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FOR DEBATE

Cytoreductive surgery and peri-operative intraperitoneal chemotherapy as a curative approach to pseudomyxoma peritonei syndrome

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Peritoneal carcinomatosis, regardless of primary tumour type, has always been a lethal condition. Recently special treatments using cytoreductive surgery with peritonectomy procedures combined with peri-operative intraperitoneal chemotherapy have resulted in long-term survival. Pseudomyxoma peritonei may be especially appropriate for these aggressive local regional treatments.

All patients treated prior to 1999 are presented; patients left with gross residual disease after surgery were not given intraperitoneal chemotherapy, but were later treated with intravenous chemotherapy after cytoreduction. The intraperitoneal chemotherapy was given in the peri-operative period, starting with mitomycin C. For patients whose pathology showed adenomucinosis, intraperitoneal chemotherapy was limited to treatment in the operating theatre with heated mitomycin C. Patients with mucinous adenocarcinoma or pseudomyxoma/adenocarcinoma hybrid had, in addition to mitomycin C, 5 consecutive days of intraperitoneal 5-fluorouracil. A complete cytoreduction was defined as tumour nodules <2.5 mm in diameter remaining after surgery. The histopathology categorized the patients as adenomucinosis, intermediate type, or mucinous carcinomatosis. A prior surgical score was used to estimate the extent of previous surgical procedures.

The morbidity of treated patients was 27% and the mortality was 2.7%. In a multivariate analysis, prognostic factors for survival included the completeness of cytoreduction ($P<0.0001$), the histopathological character of the appendix malignancy ($P<0.001$) and the extent of previous surgical interventions ($P=0.001$). Patients with a complete cytoreduction and adenomucinosis by pathology had a 5-year survival of 86%; while hybrid pathology survival at 5 years was 50%. Incomplete cytoreduction had a 5-year survival of 20% and 0% at 10 years.

Cytoreductive surgery and peri-operative intraperitoneal chemotherapy is the current standard treatment for selected patients with peritoneal surface spread of appendiceal primary tumours. Similar strategies for other patients with peritoneal surface malignancy such as peritoneal carcinomatosis from colon or gastric cancer, peritoneal sarcomatosis, or peritoneal mesothelioma should be pursued.

Key words: appendix cancer; intraperitoneal chemotherapy; pseudomyxoma peritonei; cytoreduction.

INTRODUCTION

The appendix as a primary cancer site for the seeding on peritoneal surfaces is somewhat unique.[1] Firstly, appendix cancer is of low biological aggressiveness. Rarely does it involve lymph nodes and it almost never metastasizes to the liver. These mucinous adenocarcinomas are minimally invasive in that they coat the perioneal surfaces rather than penetrate into the tissues.

Secondly, appendiceal malignancy causes peritoneal dissemination early in the natural history of the disease. The primary malignancy, usually characterized as an appendiceal adenoma, enlarges so that the walls of the appendix are stretched to bursting point. The wall of the appendix leaks tumour cells into the peritoneal cavity.

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Thus, peritoneal dissemination usually occurs prior to the involvement of lymph channels or venules in the appendiceal wall or in the mesoappendix; lymph-node metastases and liver metastases are very rarely found.

Thirdly, the mucinous tumour accumulates at anatomic sites resectable by the peritonectomy procedures. The mucus provides the fluid for widespread dissemination of the tumour cells to specific anatomic sites within the abdomen. These are the surfaces which absorb peritoneal fluid and those that are dependent, especially the right retrohepatic space and the pelvis. Peritoneal fluid is absorbed on the undersurface of the right hemidiaphragm through the lymphatic lacunae and on the greater and lesser omental surfaces through lymphoid aggregates. Dependent portions of the abdomen and pelvis become a site for mucinous tumour accumulations. Therefore, tumour volume will be greatest within the greater and lesser omentum, within the pelvis, beneath the right lobe of the liver, in the right retro-hepatic space, at the ligament of Treitz, and in the abdominal gutters.

A fourth unusual feature of appendical malignancy is the redistribution phenomenon.[2] Small bowel, which is active in peristalsis nearly all of the time, prevents non-invasive cancerous deposits from implanting on its surface. The small bowel becomes compartmentalized as a tumour-free area. The stomach and large bowel are variably involved, but to a lesser extent than quiescent surfaces such as the liver, gallbladder and parietal peritoneum. This sparing of the small bowel surfaces makes cytoreductive surgery, with a near complete removal of all cancer from the abdominal cavity, a possibility.

Finally, the appendix is located within a body cavity, so that all surfaces involved by the malignant process are exposed to high concentrations of regional chemotherapy. Tumour removal by the cytoreductive surgery can be augmented by regional chemotherapy to prevent residual tumour cells from implanting in the traumatized peritoneal surfaces and causing progressive disease at a later time.

In summary, there are five distinctive features of appendiceal malignancies that allow for a curative approach to peritoneal dissemination from this primary site. For this reason, peritoneal surface spread from appendiceal cancer is considered a paradigm for treatment of selected patients with abdominal and pelvic dissemination of gastrointestinal malignancy limited to peritoneal surfaces. Progress with this unusual disease process may lead the clinical researcher to success in the treatment or in the prevention of peritoneal carcinomatosis from other gastrointestinal cancers.

OVERALL TREATMENT STRATEGY

The methods used to definitively treat appendiceal malignancy combine maximal surgery with maximal regional chemotherapy. These two therapies are blended together into a single treatment plan. The surgery involves between one and six peritonectomy procedures.[3] These peritonectomy procedures utilize electro-evaporative surgery to gain a minimal but adequate margin of excision.[4] Intraperitoneal chemotherapy is used peri-operatively.[5]

DATA ANALYSIS

Age, sex, preresection lesion size, presence *vs* absence of ascites, pre-operative carcinoembryonic antigen, free interval from diagnosis of primary appendiceal malignancy until treatment of peritoneal carcinomatosis, distribution of tumour, intraoperative blood requirement, presence *vs* absence of lymph-node metastases, post-operative complications and extent of surgery were not found to be significant prognostic variables.[6] However, histopathology of malignancy, completeness of cytoreduction and extent of prior surgery were significant. The survival curves for these clinical variables were calculated based on the method of Kaplan and Meier. A log-rank test was calculated to compare survival curves. *P*-values were calculated for each analysis.[7]

SURVIVAL BY COMPLETENESS OF CYTOREDUCTION

The mean follow-up of 385 pseudomyxoma peritonei syndrome patients was 37.6 months. After the completion of cytoreductive surgery, all these patients had the abdomen inspected for presence or absence of residual disease. A completeness of cytoreduction score was determined for all patients. The completeness of cytoreduction score was based on the size of individual tumour nodules remaining unresected.[8] Table I describes the completeness of cytoreduction (CC) score. It should be noted that the number of nodules and their distribution were not considered in assessing the completeness of cytoreduction. Patients who had a confluence of malignancy so that sheets of tumour >2.5 cm remained after the cytoreduction were given a CC-3 score. In Figure 1, the survival of patients who had a complete cytoreduction (CC-0 and CC-1) is compared to those with an incomplete cytoreduction (CC-2 and CC-3). Survival differences were significant with a *P*-value of <0.0001. There were no significant differences in survival between patients with CC-2 and CC-3 cytoreductions.

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 designations of adenomucinosis, intermediate type and mucinous adenocarcinoma have been described.[9]

Table 1 Completeness of cytoreduction score

CC-0 (*en bloc* resection	Nodules not visible
CC-1 (complete cytoreduction)	Nodules <0.25 cm
CC-2 (incomplete cytoreduction, moderate residual disease)	Nodules $\geq$0.25 cm$\leq$2.5 cm
CC-3 (incomplete cytoreduction, gross residual disease)	Nodules >2.5 cm

The number of nodules and their distribution were not considered in the completeness of cytoreduction score, only the size of the largest residual tumour nodule.

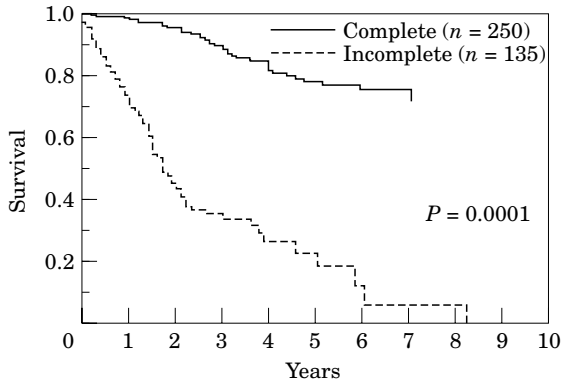

Figure 1 Survival by cytoreduction. (Modified from reference 7 with permission.)

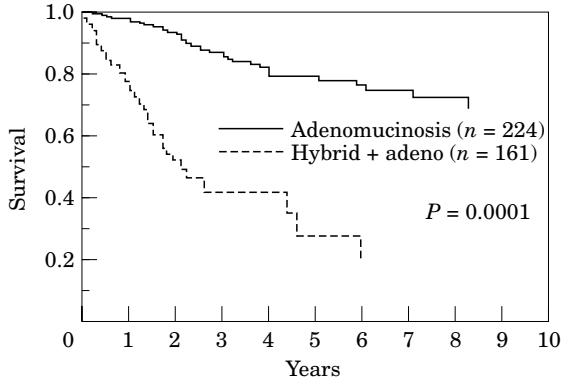

Figure 2 Survival by histology. (Modified from reference 7 with permission.)

Adenomucinosis included minimally aggressive peritoneal tumours that produced large volumes of mucous ascites. The primary appendiceal tumour was described as a cystadenoma. Intermediate type showed predominantly adenomucinosis but was combined with focal areas of mucinous adenocarcinomas. Mucinous adenocarcinomas showed invasion and atypia. Figure 2 shows the survival of these appendix malignancy patients by histology. The survival differences between patients with adenomucinosis and those with intermediate type or mucinous adenocarcinoma were significant with a *P*-value of <0.0001. A non-invasive histopathology is extremely important in selecting patients who were most likely to benefit from this treatment strategy. There were no significant differences between patients with intermediate type and mucinous adenocarcinoma histology.

SURVIVAL BY PRIOR SURGICAL SCORE

When the previous operative notes on these patients were reviewed, a judgement was made regarding the anatomic sites of prior surgical dissections. The summation of these dissections was recorded on a diagram of the abdominopelvic regions.[8] This allowed an assessment of the anatomic locations in which prior surgery had been performed. Table 2 shows how the prior surgical score was compiled. In patients with a prior surgical score (PSS) of 0, diagnosis of peritoneal carcinomatosis was obtained through biopsy only, or by laparoscopy plus biopsy. PSS 1 indicated only a prior exploratory laparotomy. PSS 2 indicated exploratory laparotomy with some resections. Usually this was a greater omentectomy or greater omentectomy plus a right colectomy. A prior surgical score of 3, indicated patients had undergone attempted 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 by prior surgical score is shown in Figure 3. Patients with PSS scores of 0–2 had an improved survival when compared to those with a PSS of 3. The *P*-value was 0.001.

SURVIVAL ANALYSIS BY COX SEMI-PARAMETRIC MODEL

All of the significant clinical features were investigated in order to determine their dependent *vs* independent status. The independent variable was determined to be complete *vs* incomplete cytoreduction. All the other clinical features investigated were found to have no independent predictive values. Complete *vs* incomplete cytoreduction had a risk ratio of 9.98. The 95% confidence limits were 4.23–23.09.

Table 2 Prior surgical score (PSS)

PSS 0	(none)	Biopsy only
PSS 1	(minimal)	Exploratory laparotomy, 1 to 2 regions
PSS 2	(moderate)	Exploratory laparotomy with resections, 2 to 5 regions
PSS 3	(heavy)	Extensive prior cytoreduction, >5 regions

Table 3 Suggested changes in the use of chemotherapy for gastrointestinal cancer

Chemotherapy methodology	Change suggested
1. Route	Intraperitoneal not intravenous
2. Timing	Peri-operative not systemic adjuvant
3. Patient selection	Minimal peritoneal surface not systemic disease
4. Target	Spread not metastases
5. Surgical approach	Peritonectomies not debulking
6. Results	Benefit not prior failure

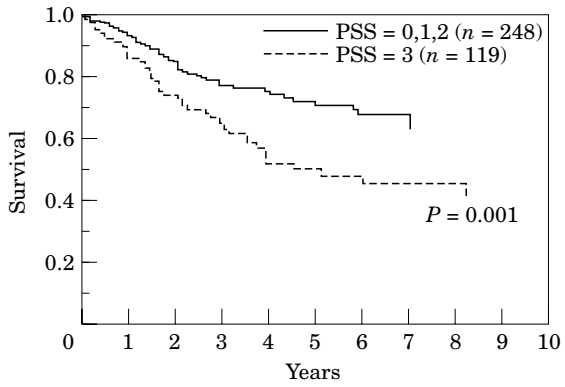

Figure 3 Survival by prior surgical score. Data were not available on 18 patients. (Modified from reference 7 with permission.)

MORBIDITY AND MORTALITY OF 155 CONSECUTIVE PATIENTS TREATED IN 1998 AND 1999

The extensive cytoreductive surgery combined with early post-operative intraperitoneal chemotherapy presents a major physiological insult to these patients. 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 mortality associated with the adjuvant chemotherapy administration.[10] Stoma construction rarely occurred in patients with adenomucinosis although 7% of patients with intermediate type or mucinous adenocarcinoma required a permanent ileostomy.[10]

DISCUSSION

In this treatment strategy for patients with pseudomyxoma peritonei from appendiceal origin, there were several distinct changes in the use of both surgery and chemotherapy (Table 3). Surgery was more extensive and more meticulous than in other cytoreductive protocols. Because of the very limited penetration of tumour nodules by chemotherapy, the cytoreduction attempted to reduce the cancer within the abdomen and pelvis to its smallest volume. This involved the use of peritoneal stripping procedures, now commonly referred to as peritonectomy procedures. 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 palliative surgical approach to peritoneal carcinomatosis.

Several changes occurred in the use of chemotherapy in this patient population. First of all, the route of chemotherapy administration was changed from the intravenous to intraperitoneal route. Maximal doses of peri-operative intraperitoneal mitomycin C and intraperitoneal 5-fluorouracil were used intraoperatively and for the first 5 post-operative days. This chemotherapy was instilled before the onset of wound healing. Once fibrinous deposits became organized, the chemotherapy would be unable to reach the residual cancer cells and local recurrence would occur.

The timing of chemotherapy administration was changed also. Chemotherapy was used in the peri-operative period. In fact, chemotherapy was used 4–6 weeks after surgery in an adjuvant setting.

Also, the selection of patients for treatment was changed. Patients with minimal peritoneal surface residual disease were treated more successfully. Patients with

large volume residual disease in the abdomen did not achieve a complete response. The target of these therapies was not metastases present at distal sites such as the liver, bone marrow or lungs; rather the target for these therapies was directed at microscopic residual disease on both the parietal and visceral surfaces. Patients with metastases that could not be resected with the cytoreductive surgery were excluded from these treatments.

These changes in surgical approach and changes in the use of chemotherapy in patients with peritoneal carcinomatosis resulted in benefits as a result of these aggressive treatment strategies. The prior failures of palliative chemotherapy can be converted to successes with peri-operative intraperitoneal chemotherapy. These combined treatments are currently the standard of practice for patients with pseudomyxoma peritonei of appendiceal origin.

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