New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome?

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Appendiceal mucinous neoplasms sometimes present with peritoneal dissemination, which was previously a lethal condition with a median survival of about 3 years. Traditionally, surgical treatment consisted of debulking that was repeated until no further benefit could be achieved; systemic chemotherapy was sometimes used as a palliative option. Now, visible disease tends to be removed through visceral resections and peritonectomy. To avoid entrapment of tumour cells at operative sites and to destroy small residual mucinous tumour nodules, cytoreductive surgery is combined with intraperitoneal chemotherapy with mitomycin at 42°C. Fluorouracil is then given postoperatively for 5 days. If the mucinous neoplasm is minimally invasive and cytoreduction complete, these treatments result in a 20-year survival of 70%. In the absence of a phase III study, this new combined treatment should be regarded as the standard of care for epithelial appendiceal neoplasms and pseudomyxoma peritonei syndrome.

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Introduction

Epithelial appendiceal neoplasms (figure 1) are unusual but not rare and are estimated to make up about 1% of colorectal cancer cases in the USA,[1] about 1500 cases per year. These epithelial tumours of the appendix are gastrointestinal malignant diseases with a unique natural history that makes them especially suited for comprehensive locoregional treatment. In this review, we compare the available evidence[2–5] for such treatment and recommend a new standard of care.

Unique clinical features and diagnosis

Epithelial appendiceal neoplasms

Table 1 summarises the unique characteristics of these tumours. Appendiceal neoplasms show varying amounts of invasiveness. About 75% are non-invasive and grow slowly, allowing patients to survive a decade or longer even without specialised treatments. However, some appendiceal tumours are very invasive, progress rapidly, and can cause death 1–2 years after the initial diagnosis.

Nearly all patients with these tumours have peritoneal dissemination at the time of diagnosis,[5] a notable contrast with colorectal cancer, in which only about 15% of patients present with carcinomatosis. However, progression is usually confined to the peritoneal space, and most patients with minimally invasive tumours die from loss of intestinal function when mucinous tumours (>60% of the field of view through the microscope contains mucus and no cancer cells)[6] impede the abdomen and pelvis.

Initial symptoms are usually the result of the mucinous neoplasm invading the peritoneal cavity. The tumour affects very little of the appendix, but substantial amounts of the abdominal and pelvic surfaces. However, some patients present with a tumour that has perforated the appendix.

Most patients with appendiceal neoplasms have no lymphatic or haematogenous metastases;[7] 2% of patients have metastases in the lymph nodes and 2% in the liver; thus extensive locoregional treatments can eliminate the disease. Surgical management of the primary tumour is usually appendicectomy or caecectomy, and an appendiceal lymph-node dissection is needed to rule out regional lymph-node metastases.[7]

Appendiceal mucinous neoplasms spare the small bowel, which qualifies them for aggressive locoregional treatment.[8] Even though large volumes of mucinous neoplasm are sometimes located within the greater and lesser omentum, the space between the liver and the diaphragm, and within the pelvis, the small bowel is usually free of disease. Carmignani and colleagues[8] reported that the almost constant peristaltic activity of the small bowel prevents neoplastic cells from adhering to its surfaces or to the small-bowel mesentery, except to the part of the jejunum that is adjacent to the ligament of Treitz and the terminal ileum or ileocaecal-valve area, which are tethered by a short mesentery to the retroperitoneum.

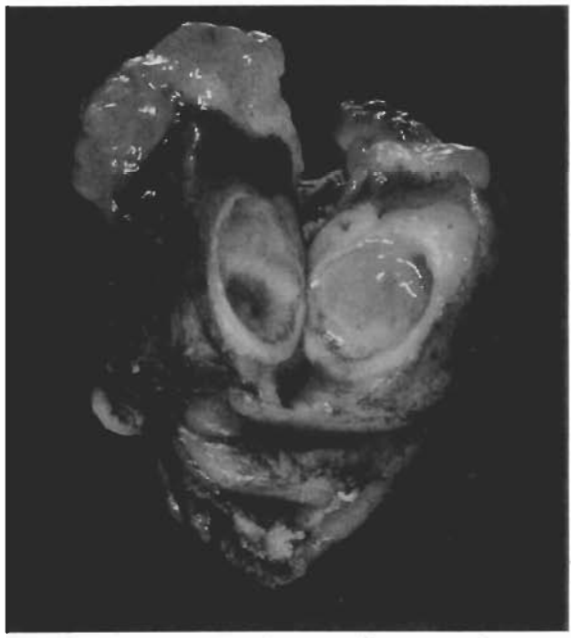

Figure 1: Distal portion of appendix has ruptured from pressure of mucin accumulation within mucocele

	Appendiceal epithelial neoplasm	Colorectal cancer
Incidence (cases per year in USA)	1500	150 000
Mucinous histology	85%	15%
Aggressiveness pathology	10%	95%
Lymph-node metastases at initial diagnosis	2%	50%
Liver metastases at initial diagnosis	2%	20%
5-year survival with traditional surgical treatment	30%	70%
10-year survival with combined treatment	60%	NA

NA=not available.

Table 1: **Contrasting features of appendiceal neoplasms and colorectal cancer**

Invasive adenocarcinoma

Before surgery confirms the diagnosis, patients with adenocarcinoma of the appendix are usually diagnosed with appendicitis, a right lower quadrant abscess, or a tumour mass. Mucinous appendiceal adenocarcinomas have usually perforated before diagnosis,[9] causing the tumour to spread to the ovary, or to present as peritoneal carcinomatosis within a hernia sac. An aggressive mucinous adenocarcinoma can invade the retroperitoneum and appear as a mucus accumulation in the buttock or thigh. Also, the tumour could invade the abdominal wall with an enterocutaneous fistula or the bladder with an enterovesical fistula. The right ureter can also be invaded by a mucus-containing tumour, and invasion of the urinary bladder has also been recorded. If symptoms other than increasing abdominal girth or appendicitis arise, the tumour is probably aggressive.

Pseudomyxoma peritonei syndrome

These minimally invasive appendiceal epithelial neoplasms constitute a large proportion of the cases of appendiceal neoplasms. They have a high propensity for spread to peritoneal surfaces, but almost never metastasise through lymphatic channels into lymph nodes, or through venules into the liver.[7] After the tumour ruptures the wall of the appendix (figure 1), adenomucinosis can progress for months or even years within the abdomen and pelvis without causing any symptoms. As the disease progresses, the peritoneal cavity becomes filled in a characteristic pattern with mucinous neoplasm and mucinous ascites. The greater omentum is thickened (omental cake) and infiltrated extensively by the tumour (figure 2). All parts of the abdomen that entrap malignant cells also contain tumour, including the undersurface of the right and left hemidiaphragms, the right subhepatic space, the splenic hilus, the right and left abdominal gutters, and the pelvis and cul-de-sac. An important clinical feature of pseudomyxoma peritonei is that tumours spare the mobile portions of the small bowel (figure 2), and the involved parietal and visceral peritoneal surfaces can thus be removed by peritonectomy.

The symptoms and signs of pseudomyxoma peritonei differ greatly from those of appendiceal adenocarcinoma. The most common symptom in both men and women with pseudomyxoma peritonei syndrome is a gradually increasing abdominal girth.[10] Women often develop an ovarian mass, usually on the right side, which is commonly diagnosed at a routine gynaecological examination, and men can have new-onset hernia as the next most frequent symptom.[10] The hernia sac is filled by mucin, a mucinous tumour, or both. The third most common presenting feature is appendicitis, a clinical manifestation of a ruptured appendiceal mucocele with local inflammation.[7]

Pseudomyxoma peritonei syndrome can also develop months or even years after planned laparoscopic appendicectomy, if a mucocele is found and ruptures during the procedure. Table 2 shows the symptoms and

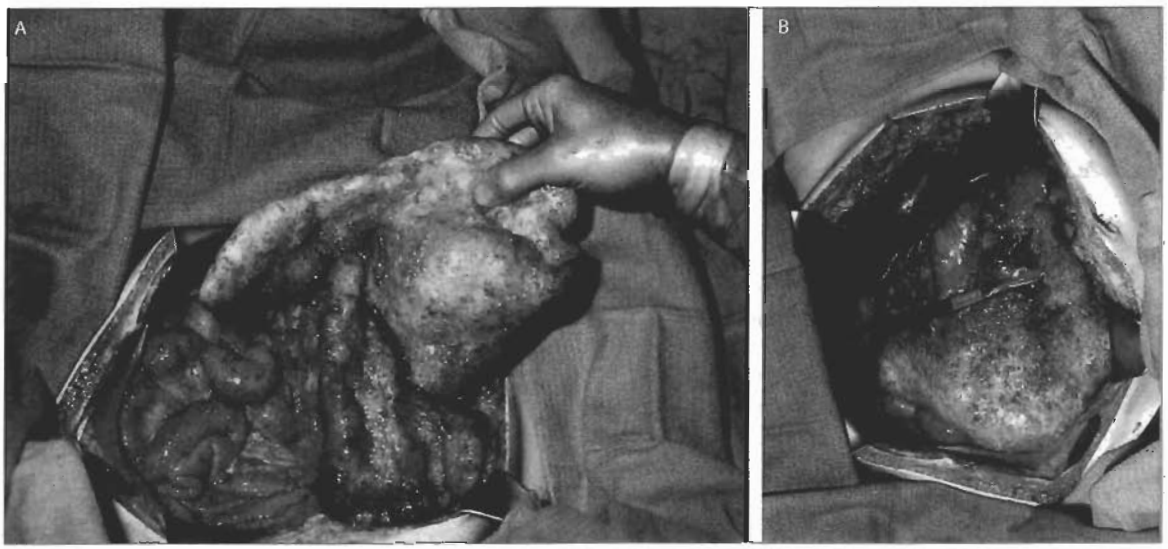

Figure 2: **Pseudomyxoma peritonei syndrome**
(A) Omental cake characteristic of pseudomyxoma peritonei syndrome. (B) Small bowel is spared when omentum is raised.

signs of pseudomyxoma peritonei syndrome as reported by Esquivel and Sugarbaker.[10]

When a patient presents with increasing abdominal girth as a result of presumed malignant ascites, diagnosis is usually established with a paracentesis or laparoscopy and biopsy. In many women with this disease an ovarian tumour will be found. In all instances, paracentesis or laparoscopy with a biopsy should be done 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 they could cause the tumour to seed into the abdominal wall, greatly reducing the probability that the disease will be eradicated.

	Men (n=105)	Women (n=112)
Appendicitis	36 (34%)	22 (20%)
Increased abdominal girth	28 (27%)	21 (19%)
Ovarian mass	NA	44 (39%)
Hernia	26 (25%)	4 (4%)
Ascites	5 (5%)	4 (4%)
Abdominal pain	5 (5%)	3 (3%)
Other	5 (5%)	14 (13%)

NA=not applicable

Table 2: **Frequency of symptoms and signs of pseudomyxoma peritonei syndrome[10]**

Treatment

Treatment options for malignant diseases are determined by the anatomical location of the cancer and by its biological aggressiveness. Appendiceal epithelial neoplasms differ greatly from other gastrointestinal cancers in both these categories. Unfortunately, in the past, statistics have been combined for appendiceal neoplasms and colorectal cancer. The international classification of disease designates appendiceal neoplasms together with colorectal cancer. This disease has a unique natural history and needs very different treatment from colon cancer. For example, there is a window of time in which all residual appendiceal neoplasms remaining after cytoreduction come into contact with the chemotherapy solution, making them good candidates for locoregional treatment.

Management in absence of peritoneal dissemination

In patients with invasive non-mucinous adenocarcinoma of the appendix, a right hemicolectomy can double the survival achieved with routine appendicectomy.[11] Therefore, all patients with invasive appendiceal adenocarcinoma, whether or not lymph nodes are involved, should receive a right hemicolectomy either during the appendicectomy or in a subsequent procedure. When the surgeon finds aggressive tumour in the appendix during an appendicectomy, emergency cryostat sectioning should be done. If the bowel is prepared adequately and if adenocarcinoma can be diagnosed definitively, a right hemicolectomy should then be done immediately. In some patients, a caecectomy with preservation of the ileocaecal valve has been used, and this procedure is recommended if the appendiceal lymph nodes are negative by cryostat sectioning.

Management of mucinous neoplasms with peritoneal dissemination

Tumour tissue is removed from the abdominal gutters, pelvis, right subhepatic space, and right and left subphrenic spaces by use of a greater omentectomy, lesser omentectomy, splenectomy, or peritonectomy.[12] The probability that a peritonectomy will eradicate the tumour from all surfaces in the abdomen and pelvis is controlled by two factors: the size of the tumour and its invasive capabilities. A small tumour will have negligible or no extension through the serosal layer, so that peritonectomy with electrosurgical dissection (figure 3) will result in a small but adequate margin of resection.[12] In a larger tumour, invasion through the serosal layer is expected, yet, on structures undamaged by deeper electrosurgical dissection, a negative margin is still possible. However, larger tumours on small-bowel surfaces will need resection to eradicate mucinous adenocarcinoma. By contrast, adenomucinous nodules will not invade through the serosal layer and can be resected adequately by peritonectomy.

For the many mucinous appendiceal neoplasms that are perforated at the time of surgery and that result in

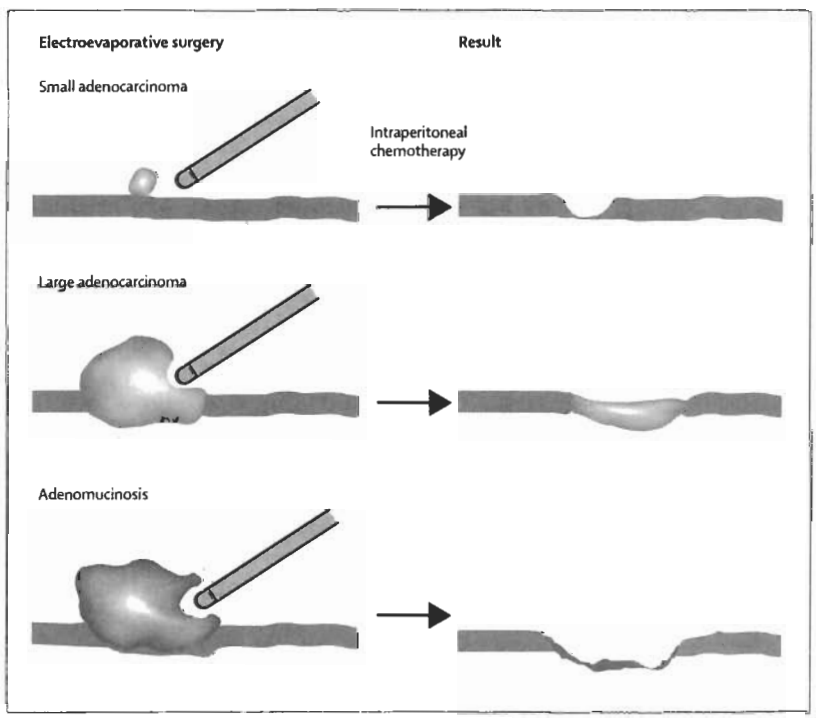

Figure 3: **Peritonectomy with electrosurgical dissection for removal of tumours**

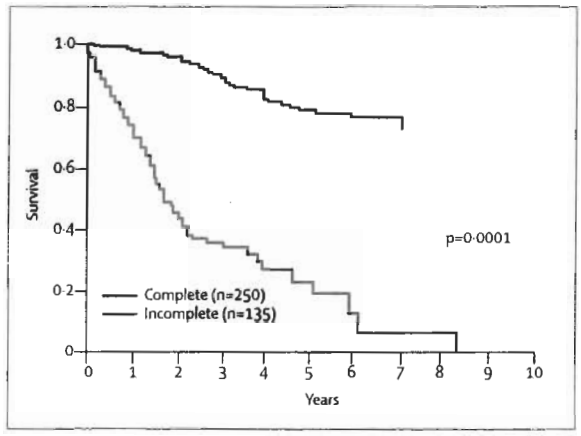

Figure 4: Patient survival by extent of cytoreduction of appendiceal malignant disease with peritoneal dissemination

peritoneal carcinomatosis or pseudomyxoma peritonei, peritonectomy is combined with intraperitoneal chemotherapy.

After resection, and with the abdomen open, the peritoneal space is washed thoroughly with warm (41·5°C) mitomycin solution by the surgeon's hand with gauze debridement of all surfaces. Also, a window of time exists in the early postoperative period when all intraperitoneal surfaces are available for treatment with intraperitoneal fluorouracil. Consistent exposure of all peritoneal surfaces to intraperitoneal chemotherapy can be achieved if the chemotherapy is used during the first week after surgery. As the postoperative fluorouracil solution remains in the abdominal and pelvic space, the solution can be distributed by turning the patient alternately on to their right and left side and into the prone position.[13]

In a prospective investigation of this technique, perioperative intraperitoneal chemotherapy increased the frequency of anastomotic disruptions. Patients who have had previous extensive surgery who need many hours of adhesion lysis, are more likely to develop fistulas after surgery, presumably because of the combined effects of damage to the small bowel from electrosurgical dissection of adhesions (seromuscular damage), and systemic effects of intraperitoneal chemotherapy on the intestine (mucosa and submucosa damage).

Intravenous chemotherapy is recommended for patients who have peritoneal dissemination of high-grade appendiceal mucinous neoplasm and second-look surgery is recommended about 6 months after the procedure in some patients, usually those who need ostomy closure. If small tumour foci are found on the peritoneal surface of the abdomen or the pelvis at the staging celiotomy, the nodules are resected and a final intraperitoneal chemotherapy is done. Cytoreductive surgery and intraperitoneal chemotherapy are not effective for tumours within the abdominal wall.

Definitive treatment of peritoneal carcinomatosis or pseudomyxoma peritonei should be done in a timely way. Every non-definitive debulking surgical intervention makes potentially curative cytoreductive surgery more difficult and because the peritoneum acts as the first line of defence against peritoneal dissemination, every effort should be made to keep it intact for optimum results in these procedures. Also, whereas the small bowel is spared early in the natural history of mucinous appendiceal neoplasms and pseudomyxoma peritonei, the fibrous adhesions that inevitably result after several surgical procedures will become infiltrated by tumour, leading to widespread involvement of the small bowel. Eventually, safe cytoreduction becomes impossible, and the effects of the intraperitoneal chemotherapy by itself are not adequate to keep the patient free of disease.

Outcomes

The results of treatments for peritoneal surface dissemination of appendiceal neoplasms have been unexpectedly good. In 385 patients with either peritoneal adenomucinosis or mucinous carcinomatosis who were followed up for an average of 37·6 months,[14] all had documented peritoneal surface disease, and most had large tumours. After cytoreductive surgery, all patients had their abdomen inspected for residual disease and the completeness of cytoreduction was scored for all patients on the basis of the size of remaining tumours.[15] Figure 4 shows the survival of patients who had a complete cytoreduction compared with those who had an incomplete cytoreduction. In statistical analysis of these data, survival did not differ significantly between patients with near complete cytoreductions and those with grossly incomplete cytoreductions. Furthermore, the only variable that was an independent predictor of survival was the completeness of cytoreduction (complete *vs* incomplete).[14]

Survival differed between patients with adenomucinosis and those with hybrid or mucinous adenocarcinoma ($p<0·0001$). Patients with non-invasive disease are therefore more likely to benefit from this treatment strategy. No significant differences were noted between patients with hybrid histology and those with mucinous adenocarcinoma.[14,15] Furthermore, patients with negligible or moderate extent of previous surgery had an improved survival compared with those who had had extensive previous surgery ($p=0·001$).[14]

This finding shows the importance of the peritoneum as a protective barrier in patients in whom the tumour has spread to this site. Multiple previous dissections had a negative effect on survival when all patients were included in the analysis, but not when patients who had had complete cytoreduction were excluded, suggesting that previous debulking can worsen prognosis by impeding complete removal of the tumour in some patients. Debulking surgery with incomplete cytoreduc-

tion allows neoplastic cells to implant on abdominal and pelvic surfaces that have been cleared of peritoneum. Once these neoplastic cells implant deep to the peritoneum, removal with an adequate margin is unlikely.[16]

Analysis[17] of 21 patients with adenocarcinoid of the appendix with peritoneal carcinomatosis showed that median survival of patients who had complete cytoreduction and intraoperative and postoperative intraperitoneal chemotherapy was 18·5 months (range 3·2–95·1); 5-year survival was 25%. In some patients, an attempt at complete resection is warranted. If debulking results in gross residual disease, only palliative surgical efforts associated with low morbidity and mortality are indicated because survival is limited.

Extensive cytoreductive surgery combined with early postoperative intraperitoneal chemotherapy is associated with high morbidity.[18] Nevertheless, only 2–10% of patients who receive this treatment die. Anastomotic leaks were more common in these patients than in those who have conventional surgery (5%).[18–31] Overall morbidity in patients with grade III–IV disease was 20–50%. No morbidity or mortality was associated directly with administration of intraperitoneal chemotherapy. Rather, the frequency of complications depended on the extent of the surgery, number of peritonectomy procedures, and time needed to complete the cytoreduction (table 3).[18–31]

Traditionally, appendiceal epithelial neoplasms have been managed by serial debulking, which removes the bulk of the disease. Although the midabdomen can be cleared by suctioning the mucous neoplasm, washing the intestinal surfaces, and resection of the greater omentum, disease often remains around the liver and pelvis. Because the tumour recurs after 2–3 years, debulking is often repeated, but is often more difficult at this time. After three or four debulkings, loops in the small bowel become encased with scar tissue and mucinous neoplasm, and further surgery is impossible. The function of the gastrointestinal tract is gradually restricted by the accumulation of a large mucinous tumour now embedded within the scar tissue, and the patient dies from long-term starvation. Sometimes, systemic chemotherapy can be of transient benefit.[4]

In 1994, Gough and co-workers[2] showed a median survival of about 6 years in 56 patients with pseudomyxoma peritonei who were treated by serial debulking and intraperitoneal fluorouracil or phosphorus-32. Only a few patients were alive after 10 years' and 20 years' follow-up. Unfortunately, the investigators did not compare the differences in long-term survival of these patients with those who had surgical debulking only.

Misdraji and colleagues[4] reported on 107 patients with a median survival of about 7·5 years, and a 20-year survival of 25% after serial debulking and perioperative intraperitoneal chemotherapy. The number of patients in this group who received aggressive locoregional treatment is not known.

	n	Morbidity	Mortality	Ref
CRS, HIIC, and EPIC*	356	68 (19%)	7 (2%)	18
CRS and DIC	14	5 (36%)	0 (0%)	19
CRS and EPIC	181	31 (17%)	4 (2%)	20
CRS, HIIC, and EPIC†	60	21 (35%)	3 (5%)	21
CRS, HIIC, and EPIC*	200	54 (27%)	4 (2%)	22
CRS and HIIC†	64	35 (55%)	6 (9%)	23
CRS and EPIC*	13	7 (54%)	1 (8%)	24
CRS and HIIC†	216	54 (25%)	6 (3%)	25
CRS and HIIC*	34	12 (35%)	0 (0%)	26
CRS and HIIC†	77	23 (30%)	9 (12%)	27
CRS and HIIC*	33	9 (27%)	0 (0%)	28
CRS and HIIC*	102	36 (35%)	8 (8%)	29
CRS and HIIC*	67	23 (34%)	3 (4%)	30
CRS and HIIC†	209	25 (12%)	2 (1%)	31

CRS=cytoreductive surgery. HIIC=heated intraoperative intraperitoneal chemotherapy. EPIC=early postoperative intraperitoneal chemotherapy. DIC=delayed intraperitoneal chemotherapy. *open. †closed.

Table 3: **Morbidity and mortality after treatment for peritoneal surface malignant diseases**

In another study,[4] patients had serial debulking and intermittent intraperitoneal fluorouracil several weeks later. Although their initial results were excellent and 70% of patients were alive at 10 years, the Kaplan-Meier distribution predicted no survivors at 20 years. From these three reports it is clear that serial debulking can lengthen survival but is unlikely to cure patients with appendiceal epithelial neoplasms.

Approaches to management

Appendiceal neoplasm with peritoneal dissemination could be an indolent disease process. The assessment of any treatment regimen should allow for a minimum of 10 years' follow-up,[4] and follow-up of 20 years would be ideal. A 20-year follow-up with cytoreductive surgery and perioperative intraperitoneal chemotherapy was reported by Sugarbaker and colleagues,[5] who showed that patients who had complete cytoreduction for less-aggressive disease had a projected survival of 70% at 20 years (figure 5), a sharp contrast with the results achieved with serial debulking. However, these results should be interpreted with the knowledge that these treatment strategies have not been compared directly.

Unfortunately, follow-up has not been so extensive for treatment of appendiceal tumours and pseudomyxoma peritonei syndrome. Table 4[14,32–37] shows outcomes from the studies of combined treatment, which have been reviewed by Glehen and co-workers.[38] These positive results have led to establishment of treatment centres for appendiceal neoplasm in the USA and in nearly all countries in Europe.

In the UK, combined treatments have become a part of the overall plan for healthcare. Moran and colleagues[17] have established a treatment centre dedicated to management of appendiceal malignant diseases and pseudomyxoma peritonei syndrome, to which any patient enrolled in the UK National Health Service, from

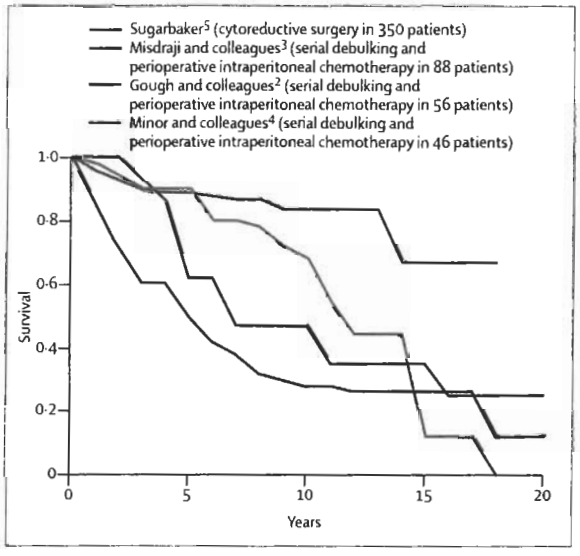

Figure 5: **Survival in patients with pseudomyxoma peritonei syndrome**

anywhere in the UK, can be referred. The centre, based in Basingstoke, UK, started treatment for this disease in 1994, and about 40 cytoreductions are done there every year. Because of the large number of patients needing treatment for appendiceal malignant diseases with peritoneal surface dissemination, a second treatment centre was established in 2002 in Manchester, UK. These centres have meant that referral to a treatment centre is now standard practice for this disease in the UK and allows doctors to use standard treatments, improve treatment regimens, and refine the surgical skills needed for optimum management of these patients. This approach has improved patient care and reduced costs because patients can be referred early before disease progresses to a symptomatic state.

A new standard of care

Ideally, new treatments should evolve through the clinical trials process. A phase III trial should be undertaken to compare traditional treatment options with new treatments. However, until such data are available, the issue remains of which treatment option is best for these patients. The available evidence suggests that cytoreductive surgery with perioperative intraperitoneal chemotherapy should replace serial debulking as the standard of care for patients with peritoneal spread of appendiceal epithelial neoplasms.

However, phase III trials are difficult to do in this setting because they would need to compare a potentially curative treatment option with a palliative one. Patients are thus likely to be reluctant to be randomised, no matter how carefully the trial is designed and explained. Follow-up of about 20 years would be needed to assess the best treatment plan. However, such long-term follow-up would mean that meaningful data might never be available within the lifetime of the principal investigator. Furthermore, the disease is uncommon and only a few institutions, especially those designated as pseudomyxoma peritonei treatment centres, can accumulate sufficient numbers of patients to give meaningful results. The only trial that would accumulate sufficient patients for assessment over a reasonable time would be a multinational trial with most of the institutions participating from the USA and Europe, meaning the expense and the coordination would probably be prohibitive. Acceptance of combined treatment as the standard of care would allow treatment centres to investigate new and possibly more effective locoregional treatment strategies that can improve the overall results and decrease morbidity and mortality by prospective randomised studies. The skills, judgments, and treatments offered vary between the many treatment centres, and results of treatment might not therefore be consistent. With experience, the morbidity and mortality associated with cytoreductive surgery and intraperitoneal chemotherapy should lessen, as should objections to this procedure. Physicians at experienced centres learn that addition of chemotherapy as a planned part of cytoreductive surgery improves patient care rather than results in excessive morbidity and mortality. Correct selection of patients is an important part of successful treatment of this disease.

Several distinct changes (table 5) are needed to the surgical techniques used to treat patients with peritoneal dissemination of an appendiceal mucinous neoplasm. Because chemotherapy has little effect on large tumours, definitive cytoreduction should be attempted to reduce

	n	3-year survival	5-year survival	Morbidity	Mortality	Ref
Mitomycin and fluorouracil	385	74%	63%	(27%)	(2·7%)	32
Mitomycin	46	81%	NA	(39%)	(8%)	14
Mitomycin	23	61%	NA	NA	NA	33
Cisplatin or mitomycin	33	NA	96%	(33%)	(3%)	34
Cisplatin or mitomycin or fluorouracil	28	NA	75%	(36%)	(7%)	35
Cisplatin or mitomycin	27	80%	50%	(44%)	(0%)	36
Mitomycin and fluorouracil	65	NA	65%	(20%)	(6%)	37

NA=not available. *Complete cytoreductions only.

Table 4: **Outcomes after cytoreductive surgery and perioperative intraperitoneal chemotherapy for mucinous appendiceal tumours with peritoneal dissemination**

	Change suggested
Chemotherapy route	Intraperitoneal rather than intravenous
Chemotherapy timing	Perioperative rather than systemic adjuvant
Patient selection	Those with negligible residual peritoneal surface disease rather than systemic disease
Chemotherapy target	Peritoneal spread rather than systemic metastases
Surgical approach	Peritonectomies rather than debulking
Treatment results	Long-term survival rather than previous failure

Table 5: **Suggested changes to management of appendiceal mucinous neoplasms with peritoneal dissemination**

the cancer within the abdomen and pelvis to its smallest volume. Such reduction requires use of peritoneal stripping, now commonly referred to as peritonectomy, in which the patient often needs to spend many hours in the operating theatre. Frequently, the abdomen is left without peritoneal surfaces except for that found on the small bowel. This approach is a change from the previous conservative surgical approach to peritoneal carcinomatosis.

Several changes are also needed in the use of chemotherapy in these patients. Administration of chemotherapy should change from intravenous to intraperitoneal with maximum doses of mitomycin and intraperitoneal fluorouracil. Intraperitoneal chemotherapy should be done perioperatively to contact all abdominal and pelvic surfaces before wounds start to heal. Once fibrinous deposits become organised, chemotherapy will not be able to reach residual tumours and local recurrence will occur where the surfaces are adherent. Perhaps most important for favourable results, selection of patients for treatment should change. Patients should receive maximum cytoreductive surgical procedures before residual peritoneal surface disease is treated. The target of these treatments should be directed at minimal residual disease on both the parietal and visceral surfaces. Patients with metastases that cannot be resected or with gross residual disease of the peritoneal surface after cytoreductive surgery has been done should be excluded from these treatments. With these changes in surgical approach and chemotherapy, patients with peritoneal dissemination of appendiceal mucinous tumours could have a chance at a cure.

Search strategy and selection criteria

Referenced papers were collated from my personal collection. Further references were identified from searches of MEDLINE and PubMed from July,1, 1995 to Dec, 31, 2004 with the terms "appendix neoplasm", "intraperitoneal chemotherapy", "peritonectomy", and "cytoreductive surgery". References were selected to provide a balanced and representative overview of a complex subject with an extensive base of published work. Only papers published in English were included.

Conflict of interest

I declare no conflicts of interest.

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