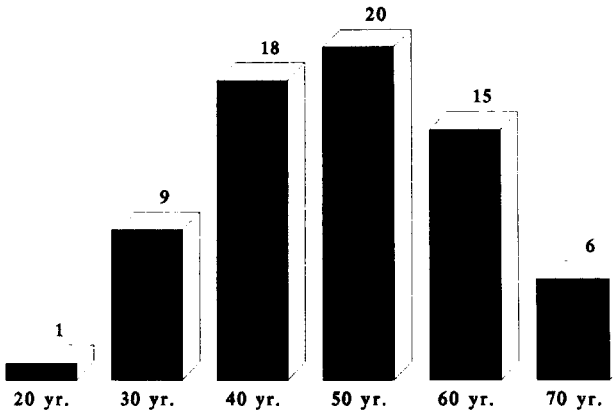

Figure 1. Age groups of patients with appendiceal cancer.

the surgical findings and histopathologic sections. Thirty-eight of 69 cases (55.1 percent) were identified as pseudomyxoma peritonei, 36.2 percent of cases (25/69) were identified as cystadenocarcinoma, and 8.7 percent of cases (6/69) were identified as adenocarcinoma (Table 1). The three-year survival rate is 89.5 percent in patients with pseudomyxoma peritonei, 34.5 percent in patients with cystadenocarcinoma, and 38.1 percent in patients with adenocarcinoma. There is a significant difference between pseudomyxoma peritonei and the two other types ($P < 0.01$) (Fig. 2).

All 69 patients had surgical and pathologic confirmation of peritoneal seeding. The tumor volume was extensive in 89.9 percent of cases (62/69), and it was moderate in 10.1 percent of cases (7/69) (Table 3). The three-year survival rate is 66.3 percent in patients with extensive tumor volume and 100 percent in patients with moderate tumor volume. There is no statistical difference between these groups ($P > 0.1$).

Fifty-four of 69 cases (78.3 percent) had ascites, and 21.7 percent of cases (15/69) had no ascites

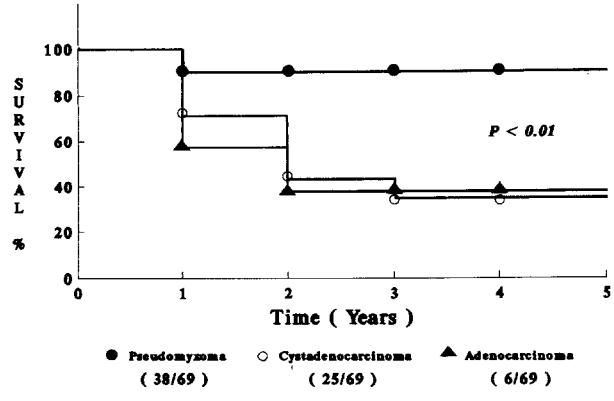

Figure 2. Survival according to surgical-pathologic types in patients with appendiceal cancer.

Table 3.
Pathologic Findings at the Time of Definitive Treatment

Surgical-pathologic types	
Pseudomyxoma peritonei	38 (55.1%)
Cystadenocarcinoma	25 (36.2%)
Adenocarcinoma	6 (8.7%)
Tumor volume	
Extensive	62 (89.9%)
Moderate	7 (10.1%)
Ascites	
Present	54 (78.3%)
Absent	15 (21.7%)
Residual disease	
R-0	2 (2.9%)
R-1	43 (62.3%)
R-2	19 (27.5%)
R-3	5 (7.2%)
Metastases	
Liver	2 (2.9%)
Lung	2 (2.9%)
Lymph nodes	3 (4.3%)
Subcutaneous	1 (1.4%)

(Table 3). The three-year survival rate is 68.5 percent in patients with ascites and 71.4 percent in patients without ascites. There is no statistical difference between these groups ($P > 0.1$).

The classification of residual disease after cytoreductive surgery is described in Table 1. There were two cases of R-0, 43 cases of R-1, 19 cases of R-2, and five cases of R-3. The three-year survival rate is 100 percent in R-0, 91.6 percent in R-1, 47.8 percent in R-2, and 20.0 percent in R-3. There is a significant difference between these groups ($P < 0.01$) (Fig. 3).

Lymphatic or hematogenous metastasis was present at the time of or prior to cytoreductive surgery in eight patients (Table 3). Patients with metastasis showed a 28.6 percent three-year survival rate. In comparison, the prognosis of patients with peritoneal implants but without lymphatic or hematogenous metastasis (61/69) was significantly improved ($P < 0.01$), showing a 75.1 percent three-year survival rate (Fig. 4).

Complications following cytoreductive surgery and early postoperative intraperitoneal chemotherapy are shown in Table 4. The incidence of the complications was 34.8 percent (24/69). There is no statistical difference in survival between the patients without complication and the patients with complication ($P > 0.1$). There was a single postoperative death in a patient with central venous catheter sepsis.

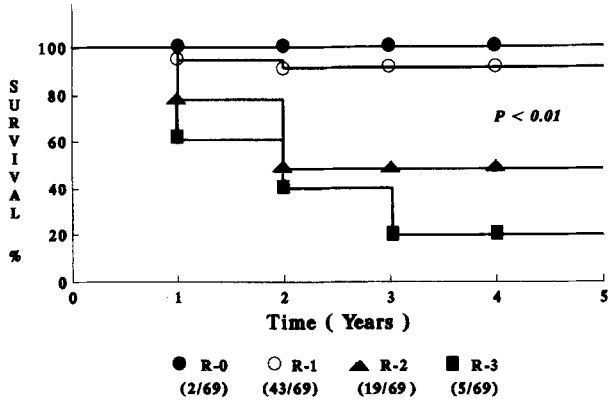

Figure 3. Survival according to volume of residual disease in patients with appendiceal cancer.

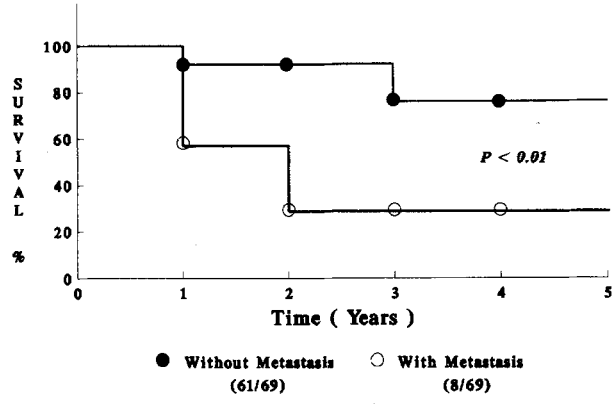

Figure 4. Survival according to the presence of lymphatic or hematogenous metastases in patients with appendiceal cancer.

Table 4.
Complications

Complication	Number of Patients; 24/69 (34.8%)
Small bowel fistula	8
Anastomotic leakage	2
Urine leakage	1
Duodenal leakage	1
Gastroesophageal reflux	2
Subphrenic abscess	1
Postoperative bleeding	3
Pancreatitis	1
Central venous catheter sepsis	2
Bile leakage	1
Peritonitis	1
Left hepatic artery ligated	1

Follow-up studies for all patients have shown that 46.4 percent of patients (32/69) were alive with no evidence of disease (NED), 23.2 percent of patients (16/69) were alive with disease (AWD), 21.7 percent of patients (15/69) died of disease (DOD), and 8.7 percent of patients (6/69) died of other causes (DOC) (Table 1).

Treatment-Failure Analysis

In a treatment-failure analysis that includes all observations, only 12 of the total of 69 patients developed hematogenous or lymphatic metastases, as shown in Table 5. Three patients developed liver metastases. In only one of these patients was there simultaneous local recurrence of disease, and in this patient there was never a complete cytoreduction. Lymph node metastases developed in three patients, and all three of these patients are deceased. One died of other causes. One of these patients had metastasis recurring on abdominal surfaces as well as progressive retroperitoneal lymph node disease. Both other patients remained disease free on abdominal surfaces despite recurrence. Two patients had lung metastases, and one underwent a pulmonary resection. This patient remains NED. One patient died of lung metastases without disease on peritoneal surfaces. Two patients developed both lymph node and lung metastases. These were distant lymph nodes in the groin

Table 5.
Failure Analysis

Metastatic Site	Number (%) of Patients	Status	Peritoneal Surfaces Recurrence
Liver	3 (4.2)	1 DOD 2 AWD	1/3
Right colic lymph nodes	3 (4.2)	2 DOD 1 DOC	1/3
Lung metastases only	2 (2.9)	1 DOD 1 NED	0/2
Lung and distant lymph nodes	2 (2.9)	2 DOD	1/2
Subcutaneous only	1 (1.4)	1 DOD	0/1
Bone only	1 (1.4)	1 DOD	0/1

Implantation Site	Number (%) of Patients	Status
Peritoneal surfaces	23 (33.3)	14 AWD, 9 DOD
Porta hepatis requiring percutaneous biliary stent	3 (4.3)	2 AWD, 1 DOD
Pleural	4 (5.8)	1 NED, 2 AWD, 1 DOD
Pericardial	1 (1.4)	1 DOD

and left axillary nodes. One of these patients had metastasis recurring on peritoneal surfaces. Another patient with lymph node and lung metastases had extensive local recurrence. One patient developed subcutaneous metastases. Approximately 100 subcutaneous nodes occurred over the entire body. There were no other sites of disease. A single patient developed isolated bony metastases (Table 5).

Spread by implantation of the cancer around the peritoneal pleural cavity as a pattern of disease persistence or recurrence was seen in 23 patients. Three patients developed biliary obstruction and required percutaneous stenting. Three patients developed disease within the pleural cavity. This has not yet led to the demise of any our patients. Two patients had the disease in the left pleural cavity, and two had it in the right chest. One patient underwent a thoracotomy and intrapleural chemotherapy with 5-fluorouracil and mitomycin C, and a second patient was treated with intrapleural chemotherapy alone. A single patient was thought to have pericardial effusion secondary to tumor infiltration from the right pleural space. The pericardial tumor was not biopsy confirmed but was thought to lead to the rapid demise of this patient.

DISCUSSION

The natural history of appendiceal malignancy complicated by peritoneal carcinomatosis has never been clearly defined in the past. This series of 69 patients allows us to formulate a concept for the progression of this disease. In the natural history presented here, one must now factor in a novel treatment strategy that seems to salvage many of these patients. This tumor occurs in a thin-walled tubular structure. This results in a high incidence of perforation and seeding of tumor cells into the free peritoneal cavity. Only rarely does the tumor metastasize to the lymph nodes or liver. In this series, only 12 of 69 patients (17.4 percent) developed metastases. Systemic spread may also occur but was unusual. In this failure analysis, all observations from diagnosis of recurrence until the patient's death were recorded.

The natural history of appendiceal cancer is very similar to the natural history of ovarian malignancy. In this disease, a thin-walled structure, the ovarian capsule, frequently perforates before any other symptoms occur. This results in peritoneal seeding early in the natural history of the disease process. In this malignancy, ascites is commonly the initial manifestation of the disease process.

A second important feature of this disease is its low-grade tumor biology. Not only is the tumor rarely found to enter lymphatic channels or vascular channels, but its margins are pushing rather than infiltrating. Tumor cells exist within a copious mucinous matrix and become symptomatic because of this mucin production rather than because of compromise of bowel function. Grade I cystadenocarcinoma tumor closely resembles the tissue of origin, the appendiceal epithelium. Signet-ring cells and extensive mucous production surrounding these tumor cells are usually seen. It is this noninvasive character of the tumor that makes it amenable to complete cytoreduction by a peritoneal stripping procedure.[9]

Spread of disease by implantation onto peritoneal surfaces, into the porta hepatis, into the pleural spaces, or into the pericardial space was the most common type of recurrence in this group of patients. Twenty-three patients developed this mechanism of disease recurrence. Biliary tract obstruction requiring percutaneous biliary stenting was required in three patients. Disease on pleural surfaces was seen in four patients. In two it was on the right side, and in two it was on the left. One patient developed a pericardial effusion and died as a result of this. Recurrent intestinal obstruction was infrequently seen either at presentation or during follow-up. Presumably, the mucinous tumor within the abdomen was free to expand and did not result in narrowing of the bowel lumen. Tumor expanding within the porta hepatis was limited by the surrounding hepatic parenchyma. Its progression of disease narrowed and then obstructed the common bile duct.

It is unlikely that cytoreductive surgery by itself would be effective for long-term control of appendiceal cancer with peritoneal carcinomatosis. Many surgeons have attempted to control cystadenocarcinoma by surgery alone. It is likely that surgery must be combined with intraperitoneal chemotherapy to be effective. The more complete the cytoreduction, the more effective the long-term control of this disease (Fig. 3). The similar survival of patients with bulky disease preoperatively to those with low-volume disease preoperatively most likely reflects the ability of the peritonectomy procedures to reduce the volume to an R-1 extent in a majority of patients.

The grade of cancer not unexpectedly correlates with long-term survival and with the completeness of cytoreduction (Fig. 2). Also the metastatic capacity of the tumor as indicated by lymph node involvement or intrahepatic metastases was a strong prognostic factor (Fig. 4). Local treatments such as cytoreductive surgery and intraperitoneal chemotherapy cannot be expected to cure systemic disease.

REFERENCES

1. Pugeda FV, Hinshaw JP. Primary adenocarcinoma of the appendix. Dis Colon Rectum 1969;12:457–61.
2. Gilhome RW, Johnston DH, Clark J, Kyle J. Primary adenocarcinoma of the vermiform appendix: report of a series of ten cases, and review of the literature. Br J Surg 1984;71:553–5.
3. Lyss AP. Appendiceal malignancies. Semin Oncol 1988;2:129–37.
4. Sugarbaker PH. Cancer of the appendix and pseudomyxoma peritonei. In: Fazio VW, ed. Current therapy in colon and rectal surgery. Philadelphia: BC Decker, 1990:295–301.
5. Sugarbaker PH. Curative treatment of peritoneal carcinomatosis from grade I mucinous adenocarcinoma. Surg Rounds 1988;11:45–63.
6. Sugarbaker PH. Surgical treatment of peritoneal carcinomatosis. Can J Surg 1989:32(Suppl 3):164–70.
7. Sugarbaker PH. Cytoreductive approach to peritoneal carcinomatosis: peritonectomy and intraperitoneal chemotherapy. Postgrad Adv Colorectal Surg 1991;I–X:1–13.
8. Sugarbaker PH. Rationale for integrating early postoperative intraperitoneal chemotherapy into the surgical treatment of gastrointestinal cancer. Semin Oncol 1989;16(Suppl 4):83–97.
9. Sugarbaker PH, Landy D, Jaffe G, Pascal R. Histologic changes induced by intraperitoneal chemotherapy with 5-fluorouracil and mitomycin C in patients with peritoneal carcinomatosis from cystadenocarcinoma of the colon or appendix. Cancer 1990;65:1495–501.