Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy: A New Standard of Care for Appendiceal Mucinous Tumors with Peritoneal Dissemination

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ABSTRACT

In the past, mucinous appendiceal tumors and the pseudomyxoma peritonei syndrome were treated with serial debulking procedures. Some benefit was achieved, but no long-term survivals were seen. A new standard of care that involves the complete removal of all visible disease using peritonectomy procedures combined with intraperitoneal chemotherapy washing has developed. This new approach is jeopardized when extensive prior surgical procedures have violated the peritoneum as a first line of defense of the host against carcinomatosis. In patients who have a complete cytoreduction, a 5-year survival of 80% is expected. In patients who have an incomplete cytoreduction, no 10-year survivors are seen. These studies suggest a new standard of care for appendiceal mucinous tumors with peritoneal dissemination.

KEYWORDS: Cytoreductive surgery, peritonectomy procedures, intraperitoneal chemotherapy, adenomucinoses, mucinous carcinomatosis

Objectives: Upon completion of this article, the reader will be acquainted with a new and more effective treatment plan for an unusual disease: mucinous appendiceal cancer with peritoneal dissemination.

Neoplasms of the appendix are rare gastrointestinal tumors. They constitute 0.4% of all intestinal neoplasms. Only 1% of all large bowel cancers arise from the appendix. The infrequent occurrence, a unique natural history, and a complex histopathology of appendiceal malignancy have caused the therapy to be complex. For epithelial malignancy of the appendix, a majority of the tumors have perforated at the time of definitive surgical treatment; consequently, the physician is required to manage the primary tumor and its peritoneal surface

dissemination. Despite carcinomatosis often in large volume present at the time of initial diagnosis, liver metastases and lymph node metastases seldom occur throughout the duration of the disease. To improve salvage of patients with perforated tumors and those with documented distant spread within the abdominal cavity, a new and curative approach to this previously uniformly lethal condition (the spread of tumor on peritoneal surfaces) is now widely accepted as a standard of practice.

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SURVEY OF APPENDICEAL MALIGNANT TUMORS

The two most commonly occurring malignant tumors of the appendix are carcinoid and adenocarcinoma. Approximately two thirds of appendiceal malignancies are carcinoid. The other one third are variations of adenocarcinoma. A survey of five different histologic types of appendiceal malignancy is presented in Table 1.

Carcinoid Tumors

The most common tumor within the appendix is the carcinoid. This neuroendocrine tumor is usually found incidentally during the removal of an asymptomatic appendix. A small, hard tumor mass of yellow coloration is found in the distal portion of the appendix. The appendix is the site of 45% of all gastrointestinal carcinoid tumors. Although 90% of appendiceal carcinoids are incidental findings, ~10% result in acute appendicitis. The combination of mucinous appendiceal malignancy and a carcinoid tumor in the same appendix specimen has been observed; finding two separate rare tumors in the same small organ raises interesting questions about the high cancer propensity in this small organ.

Adenocarcinoid Tumors of the Appendix (Goblet Cell Carcinoid)

A small percentage of carcinoid tumors have malignant epithelial cells producing abundant mucus scattered among the carcinoid tumor cells. In the Washington Cancer Institute series the adenocarcinoid patients were 2.5% of the total number with appendiceal malignancies. Usually these tumors have dissecting mucus diffusely infiltrating the wall of the appendix rather than an innocuous occurrence at the tip of the organ as is usually seen with a carcinoid. More frequently than with carcinoid tumors, the adenocarcinoid arises as acute appendicitis. The 5-year survival rate of such patients is greatly reduced compared with that of patients with carcinoid. This occurs because adenocarcinoid patients usually have extensive peritoneal carcinomatosis at the time of initial diagnosis. These patients have dissecting mucus produced in large quantity by the cancer. The wide distribution on peritoneal surfaces results in a grim prognosis unless they receive special treatments for peritoneal surface malignancy.¹

Epithelial Malignancy of the Appendix

The most common varieties of epithelial malignancy within the appendix are mucinous adenomas or mucinous adenocarcinomas. The mucinous tumors are 20 times more common than the intestinal type of adenocarcinoma in the Washington Cancer Institute

database. In contrast, only ~15% of colonic adenocarcinomas are of the mucinous variety. The preponderance of mucinous tumors is probably related to the high proportion of goblet cells within the appendiceal epithelium. A comparison of clinical and histologic features of colorectal and appendiceal malignant tumors is presented in Table 2.

On gross examination, it may be difficult or impossible to distinguish a mucinous tumor of the appendix from a benign mucocele. Both benign and malignant tumors of the appendix are likely to cause appendicitis, and there may be mucin collections within the right lower quadrant or throughout the abdominopelvic space. Two questions should be answered that will histopathologically separate tumors as inconsequential with complete removal from those capable of causing death from progressive pseudomyxoma peritonei syndrome:

1. Is there invasion through the appendiceal wall by neoplastic tumors and perforation?
2. Are atypical epithelial cells found within the extra-appendiceal mucin collection?

If either of these clinical features occurs, special follow-up and aggressive treatments are required.

The most common clinical entity arising from an appendiceal tumor is the pseudomyxoma peritonei syndrome.² This clinical entity has a perforated appendiceal adenoma or villous adenoma as its primary site. Hyperplastic polyps, adenomatous polyps, and villous polyps within the appendix that have resulted in an appendiceal perforation are implicated in the pseudomyxoma peritonei syndrome.^{3,4} The mucus accumulations that are distributed in a characteristic fashion around the peritoneal cavity are referred to as adenomucinosis.^{5,6} Histologically, epithelial cells in single layers are surrounded by pools of mucin. These epithelial cells show little atypia, absent mitosis, and result in mucinous tumor accumulations that follow the flow of peritoneal fluid within the abdomen and pelvis. Invasion of organs by mucinous tumor does not occur. Disruption of enteric function results from mucinous tumor accumulation in large volume compressing stomach and loops of bowel.

A second less common histologic type of appendiceal adenocarcinoma is the intestinal type of tumor. It is often referred to as the nonmucinous histologic type. This cancer is usually located at the base of the appendix and resembles colonic adenocarcinoma in its histopathologic appearance. It is locally invasive and results in carcinomatosis proximal to the appendix, usually in the right paracolic sulcus and pelvis, especially in the cul-de-sac. This malignancy is 20 times more likely to have positive lymph nodes than adenomucinosis.⁷

Table 1 Comparison of Five Different Appendiceal Tumors

	Carcinoid	Adenocarcinoid	Pseudomyxoma Peritonei	Mucinous Adenocarcinoma	Adenocarcinoma Intestinal Type
Approximate incidence	66%	Rare	20%	Rare	10%
Location	Tip of appendix	Diffuse along appendix	Middle to tip of appendix	Diffuse along appendix	Base of appendix
Major symptom	Incidental finding	Expanding abdomen, ovarian mass	Expanding abdomen, ovarian mass, hernia, appendicitis	Appendicitis	Appendicitis
Prognosis	< 1 cm 100% cure > 2 cm 50% cure	84% cure 5 years if unperforated; 30% cure 5 years if perforated	Localized 100% cure Adenomucinos 90% cure at 5 years	Poor	Follows Dukes' stages A—80% cure B—50% cure C—20% cure
Histopathology of peritoneal surface implants	Carcinoid	Carcinoid plus mucinous adenocarcinoma	Adenomucinos	Mucinous carcinomatosis	Intestinal type (nonmucinous) adenocarcinoma
Clinical syndromes	Carcinoid	Mucinous peritoneal carcinomatosis	Pseudomyxoma peritonei	Mucinous peritoneal carcinomatosis	Peritoneal carcinomatosis
Treatment	< 1 cm appendectomy only > 2 cm right colectomy + cytoreductive surgery	Appendectomy only or cytoreductive surgery + intraperitoneal chemotherapy	Appendectomy + cytoreductive surgery + intraperitoneal chemotherapy	Cytoreductive surgery + intraperitoneal chemotherapy	Right colectomy or cytoreductive surgery + intraperitoneal chemotherapy if peritoneal implants

In separating pseudomyxoma peritonei, adenocarcinoma, and mucinous adenocarcinoma, it must be remembered that these represent a spectrum of disease and are probably not distinct clinical entities. Benign mucocoele is not included as an appendiceal tumor but is rather a cystic process. A perforated mucocoele resulting from an appendiceal polyp usually develops into pseudomyxoma peritonei. Tumors that histologically are between adenomucinos and mucinous carcinomatosis are designated as hybrid type.

Table 2 Comparison and Contrast of Colorectal and Appendiceal Malignant Tumors

	Colon	Appendix
Adenocarcinoma incidence	85%	10%
Carcinoid incidence	< 1%	70%
Mucinous adenocarcinoma	10%–15%	20%
Signet ring adenocarcinoma	1/1000	1/10
Adenocarcinoid	Not reported	Rare
Differentiation of adenocarcinoma	20% well 60% moderate 20% poor	60% well 20% moderate 20% poor
Associated malignancy	Unusual	Common

A third histologic type of appendiceal adenocarcinoma is the mucinous adenocarcinoma. This more invasive tumor type tends to involve the appendix diffusely. Yan and colleagues described three different variants as well, moderately, and poorly differentiated. The poorly differentiated histologic type contains signet ring cells.⁸ Ronnett and colleagues in their histologic description of the mucinous appendiceal tumors found a small proportion of patients with pseudomyxoma peritonei syndrome with small foci of mucinous adenocarcinoma within the large volume of adenomucinosi.⁴ Clinically, these tumors arose with the typical pseudomyxoma peritonei syndrome but were associated with a reduced prognosis similar to that of patients with mucinous carcinomatosis.⁹ Tumors with a predominant histology of adenomucinosi but foci (less than 5% of fields) of mucinous adenocarcinoma are referred to as hybrid histologic type.

DIAGNOSIS OF EPITHELIAL APPENDICEAL TUMORS

The preoperative diagnosis in patients with adenocarcinoma of the appendix is usually appendicitis, a right lower quadrant abscess, or tumor mass (Table 3). Mucinous appendiceal cancer has usually perforated prior to diagnosis.¹⁰ This results in tumor spread bilaterally to the ovary, or the tumor may arise as peritoneal carcinomatosis within a hernia sac. An aggressive mucinous adenocarcinoma may invade the retroperitoneum and appear as a mucus accumulation in the buttock or thigh. Also, abdominal wall invasion with an enterocutaneous fistula or bladder invasion with an enterovesical fistula may occur. Obstruction of the right ureter by a mucus-containing mass or invasion into the urinary bladder has also occurred.

Pseudomyxoma Peritonei Syndrome

These minimally invasive appendiceal tumors have a high propensity for spread to peritoneal surfaces but are unlikely to metastasize through lymphatic channels into lymph nodes or through venules into the liver.⁷

Table 3 Diagnosis of Appendix Cancer at Time of Laparotomy in 296 Case Reports

Diagnosis	No. of Patients	Percent
Acute appendicitis	139	47
Ruptured appendix with or without abscess	53	18
Intra-abdominal cancer or right lower quadrant mass	30	10
Inguinal hernia or chronic appendicitis	17	5
Incidental operations except for cholecystitis*	14	—
Cholecystitis (acute and chronic)†	10	—
Ovarian tumor or cyst	10	—
Small bowel obstruction	8	—
Right-sided groin mass or fistula	6	—
Acute abdomen	4	—
Appendiceal carcinoma	3	—
Hydronephrosis	2	—
Total	296	—
Autopsy finding‡	10	—

*Preoperative diagnoses include gynecologic cases (eight) and one each of incisional hernia, gastric, esophageal, and sigmoid cancer, duodenal ulcer, and torsion of the small bowel.

†Not listed as incidental because the present symptom complex may have been related to appendiceal disease in some cases.

‡Some patients died with a postmortem diagnosis of metastatic malignancy.

Modified from Lyss.¹⁰

After the appendiceal tumor ruptures the wall of the appendix, adenomucinosi may progress for months or even years within the abdomen and pelvis without causing other symptoms (Fig. 1). When this occurs, the clinical syndrome termed pseudomyxoma peritonei occurs. The peritoneal cavity becomes filled in a characteristic pattern with mucinous tumor and mucinous ascites. The greater omentum is greatly thickened (omental cake) and extensively infiltrated by tumor (Fig. 2). All parts of the abdomen that entrap malignant cells are also layered by tumor, which involves the undersurface of the right and left hemidiaphragms, the right subhepatic space, the splenic hilus, the right and left abdominal gutters, and especially the pelvis and cul-de-sac. An important clinical feature of pseudomyxoma peritonei is the sparing of the mobile portions of the small bowel by this process (Fig. 3). Because the small bowel is spared of tumor involvement, removal of the involved parietal and visceral peritoneal surfaces by peritonectomy procedures combined with intraperitoneal chemotherapy may provide long-term disease-free survival in over 80% of patients.

The symptoms and signs of pseudomyxoma peritonei are quite different from those of appendiceal adenocarcinoma. The most common symptom in both men and women with pseudomyxoma peritonei syndrome is a gradually increasing abdominal girth.¹¹ In women, the second most common symptom is an

Figure 1 The distal portion of the appendix has ruptured from the pressure of mucin accumulation within the mucocoele. Adenomatous epithelial cells become widely distributed on peritoneal surfaces. The silk suture is on the base of the appendix.

ovarian mass, usually on the right side and frequently diagnosed at the time of a routine gynecologic examination. In men, the second most common symptom is a new-onset hernia. The hernia sac is found to be filled by mucin and/or mucinous tumor. In both males and females, the third most common presenting feature is appendicitis. This is the clinical manifestation of rupture of an appendiceal mucocoele that contains intestinal bacteria. The patients who present with appendicitis have a higher incidence of more aggressive histology and lymph node involvement. The symptoms and signs of pseudomyxoma peritonei syndrome are itemized in Table 4.

There is a caveat that should be mentioned regarding the "benign mucocoele" of the appendix. If a mucocoele of the appendix is found at the time of a planned laparoscopic appendectomy, open appendectomy should be performed.¹² Laparoscopic resection of a mucocoele is likely to cause rupture of that structure, and pseudomyxoma peritonei syndrome may then result months or even years later. Resection of the appendiceal mass without traumatic rupture and without tumor

Figure 2 "Omental cake" characteristically present in patients with pseudomyxoma peritonei. Lymphoid aggregates cause mucinous tumor cells to accumulate within greater and lesser omentum and omental appendages.

spillage results in a complete eradication of the disease process.¹³

A second caveat regarding the use of laparoscopy in patients with ascites needs to be noted. When a patient presents with increasing abdominal girth as a result of presumed malignant ascites, a paracentesis or laparoscopy with biopsy is usually performed to establish a diagnosis. In many female patients, an ovarian neoplasm is found. In others, a perforated adenocarcinoma from the colon, stomach, gallbladder, or appendix is found. The remainder of these patients have a peritoneal surface tumor such as peritoneal mesothelioma, papillary serous tumor, or primary peritoneal adenocarcinoma (formerly referred to as adenocarcinoma of unknown site). In all instances, paracentesis or laparoscopy with biopsy should be performed directly within the midline and through the linea alba. These sites can be excised as part of a midline abdominal incision. No lateral puncture sites or port sites should be used because these will seed the abdominal wall by tumor and greatly interfere with disease eradication. Cytoreductive surgery and intraperitoneal chemotherapy are not effective for tumor within the abdominal wall.

Figure 3 When the omentum is elevated, there is a sparing of small bowel by this tumor.

TREATMENT AND PROGNOSIS OF EPITHELIAL APPENDICEAL TUMORS

Management of Appendiceal Adenocarcinoma

In patients with invasive nonmucinous adenocarcinoma of the appendix, a right hemicolectomy is suggested to

result in nearly twice the survival rate that occurs following routine appendectomy.¹⁴ Therefore, all patients with invasive appendiceal adenocarcinoma, whether or not lymph nodes are involved, should receive a right hemicolectomy either during the same surgical procedure in which the appendectomy is performed or in a subsequent procedure. Certainly, when the surgeon performing an appendectomy finds that the appendix is infiltrated by an aggressive malignant process, emergency cryostat sectioning should be performed. If there is adequate bowel preparation and if a diagnosis of adenocarcinoma can be made definitively, one should proceed without hesitation with a right hemicolectomy procedure. In some patients a cecectomy with preservation of the ileocecal valve has been utilized. This is recommended if the appendiceal lymph nodes are negative by cryostat sectioning.

Management of Mucinous Tumors with Peritoneal Dissemination

A majority of patients with mucinous tumors of the appendix show perforation of the appendix at the time of exploration. In most of these patients, peritoneal carcinomatosis or pseudomyxoma peritonei is found at the time of appendectomy. In the past, this was a lethal condition without exception. More recently, peritonectomy procedures combined with intraperitoneal chemotherapy have been employed for the treatment of pseudomyxoma peritonei and peritoneal carcinomatosis.¹⁵ The essential features of this approach are diagrammed in Figure 4. The surgeon is responsible for doing as much as possible to remove all tumor on peritoneal surfaces. This is done by a cytoreductive procedure in patients who have gross spread of tumor around the peritoneal cavity. It involves a greater and lesser omentectomy and splenectomy. This is followed by peritonectomy procedures to strip tumor from the abdominal gutters, pelvis, right subhepatic space, and right and left subphrenic spaces.¹⁶

Table 4 Symptoms and Signs of Patients Presenting with Pseudomyxoma Peritonei Syndrome

	No. of Patients	Men	Women
Appendicitis	58 (27)*	36 (34)	22 (20)
Increased abdominal girth	49 (23)	28 (27)	21 (19)
Ovarian mass	44 (20)	—	44 (39)
Hernia	30 (14)	26 (25)	4 (4)
Ascites	9 (4)	5 (5)	4 (4)
Abdominal pain	8 (4)	5 (5)	3 (3)
Other	19 (9)	5 (5)	14 (12)
Total	217 (100)	105 (48)	112 (52)

*Values in parentheses are percentages.
From Esquivel and Sugarbaker, with permission.¹¹

Perioperative Intraperitoneal Chemotherapy

After the resection, and with the abdomen open, the peritoneal space is extensively washed by the surgeon's hand using gauze débridement of all surfaces. This is done in the presence of a warm mitomycin C chemotherapy solution (Fig. 5). Also, a window of time exists in which all intraperitoneal surfaces are available for intraperitoneal chemotherapy utilizing 5-fluorouracil in the early postoperative period. Uniformity of treatment with intraperitoneal chemotherapy to all peritoneal surfaces, including the surfaces dissected by the surgeon, can be achieved if the intraperitoneal chemotherapy is used during the first postoperative week. As the postoperative 5-fluorouracil chemotherapy solution is

Figure 4 Approach to the treatment of peritoneal carcinomatosis from appendix cancer.

dwelling, distribution is facilitated by systematically turning the patient alternately onto the right and left side as well as into the prone position.¹⁵

This perioperative intraperitoneal chemotherapy (combination of heated intraoperative mitomycin C and early postoperative 5-fluorouracil) has been utilized in

Figure 5 Intraoperative hyperthermic intraperitoneal chemotherapy. The skin edges are suspended on a self-retaining retractor. Warm (41–42°C) chemotherapy solution is perfused while being manually distributed throughout the abdomen and pelvis.

over 850 patients and has not been associated with an increased incidence of anastomotic disruptions.¹⁷ In patients who have had extensive prior surgical procedures who require many hours of lysis of adhesions, there is an increased incidence of postoperative bowel perforation. This is presumably a result of the combined effects of damage to small bowel from electrosurgical dissection of adhesions (seromuscular damage) and systemic effects of intraperitoneal chemotherapy on the intestine (mucosa and submucosa damage).

In patients who have high-grade appendiceal mucinous peritoneal carcinomatosis, intravenous chemotherapy is recommended. Usually, capecitabine and oxaliplatin for 6 months are appropriate.

In selected patients, usually those who require ostomy closure, at approximately 6 months after the cytoreduction with perioperative chemotherapy, a second-look surgery is recommended. If at the staging celiotomy small tumor foci are found on peritoneal surface of the abdomen or pelvis, the nodules are resected and a final intraperitoneal chemotherapy treatment is performed.

Prior Serial Debulking Jeopardizes Definitive Cytoreduction

It is important that definitive treatment of peritoneal carcinomatosis or pseudomyxoma peritonei be instituted in a timely fashion. Each nondefinitive (debulking) surgical intervention makes potentially curative cytoreductive surgery more difficult. Respect for the peritoneum as the first line of defense of the host against carcinomatosis is a requirement for optimal results using the peritonectomy procedures. Also, the relative sparing of the small bowel seen early in the natural history of peritoneal carcinomatosis and pseudomyxoma peritonei disappears after several surgical procedures have been performed. The fibrous adhesions that inevitably result become infiltrated by tumor. This leads to extensive involvement of the small bowel by the malignant process. Eventually it becomes impossible to cytoreduce the tumor safely, and the effects of the intraperitoneal chemotherapy by itself are not adequate to keep the patient disease free.

RESULTS OF TREATMENT WITH CYTOREDUCTIVE SURGERY AND INTRAPERITONEAL CHEMOTHERAPY

The results of these treatments for peritoneal surface dissemination of appendiceal malignancies are unexpectedly good. The results of treatment of 385 patients with prolonged follow-up have been reported.¹⁸

Survival by Completeness of Cytoreduction

The mean follow-up of this group of 385 patients with appendiceal malignancy was 37.6 months; all appendiceal malignancy patients including those with adenomucinoses and mucinous adenocarcinoma subtypes are included. All patients had documented peritoneal surface disease, and a majority had large-volume disease. After the completion of the cytoreductive surgery, all these patients had the abdomen inspected for the presence or absence of residual disease. A completeness of cytoreduction score was obtained for all patients. The completeness of cytoreduction score was based on the size of individual tumor nodules remaining unresected.¹⁹ A CC-0 score indicated no visible tumor remaining after surgery. A CC-1 score indicated tumor nodules smaller than 2.5 mm. A CC-2 score indicated tumor nodules between 2.5 mm and 2.5 cm. A CC-3 score indicated tumor nodules larger than 2.5 cm or a confluence of implants at any site. In Figure 6, the survival of patients who had a complete cytoreduction (CC-0 and CC-1) is compared with that of patients with an incomplete cytoreduction (CC-2 and CC-3). Survival differences were significant with a p value of less than 0.0001; patients who left the operating room after cytoreductive surgery with tumor nodules smaller than 2.5 mm in

Figure 6 Survival by cytoreduction of appendiceal malignancy with peritoneal dissemination.

diameter remaining were much more likely to survive in the long term than those with an incomplete cytoreduction. There were no significant differences in survival between patients with CC-2 and CC-3 cytoreductions (data not shown).

Survival by Histology

At the time of cytoreductive surgery and whenever possible from a review of the primary appendiceal malignancy, a histological assessment was made. The histologic subtypes of adenomucinoses, hybrid, and mucinous adenocarcinoma have been described.⁴ Adenomucinoses included minimally aggressive peritoneal tumors that produced large volumes of mucous ascites. The primary appendiceal tumor was often described as a cystadenoma. Hybrid malignancies showed adenomucinoses combined with isolated foci of mucinous adenocarcinomas (less than 5%). Mucinous adenocarcinoma showed an invasive process. Often, the signet ring morphology and poor differentiation were observed.

Figure 7 shows the survival distribution of these patients with appendix malignancy by histology. The survival differences between patients with adenomucinoses and those with hybrid or mucinous adenocarcinoma were significant with a p value of less than 0.0001. A noninvasive histopathology is extremely important in selecting patients who are most likely to benefit from this treatment strategy. There were no significant differences between patients with hybrid and mucinous adenocarcinoma histology (data not shown).

Survival by Prior Surgical Score

When the previous operative notes on these patients were reviewed, a judgment was made regarding the anatomical sites of previous surgical dissections. The summation of these dissections from all prior surgical

Figure 7 Survival by histology of appendiceal malignancy with peritoneal dissemination.

interventions was recorded on a diagram of the abdominopelvic regions.¹⁹ This allowed an assessment of the anatomical locations in which previous surgery had been performed. In patients with a prior surgical score (PSS) of 0, diagnosis of peritoneal carcinomatosis was obtained through biopsy only or laparoscopy plus biopsy. PSS 1 indicated only a previous exploratory laparotomy. PSS 2 indicated exploratory laparotomy with some resections. Usually this was a greater omentectomy or greater omentectomy plus a right colectomy. With a PSS of 3, patients had an attempt at a complete cytoreduction. This was usually greater omentectomy, right colectomy, hysterectomy, and bilateral salpingo-oophorectomy, with the possibility of other resections from both abdominal organs or parietal peritoneal regions. The survival distribution by PSS is shown in Figure 8. Patients with PSS scores of 0 through 2 had improved survival compared with those with a PSS of 3. The *p* value was 0.001.

Peritoneal Surface Malignancy – Appendix Survival by Prior Surgical Score

Figure 8 Survival by prior surgical score of appendiceal malignancy with peritoneal dissemination.

Figure 9 Survival of 21 patients with adenocarcinoid and peritoneal carcinomatosis.

Survival Analysis by Cox Semiparametric Model

All of the significant clinical features were statistically analyzed to determine their dependent versus independent status. The independent variables were determined to be complete versus incomplete cytoreduction. All the other clinical features investigated were found to have no independent predictive value. Complete versus incomplete cytoreduction had a risk ratio of 9.98. The 95% confidence limits were 4.23 to 23.09.

Results of Treatment of Patients with Adenocarcinoid Appendiceal Malignancy

In the database at the Washington Cancer Institute, 21 patients had a diagnosis of adenocarcinoid of the appendix with peritoneal carcinomatosis.¹ All patients had peritoneal seeding, and most patients had a high peritoneal carcinomatosis index. All patients were explored and cytoreduction was attempted. If the cytoreduction was complete, intraoperative and early postoperative intraperitoneal chemotherapy was used. The survival distribution of patients having surgical removal of adenocarcinoid is shown in Figure 9. In selected patients an attempt at complete cancer resection is warranted. If a debulking results in gross residual disease, only palliative surgical efforts associated with low morbidity and mortality are indicated because survival is limited.

MORBIDITY AND MORTALITY

The extensive cytoreductive surgery combined with early postoperative intraperitoneal chemotherapy presents a major physiological insult. Nevertheless, the mortality rate remains at 2% in this group of patients. Pancreatitis (7.1%) and fistula formation (4.7%) are the major complications. Anastomotic leaks were no more common in

this group of patients than in a routine general surgical setting (2.4%). The overall grade III/IV morbidity was 27%. There was no morbidity or mortality directly associated with the intraperitoneal chemotherapy administration. Rather, the incidence of complications depended on the extent of the surgery, number of peritonectomy procedures, and time required to complete the cytoreduction.¹⁷

SUMMARY OF TREATMENT STRATEGIES FOR A NEW STANDARD OF CARE FOR MUCINOUS APPENDICEAL TUMORS WITH PERITONEAL DISSEMINATION

Peritonectomy

In this treatment strategy for patients with peritoneal dissemination from appendiceal malignancy, there were several distinct changes in the techniques used for surgery. Because of the very limited penetration of tumor nodules by chemotherapy, the cytoreduction attempted to reduce the cancer within the abdomen and pelvis to its smallest volume. This required the use of peritoneal stripping procedures, now commonly referred to as peritonectomy procedures.¹⁶ These procedures often required many hours in the operating room. Frequently, they left the abdomen without peritoneal surfaces except that which was found on the small bowel. This approach represents a departure from the previous conservative surgical approach to peritoneal carcinomatosis.

Perioperative Intraperitoneal Chemotherapy

Several changes occurred in the use of chemotherapy in this population of patients. First, the route of chemotherapy administration was changed from intravenous to intraperitoneal. Maximal doses of intraperitoneal mitomycin C and intraperitoneal 5-fluorouracil were used. This intraperitoneal chemotherapy was instilled perioperatively to make contact with all the abdominal and pelvic surfaces before the onset of wound healing. Once fibrinous deposits became organized, the chemotherapy would be unable to reach the residual tumors and local recurrence would occur where the surfaces were adherent (Table 5).

The timing of chemotherapy administration was also changed. Chemotherapy was used in the perioperative period rather than 4 to 6 weeks after surgery in an adjuvant setting.

Perhaps most important for long-term favorable results, the selection of patients for treatment was changed. Only after a maximal cytoreductive surgical procedure were patients with minimal peritoneal surface disease treated. The target of these therapies was not metastases present at distant sites such as the liver, bone marrow, or lungs; rather, the target for these therapies

Table 5 Suggested Changes in the Use of Chemotherapy for Appendiceal Mucinous Tumors with Peritoneal Dissemination

Chemotherapy Methodology	Change Suggested
1. Route	Intraperitoneal versus intravenous
2. Timing	Perioperative versus systemic adjuvant
3. Patient selection	Minimal residual peritoneal surface disease versus systemic disease
4. Target	Spread versus metastases
5. Surgical approach	Peritonectomies versus debulking
6. Results	Benefit versus previous failure

was macroscopic residual disease on both the parietal and visceral surfaces. Patients with metastases that could not be resected or gross residual peritoneal surface malignancy after completion of the cytoreductive surgery were excluded from these treatments.

It has been shown that with these changes in chemotherapy and changes in surgical approach, patients with peritoneal dissemination of mucinous appendiceal tumors may have a curative treatment option. It is hoped that the previous failures of serial debulking and palliative chemotherapy for pseudomyxoma peritonei can be converted to success with this new combination of surgery plus regional chemotherapy.

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