A new standard of care for the management of peritoneal surface malignancy

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ABSTRACT

Cancer dissemination to peritoneal surfaces was, in the past, a lethal condition with a limited survival. Clinical and pharmacologic research have shown that options for both treatment and prevention are now reality. The diseases most commonly treated include peritoneal dissemination from appendiceal malignancy, colorectal malignancy, and peritoneal mesothelioma. Selection factors are important to minimize the number of treated patients who will experience short-term benefit. Treatments involve cytoreductive surgery and perioperative chemotherapy. The intraperitoneal chemotherapy in the operating room is used with heat. Although this combined approach has been criticized, the informed oncologist will seek to identify those patients that may benefit from this more optimistic concept of peritoneal dissemination of cancer.

KEY WORDS

Cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, HIPEC, carcinomatosis, peritoneal mesothelioma, appendiceal cancer, pseudomyxoma peritonei, colorectal cancer, mitomycin C

1. INTRODUCTION

The management of gastrointestinal cancer continues to evolve. Although essential for cure, proper clearance (R0 resection) of gastrointestinal cancer is not alone sufficient to control disease in all cases. The importance of maximal containment—for example, with total mesorectal excision in rectal cancer, or with complete mesocolic excision with central vascular ligation for colon cancer—is associated with reduced local recurrence and improved survival [1,2]. An increasing body of evidence suggests that knowledgeable use of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is the next step in the evolution of optimal management of selected patients with gastrointestinal malignancy and peritoneal mesothelioma [3–5].

The objectives of the present manuscript are to review the clinical tools currently available to assess carcinomatosis and to create a rationale for a new treatment strategy that involves CRS and HIPEC. Results of treatment, together with a morbidity and mortality estimate, are presented. Benefits for that approach are compared with those for other treatments for metastatic disease.

The articles reviewed in the manuscript were selected by the authors for their relevance to the discussion, the clarity of the data presentation in the manuscript, and the reliability of the data presented. The articles are selected from the authors' own work and from the collected knowledge of the carcinomatosis literature. This search was not computer-assisted.

2. QUANTITATIVE PROGNOSTIC INDICATORS

In the past, a major criticism of CRS and HIPEC has been their high morbidity and mortality. Moreover, some groups of patients subjected to these costly procedures profited little. However, with the accumulation of critical clinical research, patients can now be selected using quantitative prognostic indicators. Currently, the outcomes of CRS and HIPEC should be interpreted by evaluating the results of treatment according to quantitative prognostic indicators. These prognostic indicators can be used to refine the selection of patients so that those most likely to benefit are included and those who are unlikely to benefit are excluded [6]. The utility of the indicators lies in preventing patients from entering high-risk and costly management protocols if there is little or no likelihood of their improvement. Also, the indicators aid the decision-making process for multiple institutions around the world, allowing standardized management protocols and patient selection criteria to be established. The meaningful collaboration between the different institutions thus facilitated can increase the evidence base for the

treatment of peritoneal surface malignancy. Histopathology, the peritoneal carcinomatosis index (PCI), and radiologic imaging play a central role in refining patient selection for these complex treatments in appendiceal neoplasms, colorectal carcinomatosis, and peritoneal mesothelioma [6–8].

2.1 Biologic Aggressiveness Measured by Histopathology

2.1.1 Epithelial Appendiceal Neoplasms

Mucinous appendiceal neoplasms have a broad spectrum of aggressiveness. Adenomucinosis (called "low grade" by some histopathologists) describes a noninvasive peritoneal surface malignancy that may become widely disseminated on peritoneal surfaces. At the other end of the spectrum, peritoneal mucinous carcinoma ("high grade") may show the same propensity for widespread intraperitoneal (IP) dissemination, but with invasion through the peritoneal surface and abdominal viscera. In the Ronnett classification, an intermediate type of disease exists in which 95% or more of the fields of view show adenomucinosis, but areas of mucinous adenocarcinoma exist [7]. When survival is the endpoint, the intermediate group is included with the mucinous carcinoma group. At the Washington Cancer Institute, the patient's histologic type has a profound effect on survival after treatment by CRS and perioperative IP chemotherapy (Figure 1). The impact of histopathology on survival persists regardless of completeness of cytoreduction [8].

Recently, Bradley *et al.* [9] reviewed 101 patients with mucinous tumours of the appendix, all uniformly treated with CRS and HIPEC, classifying them as disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA), or PMCA with intermediate ("well differentiated") features (PMCA-I). Those authors concluded that survival was similar for the DPAM and PMCA-I groups, thus leading to their classification as mucinous carcinoma peritonei–low grade. Moderately-to-poorly differentiated cases were classified as mucinous carcinoma peritonei–high grade [9].

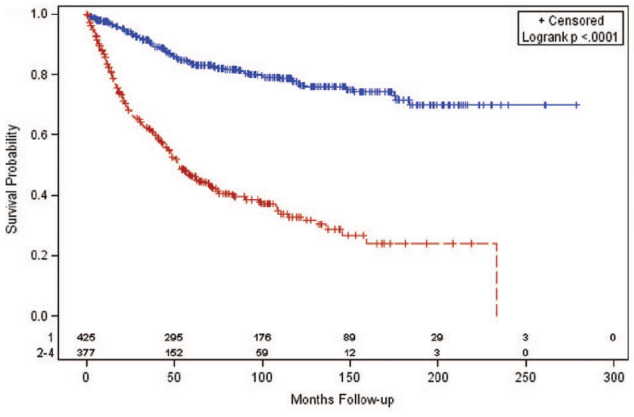

FIGURE 1 Survival of all patients with epithelial appendiceal neoplasms treated by cytoreductive surgery and intraperitoneal chemotherapy. The red line represents patients with disseminated peritoneal adenomucinosis, and the blue line, patients with peritoneal mucinous carcinoma. Reproduced, with permission, from Sugarbaker, 2009 [8].

Dichotomous categorizations of mucinous tumours of the appendix have been adopted elsewhere, and what is emerging has a profound prognostic implication for histopathology. The management of low-grade (as compared with high-grade) appendiceal mucinous tumours results in improved outcomes [8–16]. These pathology classifications are important because they give strong indications about outcome after CRS and HIPEC. Patients with low-grade tumours appear to obtain maximum survival benefit from aggressive locoregional treatments; in patients with PMCA, the results of treatment resemble those for peritoneal carcinomatosis of colorectal origin [14,15].

It may be important to establish that the descriptions of the mucinous appendiceal malignancies apply specifically to the peritoneal surface component of the disease. Although the primary appendiceal mucinous neoplasm usually shows the same histology, Ronnett identified patients in whom the primary malignancy and the tumour disseminated around the abdomen and pelvis showed discordant histologies. These findings of discordance were reported in approximately 6% of patients. Also important in interpreting the histopathology of appendiceal epithelial neoplasms are the transitions that may occur, usually between DPAM and PMCA. These transitions may have a profound influence on survival [7]. Also, the importance of "benign mucocele with rupture" should be mentioned. Patients with a localized collection of mucin in the right lower quadrant as a result of a ruptured benign mucocele should not be confused with patients who have a disseminated appendiceal epithelial neoplasm.

2.1.2 Colorectal Carcinomatosis

For peritoneal carcinomatosis arising from a colorectal primary, the importance of histopathology of the primary tumour is less definitive. In the recent French multicentre registry study, no significant difference in survival based on tumour differentiation in patients undergoing CRS with IP chemotherapy was observed [3]. On multivariate analysis, the variables found to be independent prognostic indicators for overall survival were the PCI, completeness of the surgery, lymph node status, and adjuvant chemotherapy. When disease-free survival was considered, then the experience of the centre performing the surgery also became a significant factor. The presence of liver metastases was a significant adverse prognostic factor in patients who underwent a complete cytoreduction [3].

In summary, tumour grade is not a dominant prognostic factor for carcinomatosis in colorectal cancer.

2.1.3 Peritoneal Mesothelioma

At the Washington Cancer Institute, 7 pathologic types of peritoneal mesothelioma have been categorized [17,18]. These pathologic types can be classified into 3 groups based on prognosis after CRS with IP chemotherapy: poor prognosis for the sarcomatoid, deciduoid, and biphasic types; intermediate prognosis for the papillary and epithelial types; and good prognosis for the low-grade and multicystic types.

Yan and colleagues [5] reported the largest multi-institutional registry study to date of patients with peritoneal mesothelioma treated by CRS with IP chemotherapy. Of 405 patients, 318 (79%) had epithelial tumours, and 48 (12%) had biphasic or sarcomatoid tumours. After CRS with IP chemotherapy, median survival was 63 months for patients with the epithelial type and 16 months for patients with the biphasic or sarcomatoid type ($p = 0.006$, univariate analysis).

Cerruto and colleagues [18] further defined the impact of the epithelial histologic type of peritoneal mesothelioma on survival. This group of 62 patients received uniform treatment with complete cytoreduction and HIPEC. In a multivariate analysis of 14 different histomorphologic parameters, nucleus/nucleolus size was a prognostic determinant. Adding nucleus/nucleolus size to the histologic assessment of epithelial peritoneal mesothelioma was important because most patients with peritoneal mesothelioma (>90%) have an epithelial type [18]. In the Cerruto report, survival in patients with nuclear grade I peritoneal mesothelioma treated by CRS and HIPEC was 100% at 10 years; in patients with nuclear grade II, it was 50% at 10 years. Deraco and coworkers [19] reported that the strongest factors influencing overall survival were completeness of cytoreduction and mitotic count. Nuclear grade was significant in the univariate analysis, but not in the multivariate analysis.

2.2 Extent of Disease as Measured by the PCI

The PCI is an assessment combining lesion size (0–3) with tumour distribution (abdominopelvic region: 0–12) to quantify the extent of disease as a numeric score (0–39; see Figure 2) [6]. The score is calculated at the time of surgical exploration of the abdomen and pelvis, although it can be estimated preoperatively by good-quality abdominal computed tomography (CT). The PCI is of great value in the process of deciding between a surgically aggressive complete cytoreduction and a palliative debulking procedure.

2.2.1 Epithelial Appendiceal Neoplasms

For mucinous appendiceal neoplasms that show the adenomucinosis histology, the PCI is valuable in determining prognosis. If the PCI is less than 20, this noninvasive malignancy has an excellent prognosis of 94% at 20 years when treated with CRS and perioperative IP chemotherapy [Figure 3(A)] [8]. However, if the adenomucinosis can be completely removed, even though the extent of tumour is great, the survival is 64% at 20 years. When the appendiceal mucinous neoplasm has an invasive component, as in peritoneal mucinous carcinomatosis, the PCI continues to show a statistically significant effect on survival [Figure 3(B)].

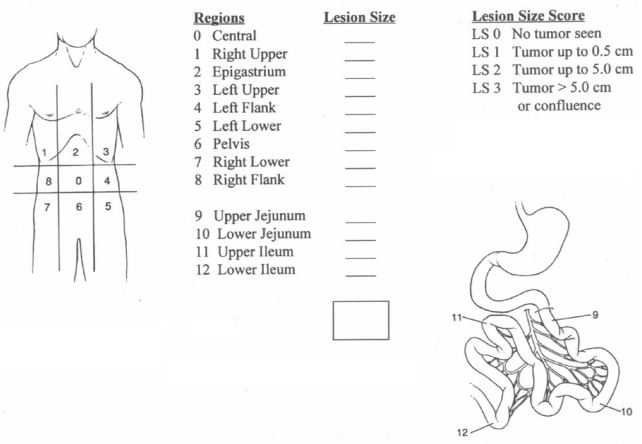

FIGURE 2 Peritoneal carcinomatosis index (PCI). Two transverse planes and two sagittal planes divide the abdomen into 9 regions. The upper transverse plane is located at the lowest aspect of the costal margin, and the lower transverse plane is placed at the anterior superior iliac spine. The sagittal planes divide the abdomen into 3 equal sectors. The lines define the 9 regions, which are numbered clockwise starting with 0 at the umbilicus and with 1 defining the space beneath the right hemidiaphragm. Regions 9–12 divide the small bowel into upper and lower jejunum and upper and lower ileum. "Lesion size score" is determined after complete lysis of all adhesions and complete inspection of all parietal and visceral peritoneal surfaces. It refers to the greatest diameter of tumour implants distributed on the peritoneal surfaces. Primary tumours or localized recurrences at the primary site that can be definitively removed are excluded from the lesion size assessment. If a confluence of disease is matting abdominal or pelvic structures together, lesion size is automatically scored 3, even if the confluence of cancerous implants is thin. The PCI is determined during the complete abdominal and pelvic exploration that is conducted before the cytoreductive surgery.

Although PCI does have considerable prognostic implications, it cannot be used to exclude patients with appendiceal epithelial neoplasms from an attempt at complete cytoreduction. Even patients with peritoneal mucinous carcinoma with a PCI greater than 20 have a long-term survival of 30%. If abdominal exploration suggests that the cytoreduction will not be complete, then a contraindication to an attempt at complete cytoreduction arises. Careful scrutiny of the extent of mucinous tumour layered out on the small bowel is an essential part of this assessment.

2.2.2 Colorectal Carcinomatosis

Results of large multicentre studies have identified several prognostic factors that can be used to improve selection of the colorectal patients with carcinomatosis who will benefit from CRS with HIPEC [3]. A consensus on these indications has been established

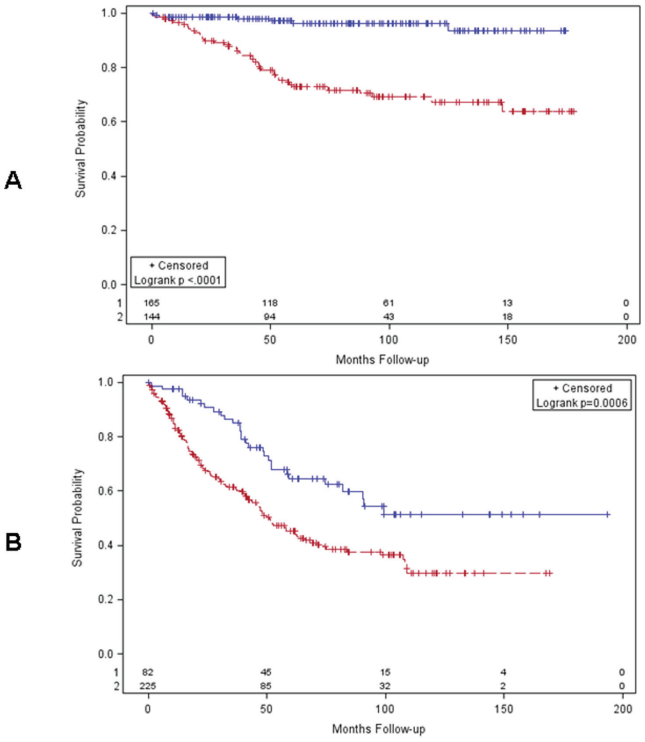

FIGURE 3 Survival by peritoneal carcinomatosis index (PCI) for mucinous appendiceal neoplasms. (A) Adenomucinosis patients with PCI 1–20 (blue line, n = *165) or 21–39 (red line,* n = *144). (B) Mucinous carcinoma patients with PCI 1–20 (blue line,* n = *82) or 21–39 (red line,* n = *225). Reproduced, with permission, from Sugarbaker, 2009* [8].

within peritoneal surface malignancy treatment centres [20]. The extent of colorectal carcinomatosis has been shown to be the most important prognostic factor determining survival even when complete cytoreduction is achieved [21].

The results of a recent multicentre study of 523 patients from 23 centers in 4 French-speaking countries are illuminating [3]. In patients with colorectal peritoneal carcinomatosis with a PCI score of less than 19, 5-year survival was 29%. When the PCI score was more than 19, the 5-year survival was 7% after treatment with CRS and perioperative IP chemotherapy.

For colorectal carcinomatosis, it has been suggested that CRS plus HIPEC is not appropriate in patients with a PCI score above 20, particularly in association with other poor prognostic factors such as evidence of lymph node involvement [22].

In cases of carcinomatosis synchronous with the primary tumour, a comparative retrospective study suggested that patients should be treated with CRS followed by HIPEC at the time of primary tumour removal [23]. This management plan avoids the theoretical risk of cancer dissemination through sites of peritonectomy and resection. The carcinomatosis treatment centers in France have recommended minimal surgery for the primary cancer with peritoneal seeding (such as diverting ostomy or exteriorization resection) before definitive resection with complete cytoreduction [3].

2.2.3 Peritoneal Mesothelioma

On univariate analysis, a recent multi-institutional registry study including 405 patients with diffuse malignant peritoneal mesothelioma identified a PCI score above 20 as a negative prognosticator for survival. Median survival was 119 months in patients with a PCI score of 20 or less, compared with 39 months in those with a PCI score above 20 ($p = 0.002$) [5]. However, the patient who has relative small-bowel sparing so that a complete cytoreduction is contemplated may be considered for complete cytoreduction.

2.3 Preoperative Radiologic Imaging by CT

Imaging by CT of the chest, abdomen, and pelvis is a useful tool in the selection of patients for CRS and HIPEC. Major systemic metastatic spread to pleural surfaces can be excluded. The location and quantity of mucinous adenocarcinoma within the peritoneal cavity can be accurately determined [24]. If the small bowel and its mesentery are involved with tumour, the chance of achieving complete cytoreduction is small. Computed tomography imaging performed with maximal intravenous and oral contrast can discriminate, with reasonable accuracy, between patients who have small-bowel compartmentalization and those who have diffuse involvement of the small bowel [24]. Frequently, diffuse involvement of small-bowel regions by mucinous tumour is seen in patients who have undergone earlier attempts at cytoreduction without the use of IP chemotherapy. Subsequent attempts at complete cytoreduction are then rendered unlikely, with a negative impact on prognosis.

For appendiceal mucinous neoplasms, Jacquet and coworkers reported two radiologic findings that predict incomplete cytoreduction: segmental obstruction of the small bowel, and tumour masses more than 5 cm in diameter associated with the small bowel and its mesentery (exclusive of the distal ileum). With those findings on preoperative CT images, patients had an 88% probability of incomplete resection; without such findings, the probability of complete resection was 92% [24].

The accuracy of CT imaging in identifying small peritoneal lesions is limited; very often, CT underestimates the volume of disease, especially in peritoneal colorectal carcinomatosis. Positron-emission tomography (PET) with the tracer fluorodeoxyglucose has an increasingly important role in the diagnosis, staging, and surveillance of malignant disease [25]. The combination of functional PET data and detailed anatomic information provided by CT in dual-modality PET/CT further improves staging accuracy [26]. Dual-modality PET/CT has shown early promise for aiding in the selection of patients for CRS with HIPEC [27,28].

In peritoneal mesothelioma, the anatomic location of the tumour is a large determinant of surgical outcome. When crucial anatomic sites within the abdomen and pelvis are involved, the chance of obtaining complete cytoreduction is significantly reduced. These crucial sites include the epigastric and the small-bowel regions [29]. Large tumours in the epigastric region may preclude a lesser omentectomy because of involvement of the right or left gastric vascular arcade. Removal of this site of disease often necessitates a total gastrectomy—a substantial undertaking, which, if not performed, will result in suboptimal cytoreduction. Also, preoperative recognition of peritoneal mesothelioma that has become distributed within the small-bowel regions allows for the identification of patients who will have suboptimal cytoreduction. A subsequent decision for nonsurgical management may be appropriate, avoiding the high morbidity and cost of a treatment that may offer little or no benefit in terms of survival.

Figure 4 sets out a decision tree for the selection of an operative or non-operative approach in peritoneal mesothelioma.

3. RATIONALE FOR PERIOPERATIVE IP CHEMOTHERAPY

The major advantage of IP therapy is regional dose intensity. After intracavitary drug administration, the peritoneal cavity is exposed to higher concentrations than are the other parts of the body. The concentration differential occurs because drug movement from peritoneal cavity to plasma (peritoneal clearance) is generally slow relative to drug clearance from the body. The penetration of IP chemotherapy into peritoneal carcinomatosis nodules is limited to between 2 mm and 5 mm, even when combined with heat [30–32]. For this reason, CRS to reduce IP tumour volume is essential before HIPEC [33,34].

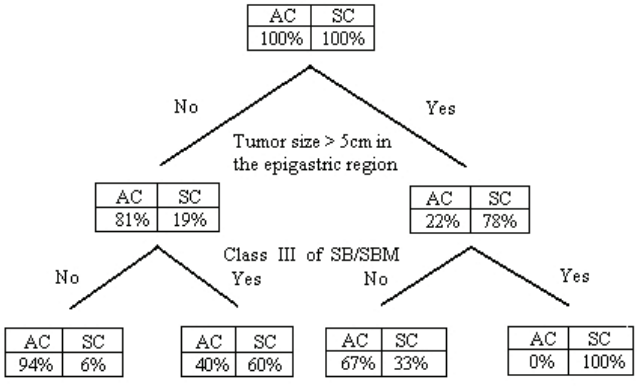

FIGURE 4 The predictive value of computed tomography scan findings by tree-structured diagram. AC = adequate cytoreduction; SC = suboptimal cytoreduction; SB/SBM = small bowel and small-bowel mesentery. Reproduced, with permission, from Yan et al.*, 2005 [29].*

Traditionally, the surgical approach to peritoneal dissemination of appendiceal mucinous neoplasms consisted of serial debulking repeated until no further benefit could be achieved. The new goal is complete removal of all visible disease through visceral resections and peritonectomy. Residual free mucinous tumour cells and adherent nodules are treated with perioperative IP chemotherapy. The most common agent is mitomycin C heated to 42°C. Application of this novel method of chemotherapy marks a fundamental shift in approach from sequential adjuvant or neoadjuvant therapy to administration of chemotherapy *simultaneously* with the surgical procedure. It is applied only when residual disease is minimal (microscopic), by the IP route or by combining IP with intravenous chemotherapy. Timing is key, with chemotherapy moving to the perioperative setting. These treatments can result in a 20-year survival of 80% when complete cytoreduction of low-grade tumours is achieved [8].

3.1 Role of Hyperthermia

Hyperthermia alone is cytotoxic at the cell and tissue levels, with formation of "heat shock" proteins [35–37]. Cancerous tissues exhibit altered thermoregulation, having only a limited vasomotor response, and so massive cellular destruction occurs on prolonged exposure to heat. In addition, studies in cultured mammalian cells and in animal tumours show that hyperthermia can enhance the cytotoxicity of some chemotherapeutic agents [38]. The commonly used intraoperative agents are mitomycin C, cisplatin, and 5-fluorouracil (5FU), used alone or in various combinations, usually administered for 30–120 minutes. For early postoperative IP chemotherapy, cell-cycle-specific drugs such as 5FU and paclitaxel are most frequently used, for up to 6 days. Perhaps the most important pharmacologic rationale for combining moderate heat (42°C) and heat-augmented chemotherapy agents in the peritoneal space is drug penetration [39].

4. MORBIDITY AND MORTALITY

For new treatments to become established, cost–benefit, efficacy, and morbidity and mortality analyses are essential. The surgical team has a responsibility to ensure that morbidity and mortality are minimized, and that the potential risks and benefits are balanced—both are fundamental in moving an experimental treatment to a standard of care [40]. The development of CRS and HIPEC treatment illustrates the importance of the learning curve. A number of centres around the world now have considerable expertise in the management of peritoneal malignancy, providing a useful insight into the factors that influence outcome. The surgeon's performance has always been key, and the concept of "the learning curve,"

a favourite of those interested in the introduction of new technologies [41]. Several authors have reported on the "global learning curve" as the knowledge base arising from specialized centers around the world increases. Experienced centres are now reporting substantial reductions in the morbidity and mortality initially seen after CRS with HIPEC [42–44]. Recent reports from the Australian group led by Morris exemplifies the improvement in perioperative outcomes, surgical results, and long-term survival that come with centralizing this complex treatment strategy in an established peritoneal surface malignancy center [45,46]. Over a 12-year period, 308 CRS procedures with IP chemotherapy were performed. That 12-year period was divided into 3 discrete periods. The numbers of older patients with higher PCI scores (>17) selected for treatment were observed to increase over that time; however, concomitant decreases were observed in the length of the postoperative stay in the intensive care unit, in the requirements for blood transfusion, and in mortality. The proportion of complete cytoreductions increased, with improved long-term survival, suggesting a maturing of the surgical approach taken to treat peritoneal surface malignancy—a result of improved patient selection, intraoperative decisions, and perioperative care.

In a recent manuscript concerning 456 patients having CRS and perioperative IP chemotherapy for an appendiceal epithelial neoplasm, the postoperative in-hospital mortality was 1.6%, and grade 4 morbidity, 7%. Reoperation for bleeding occurred in 3% of patients and for anastomotic leak in 2%. Also, intestinal fistulae were reported in 2% [47].

Continued study and publication of the risks associated with CRS and HIPEC, centralization of services, and collaboration between units will be instrumental in a continuing to reduce morbidity and mortality. The learning curve comprises a combination of surgical and institutional awareness of the issues, a willingness to learn from established units, and an understanding of the infrastructure requirements needed to sustain a service for these complex, but eminently treatable, conditions.

5. RESULTS OF TREATMENT

5.1 Epithelial Appendiceal Neoplasms

Some recent reports concerning systemic agents may be useful for the management of epithelial appendiceal neoplasms.

A few single-case reports have detailed stabilization of disease with chemotherapeutic agents and monoclonal antibodies such as bevacizumab [48,49].

A single phase II study reported treatment of patients with pseudomyxoma peritonei with systemic mitomycin C and capecitabine [50]. Of the 40 patients enrolled in the study, none had received systemic mitomycin C or 5FU before inclusion. Patients were grouped according to progressive or stable disease judged, before enrolment, to be unresectable because of tumour encasement of the stomach or because of small-bowel involvement or fistulation. Computed tomography was used to identify disease progression at regular intervals during treatment. In 15 patients (38%), systemic chemotherapy produced benefit in terms of reduction in tumour volume on CT or of disease stabilization if previously progressing. Median follow-up in these patients was 17 months; the durability of the response is not clear.

Yan and colleagues systematically reviewed the ten most recent updates before 2006 from institutions performing CRS with IP chemotherapy [4]. There were no randomized controlled trials or comparative studies. Five studies had relatively large series (more than 100 patients). The 5-year survival rates varied between 33% and 56%, and mortality rates ranged between 0% and 18%. Promising long-term results were reported. No recent historical controls have been published for comparison. With experienced centers reporting long-term (20-year) survivals of 80% in patients with low-grade disease in whom complete cytoreduction was achieved, the importance of identifying such patients is clear [8]. Figure 5 presents comparisons of patient survival at institutions performing traditional debulking treatments with or without systemic chemotherapy [51].

There is no doubt that the paradigm for a "comprehensive management plan" is the treatment of peritoneal dissemination of epithelial appendiceal neoplasms by CRS and HIPEC. The value of such a management plan is also evident in the treatment of colorectal carcinomatosis and peritoneal mesothelioma.

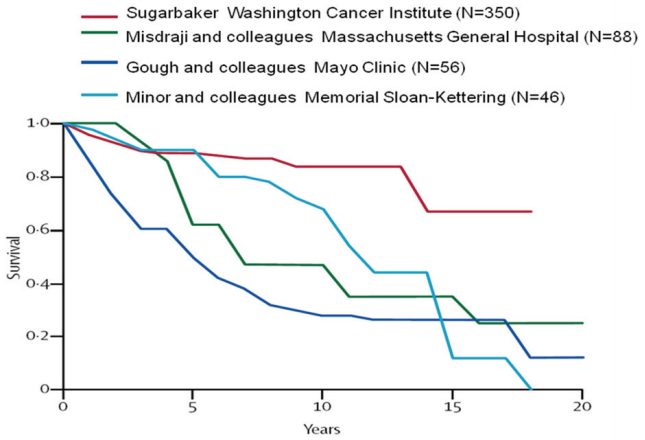

FIGURE 5 Treatment of appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome at 4 well-known centres. The only institution to use cytoreductive surgery simultaneously with chemotherapy was the Washington Cancer Institute. The other 3 institutions used serial debulking combined with systemic chemotherapy or delayed intraperitoneal chemotherapy. Reproduced, with permission, from Sugarbaker, 2006 [51].

5.2 Peritoneal Carcinomatosis from Colorectal Cancer

Since the development of new systemic chemotherapy protocols using irinotecan and oxaliplatin and of new targeted therapy with monoclonal antibodies, the prognosis in metastatic colorectal disease has improved, with median survival reaching 24 months [52–56]. The recent study by Sanoff and colleagues [56] presented 5-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer. Median survival was reported as 20.2 months, with 5% 5-year survival. Unfortunately, none of the reports provide data on objective response and survival for the subset of patients with peritoneal carcinomatosis. In the reported patients, metastatic disease sites included mostly liver and lung, in which response was readily measurable by radiologic studies.

Specific mention of patients with peritoneal carcinomatosis is rarely made. As documented in several studies, peritoneal carcinomatosis is a unique manifestation of metastatic disease, with a natural history and response to systemic chemotherapy that differs from that in liver or lung metastasis [52,57]. A recent paper from Elias *et al.* [58] reported a median survival of 23.9 months in 48 patients with isolated and limited colorectal carcinomatosis treated with palliative surgery and modern systemic chemotherapy. Based on current evidence, palliative systemic chemotherapy for patients with colorectal carcinomatosis achieves a median survival of between 7 months and 24 months. In these patients, long-term survival is almost never achieved.

Published evidence of long-term survival with systemic chemotherapy in the treatment of peritoneal carcinomatosis from colorectal cancer is lacking. In sharp contrast, a number of recent multicentre registry studies, including a phase III study, have described treatment with CRS and HIPEC. In the randomized controlled trial conducted at the Netherlands Cancer Institute, 105 patients were randomly assigned to receive either the standard treatment of systemic chemotherapy with 5FU, or the experimental treatment, which was an aggressive CRS combined with HIPEC using mitomycin C. The patients who had CRS and HIPEC received the systemic chemotherapy regimen after the experimental treatment. At a median follow-up of 21.6 months, median survival was 12.6 months in the standard therapy arm and 22.3 months in the experimental therapy arm ($p = 0.032$ by log-rank test). This group concluded that cytoreduction followed by HIPEC improves survival in patients with carcinomatosis of colorectal origin [59]. Figure 6 compares survival in colorectal carcinomatosis patients receiving CRS plus HIPEC with survival in patients receiving systemic chemotherapy alone.

In a large multicentre registry study of more than 500 patients, those treated with the combination of complete CRS with perioperative IP chemotherapy experienced median survival of 32 months and 5-year survival of 27% [22]. Moreover, the long-term results of the randomized Dutch trial comparing mitomycin C HIPEC and CRS with intravenous chemotherapy alone (5FU, leucovorin), reported a 2-year survival rate of 43% in the HIPEC group compared with 16% in the control group ($p = 0.014$) [57]. The benefits of CRS and HIPEC remained with an 8-year follow-up [60]. In the Dutch multicentre trial ($n = 562$), the probability of survival at 10 years was 37% [61].

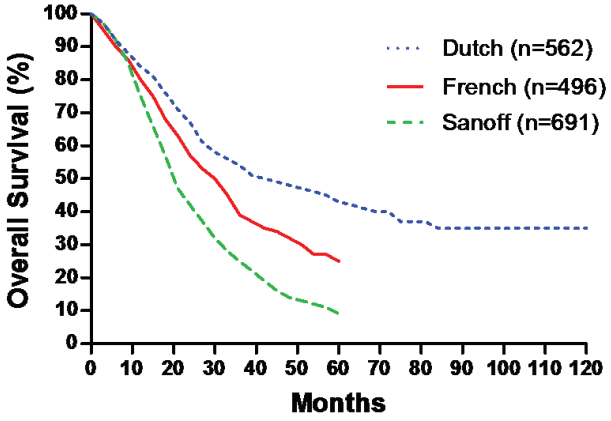

FIGURE 6 Survival of patients with metastatic colorectal cancer treated with cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy or systemic chemotherapy alone. Modified from Elias et al.*, 2010 [3], Sanoff* et al.*, 2008 [56], and Verwaal, 2009 [61].*

There is no doubt that the patients treated with comprehensive management of carcinomatosis by CRS and HIPEC are selected patients, usually with a lower volume of carcinomatosis than is generally seen by the oncologist. Elias and colleagues specifically addressed that issue, comparing 48 patients receiving systemic chemotherapy for small-volume carcinomatosis with 48 patients undergoing CRS and HIPEC. In the group treated with systemic chemotherapy, patients received a mean of 2.3 lines of treatment. The 2-year and 5-year overall survival rates were, respectively, 81% and 51% for the HIPEC group and 65% and 13% for the standard-treatment group. Median survival was 62.7 months in the HIPEC group and 23.9 months in the standard-treatment group ($p < 0.05$ by log-rank test) [58]. Although patients with isolated resectable peritoneal carcinamatosis achieved a median survival of 24 months with modern chemotherapies, only CRS plus HIPEC was able to prolong median survival to 63 months, with a 5-year survival of 51%.

Currently there is no evidence from the oncology literature to support the use of systemic chemotherapy alone to treat the subset of colon cancer patients with carcinomatosis. Until more data become available, the management strategy supported by the literature is CRS plus HIPEC.

5.3 Diffuse Malignant Peritoneal Mesothelioma

Some available evidence reports a benefit for systemic chemotherapy in the treatment of pleural mesothelioma [62]. Combination therapy with cisplatin and pemetrexed shows promise compared with the modest activity seen with single agents. However, evidence to support combination therapy in peritoneal mesothelioma is minimal, with median survival of 1 year [63,64]. Numerous phase II studies and a recent multi-institutional registry study of 405 patients demonstrated long-term benefit with CRS and HIPEC for the treatment of peritoneal mesothelioma (Table I) [5,65–71]. In the systematic review by Yan and colleagues, median survival was reported to be 53 months, with 3- and 5-year survival rates of 60% and 47% respectively. On multivariate analysis, prognostic factors independently associated with improved survival were epithelial subtype ($p < 0.001$), absence of lymph node metastases ($p < 0.001$), complete cytoreduction ($p < 0.001$), and use of HIPEC ($p = 0.002$). Based on the available evidence, the standard of care for peritoneal mesothelioma is CRS with HIPEC, supplemented by systemic chemotherapy in selected patients [5]. Treatment should given at an experienced centre.

5.4 Comparisons of the Management of Liver Metastases from Colorectal Cancer and Peritoneal Carcinomatosis from Colorectal Cancer

Liver resection for selected patients with colorectal metastatic disease is now considered a standard of care. This standard was achieved through an evolutionary process, and no prospective randomized clinical trials have been published to justify this cornerstone of colorectal cancer treatment. It is retrospective reviews of multi-institutional studies that form the basis of this strategy [72–74]. In a systematic review, Kaido and Uemoto concluded that no available level 1 evidence supported the superiority of surgical treatment over other treatments for colorectal liver metastases [75]. However, it has become evident that there are prognostic indicators that can be used to select patients likely to benefit, and that complete resection of colorectal liver metastases is required for any hope of long-term benefit [76,77].

Although there are many differences between the management strategies for liver metastases and for peritoneal metastases, the similar benefits in survival achieved with radical resection of liver metastases and with complete resection of peritoneal carcinomatosis were described by Gertsch [78]. Liver metastases are now treated with adjuvant or neoadjuvant chemotherapy combined with liver resection. Peritoneal carcinomatosis requires IP chemotherapy to be administered at the time of resection in an attempt to treat any microscopic residual disease.

Subsequently, a number of groups have drawn the parallel between these two anatomic sites of locoregional spread, suggesting that both are amenable to surgical intervention. Shen and colleagues [79] identified 55 patients over a 14-year period who underwent complete cytoreduction and HIPEC for colorectal peritoneal carcinomatosis and 95 patients who had a margin-negative hepatectomy for colorectal liver metastases. With median follow-ups of 86 months for patients with colorectal carcinomatosis and 56 months for those with liver metastases, overall 5-year survival was not significantly different at about 30% in each group. The same research group published results of 14 patients with synchronous liver metastases and peritoneal carcinomatosis from colorectal cancer who underwent CRS and HIPEC with liver resection [80]. Liver resection combined with CRS and HIPEC resulted in patient survival that was similar to the survival achieved with CRS and HIPEC alone. Overall median survival for patients with liver metastases was 23 months.

Cao *et al.* [81] recently reported results from the group in Sydney led by Morris. Outcomes in 46 patients who had complete cytoreduction for colorectal

TABLE I Phase II data showing long-term benefit with cytoreductive surgery plus perioperative intraperitoneal chemotherapy in patients with diffuse malignant peritoneal mesothelioma

Reference	*Centre*	*Senior author*	*Year*	*Patients (n)*	*Median survival (months)*
Brigand *et al.,* 2006 [65]	Centre Hospitalier Lyon-Sud, Lyon, France	Glehen	2006	15	36
Sugarbaker *et al.,* 2006 [66]	Washington Cancer Institute, Washington, DC, U.S.A.	Sugarbaker	2006	57	54
Alexander *et al.,* 2007 [67]	National Cancer Institute, Bethesda, MD, U.S.A.	Alexander	2007	49	92
Elias *et al.,* 2007 [68]	Institut Goustav–Roussy, Villejuif, France	Elias	2007	26	100
Yan *et al.,* 2007 [5]	Multi-institutional study	Yan	2009	405	53
Chua *et al.,* 2009 [69]	St. George Hospital, Sydney, Australia	Morris	2009	20	29
Yano *et al.,* 2009 [70]	Basingstoke, U.K.	Moran	2009	17	44
Baratti *et al.,* 2010 [71]	Istituto Tumori, Milan, Italy	Deraco	2010	83	60

carcinomatosis were compared with those in 237 patients who had a margin-negative liver resection for colorectal liver metastases. Of the 46 who underwent CRS, 30 (65.2%) received HIPEC. With median follow-ups of 19 months and 23 months in the peritonectomy and liver resection groups respectively, overall median survival was 37 months in both groups. These results demonstrate that, if complete cytoreduction can be achieved, CRS and HIPEC is as effective in managing peritoneal carcinomatosis as liver resection is for hepatic metastases.

6. CRITICISM OF CRS AND HIPEC

A review of the many manuscripts written on CRS and HIPEC shows that none question the absolute requirement for adequate cytoreduction to achieve long-term benefit. However, the HIPEC or HIPEC plus early postoperative IP chemotherapy techniques have not been well standardized. It is safe to say that the most effective locoregional chemotherapy regimen that maintains acceptable morbidity and mortality has not emerged. Drug selection varies widely, with oxaliplatin and 5FU often used in Europe, and mitomycin C usually used in the United States. The technique of HIPEC administration has also not been standardized. The open method ("coliseum technique") allows for extensive mechanical cleansing of abdominal and pelvic surfaces, but continues to attract criticism because of environmental safety concerns. The closed method allows for a larger volume of chemotherapy to enter the abdomen and pelvis under low pressure, but may not contact all abdominal and pelvic surfaces with chemotherapy solution.

Some observers may object that CRS and HIPEC have not been evaluated separately, and efforts are ongoing to establish the role for HIPEC in the management of carcinomatosis. Needless to say, surgeons have been trying to effectively—and potentially curatively—manage the peritoneal dissemination of cancer for many decades before perioperative IP chemotherapy was introduced. Not a single article reporting the success of surgery alone in the management of carcinomatosis has ever been published. It is highly unlikely that surgery alone would achieve a cure of carcinomatosis from appendiceal malignancy, from colorectal cancer, or from peritoneal mesothelioma. As time goes on and clinical research continues, the relative roles of combined IP chemotherapy and systemic chemotherapy will need to be made clearer.

7. DISCUSSION OF CRS PLUS HIPEC VERSUS TRADITIONAL MANAGEMENT

In many centres specializing in peritoneal surface malignancy, CRS with HIPEC (combined when appropriate with systemic chemotherapy) is now the standard of care in selected patients. Numerous centres around the world are presenting encouraging long-term survival outcomes for mucinous appendiceal neoplasms, colorectal carcinomatosis, and peritoneal mesothelioma. No alternative strategies are forthcoming; there is a paucity of published data to support systemic chemotherapy alone for this group of patients. Nevertheless, the wider oncology community has been generally reluctant to accept CRS with HIPEC.

Are additional clinical data needed before CRS and HIPEC are accepted as the standard of care for treating mucinous appendiceal neoplasms, selected low- to moderate-volume colorectal carcinomatosis, and peritoneal mesothelioma? Currently, no available data support systemic chemotherapy as an alternative to CRS and HIPEC as a standard of care. It must be remembered that no randomized controlled trials have been performed to prove that resection of colorectal liver metastases is superior to systemic chemotherapy alone, and yet that approach has been assimilated into standard treatment protocols. Although CRS and HIPEC for peritoneal carcinomatosis show a benefit similar to that for resection of liver metastasis in colorectal cancer, many oncologists continue to regard CRS and HIPEC therapy as experimental.

A recent paper from the University of Pennsylvania by Casarett and colleagues discussed quality improvement initiatives and when they should be classified as research [82]. Quality improvement has become a major force in shaping health care [83]. Two criteria were proposed to determine whether a quality improvement initiative should be viewed as research. First, if most of the patients involved are not expected to benefit directly from the knowledge to be gained, then the initiative should be reviewed and regulated as research. Second, if patients will benefit directly, and then if additional risks or burdens are imposed to make the results generalizable, the initiative should still be reviewed as research. Patients undergoing CRS with HIPEC benefit from the treatment, and the published data show that the results are generalizable. Furthermore, the risks are similar to those published for other major gastrointestinal surgeries. Is it therefore time to start considering CRS with HIPEC as an initiative to improve the quality of care in patients with peritoneal surface malignancy?

8. SUMMARY

An evolution of principles by which gastrointestinal cancer is treated can be traced starting from the end of the 1960s. Early on, the major goal of cancer surgery was clearance of the primary cancer and achievement of an R0 resection. Next, maximal containment during that resection was shown to be essential for locoregional control. Currently, not only clearance and containment, but also the knowledgeable use of CRS plus HIPEC, must be implemented as a third crucial requirement for the surgical management of selected patients with gastrointestinal cancer.

Clinical and pharmacologic parameters have been used to rethink requirements for optimal gastrointestinal cancer management. This practice-based evidence coming from multiple institutions and peer-reviewed publications shows long-term success with the new approach. As quantitative prognostic indicators have evolved, the clinical data for improved selection of patients have developed. Also, the simultaneous (not adjuvant or neoadjuvant) use of locoregional chemotherapy in the perioperative period with the surgical intervention has been widely published. Finally, as experience with this technology has increased, the associated morbidity and mortality have diminished, making the treatments applicable to a larger number of patients.

The management of mucinous appendiceal neoplasms, including pseudomyxoma peritonei syndrome, has shown marked changes since the start of the 1990s. Comparison of results from prominent institutions suggests that long-term survival is greatly improved with CRS plus HIPEC. For colorectal peritoneal carcinomatosis, no available evidence suggests that systemic chemotherapy alone is a treatment option. By contrast, multiple reports from many different institutions show that, in selected cases, CRS plus HIPEC improves median survival and produces approximately 30% cure rates. Evidence for systemic chemotherapy treatments in peritoneal mesothelioma is also lacking. By contrast, when compared with historical data, CRS plus HIPEC shows approximately 50% long-term survival and marked improvement. Acceptance of medical history in the treatment of liver metastases to reach a standard of care creates a strong rationale for acceptance of CRS plus HIPEC as a standard of care. The treatment results for both conditions as compared in multiple reports are similar.

The options for management of peritoneal surface malignancy have been expanded. Clinical data provide selection criteria for an optimal treatment that, compared with systemic chemotherapy alone, results in great benefit. Recent trends, as published by multiple institutions, suggest that, at experienced centres, CRS and HIPEC are a new standard of care for appendiceal cancer, colorectal cancer, and peritoneal mesothelioma.

9. FUTURE PROSPECTS

Despite the many accomplishments to date, continued clinical research into CRS and HIPEC is mandatory. The optimal perioperative IP chemotherapy has not been established. Neither has the optimal integration of systemic with IP therapy been established. Treatment regimens that combine a bidirectional approach (combined IP and intravenous administration) may be especially promising [84].

Data from PCI scores clearly suggest that management of patients with minimal disease will result in the best survival outcomes. Referral of patients with early carcinomatosis rather than gross disease requires a fundamental change in the attitudes of oncologists toward the efficacy of CRS and HIPEC. The continued use of suboptimal treatments that involve systemic chemotherapy alone needs to cease. Management of patients with minimal carcinomatosis must be the goal. Second-look surgery in patients at high risk for locoregional failure in colorectal cancer needs to be considered.

10. CONFLICT OF INTEREST DISCLOSURES

None of the authors has a financial conflict of interest.

11. REFERENCES

1. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986;1:1479–82.
2. West NP, Hohenberger W, Weber K, Perrakis A, Finan PJ, Quirke P. Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. *J Clin Oncol* 2010;28:272–8.
3. Elias D, Gilly F, Boutitie F, *et al.* Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol* 2010;28:63–8.
4. Yan TD, Black D, Savady R, Sugarbaker PH. A systematic review on the efficacy of cytoreductive surgery and perioperative intraperitoneal chemotherapy for pseudomyxoma peritonei. *Ann Surg Oncol* 2007;14:484–92.
5. Yan TD, Deraco M, Baratti D, *et al.* Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. *J Clin Oncol* 2009;27:6237–42.
6. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res* 1996;82:359–74.
7. Ronnett BM, Shmookler BM, Sugarbaker PH, Kurman RJ. Pseudomyxoma peritonei: new concepts in diagnosis, origin, nomenclature, and relationship to mucinous borderline (low malignant potential) tumors of the ovary. *Anat Pathol* 1997;2:197–226.
8. Sugarbaker PH. Epithelial appendiceal neoplasms. *Cancer J* 2009;15:225–35.
9. Bradley RF, Stewart JH 4th, Russell GB, Levine EA, Geisinger KR. Pseudomyxoma peritonei of appendiceal origin: a clinicopathologic analysis of 101 patients uniformly treated at a single institution, with literature review. *Am J Surg Pathol* 2006;30:551–9.
10. Sugarbaker PH, Jablonski KA. Prognostic features of 51 colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. *Ann Surg* 1995;221:124–32.
11. Loungnarath R, Causeret S, Bossard N, *et al.* Cytoreductive surgery with intraperitoneal chemohyperthermia for the treatment of pseudomyxoma peritonei: a prospective study. *Dis Colon Rectum* 2005;48:1372–9.

12. Murphy EM, Sexton R, Moran BJ. Early results of surgery in 123 patients with pseudomyxoma peritonei from a perforated appendiceal neoplasm. *Dis Colon Rectum* 2007;50:37–42.
13. Elias D, Honore C, Ciuchendea R, *et al.* Peritoneal pseudomyxoma: results of a systematic policy of complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Br J Surg* 2008;95:1164–71.
14. Smeenk RM, Verwaal VJ, Antonini N, Zoetmulder FA. Survival analysis of pseudomyxoma peritonei patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg* 2007;245:104–9.
15. Ronnett BM, Yan H, Kurman RJ, Shmookler BM, Wu L, Sugarbaker PH. Patients with pseudomyxoma peritonei associated with disseminated peritoneal adenomucinosis have a significantly more favorable prognosis than patients with peritoneal mucinous carcinomatosis. *Cancer* 2001;92:85–91.
16. Yan H, Pestieau SR, Shmookler BM, Sugarbaker PH. Histopathologic analysis in 46 patients with pseudomyxoma peritonei syndrome: failure vs. success with a second-look operation. *Mod Pathol* 2001;14:164–71.
17. Sugarbaker PH, Acherman YI, Gonzalez–Moreno S, *et al.* Diagnosis and treatment of peritoneal mesothelioma: the Washington Cancer Institute experience. *Semin Oncol* 2002;29:51–61.
18. Cerruto CA, Brun EA, Chang D, Sugarbaker PH. Prognostic significance of histomorphologic parameters in diffuse malignant peritoneal mesothelioma. *Arch Pathol Lab Med* 2006;130:1654–61.
19. Deraco M, Nonaka D, Baratti B, *et al.* Prognostic analysis of clinicopathologic factors in 49 patients with diffuse malignant peritoneal mesothelioma treated with cytoreductive surgery and intraperitoneal hyperthermic perfusion. *Ann Surg Oncol* 2006;13:229–37.
20. Esquivel J, Sticca R, Sugarbaker P, *et al.* Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. *Ann Surg Oncol* 2007;14:128–33.
21. da Silva RG, Sugarbaker PH. Analysis of prognostic factors in seventy patients having complete cytoreduction plus perioperative intraperitoneal chemotherapy for carcinomatosis from colorectal cancer. *J Am Coll Surg* 2006;203:878–86.
22. Glehen O, Kwiatkowski F, Sugarbaker PH, *et al.* Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol* 2004;22:3284–92.
23. Pestieau SR, Sugarbaker PH. Treatment of primary colon cancer with peritoneal carcinomatosis: comparison of concomitant vs. delayed management. *Dis Colon Rectum* 2000;43:1341–6.
24. Jacquet P, Jelinek JS, Chang D, Koslowe P, Sugarbaker PH. Abdominal computed tomographic scan in the selection of patients with mucinous peritoneal carcinomatosis for cytoreductive surgery. *J Am Coll Surg* 1995;181:530–8.
25. Blodgett TM, Meltzer CC, Townsend DW. PET/CT: form and function. *Radiology* 2007;242:360–85.
26. Antoch G, Saoudi N, Kuehl H, *et al.* Accuracy of whole-body dual-modality fluorine-18–2-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography (FDG-PET/CT) for tumor staging in solid tumors: comparison with CT and PET. *J Clin Oncol* 2004;22:4357–68.
27. Pfannenberg C, Konigsrainer I, Aschoff P, *et al.* ^{18}F-FDG-PET/CT to select patients with peritoneal carcinomatosis for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol* 2009;16:1295–303.
28. Passot G, Glehen O, Pellet O, *et al.* Pseudomyxoma peritonei: role of ^{18}F-FDG PET in preoperative evaluation of pathological grade and potential for complete cytoreduction. *Eur J Surg Oncol* 2010;36:315–23.
29. Yan TD, Haveric N, Carmignani P, Chang D, Sugarbaker PH. Abdominal computed tomography scans in the selection of patients with malignant peritoneal mesothelioma for comprehensive treatment with cytoreductive surgery and perioperative intraperitoneal chemotherapy. *Cancer* 2005;15:839–49.
30. Gilly FN, Carry PY, Sayag AC, *et al.* Regional chemotherapy (with mitomycin C) and intra-operative hyperthermia for digestive cancers with peritoneal carcinomatosis. *Hepatogastroenterology* 1994;41:124–9.
31. Glehen O, Beaujard AC, Arvieux C, Huber O, Gilly FN. Peritoneal carcinomatosis. Surgical treatment, peritonectomy and intraperitoneal chemohyperthermia [French]. *Gastroenterol Clin Biol* 2002;26:210–15.
32. Sugarbaker PH. Intraperitoneal chemotherapy and cytoreductive surgery for the prevention and treatment of peritoneal carcinomatosis and sarcomatosis. *Semin Surg Oncol* 1998;14:254–61.
33. Barakat RR, Sabbatini P, Bhaskaran D, *et al.* Intraperitoneal chemotherapy for ovarian carcinoma: results of long-term follow-up. *J Clin Oncol* 2002;20:694–8.
34. Elias D, Blot F, El Otmany A, *et al.* Curative treatment of peritoneal carcinomatosis arising from colorectal cancer by complete resection and intraperitoneal chemotherapy. *Cancer* 2001;92:71–6.
35. Gerweck LE. Hyperthermia in cancer therapy: the biological basis and unresolved questions. *Cancer Res* 1985;45:3408–14.
36. Oleson JR, Calderwood SK, Coughlin CT, *et al.* Biological and clinical aspects of hyperthermia in cancer therapy. *Am J Clin Oncol* 1988;11:368–80.
37. Lindquist S. The heat-shock response. *Annu Rev Biochem* 1986;55:1151–91.
38. Urano M, Kuroda M, Nishimura Y. For the clinical application of thermochemotherapy given at mild temperatures. *Int J Hyperthermia* 1999;15:79–107.
39. Jacquet P, Averbach A, Stuart OA, Chang D, Sugarbaker PH. Hyperthermic intraperitoneal doxorubicin: pharmacokinetics, metabolism, and tissue distribution in a rat model. *Cancer Chemother Pharmacol* 1998;41:147–54.
40. Sugarbaker PH. Clinical research to standard of care: when does the transition occur? *Ann Surg Oncol* 2003;10:825–6.
41. Nizard RS, Porcher R, Ravaud P, *et al.* Use of the CUSUM technique for evaluation of a CT-based navigation system for total knee replacement. *Clin Orthop Relat Res* 2004;(425):180–8.
42. Moran BJ. Establishment of a peritoneal malignancy treatment centre in the United Kingdom. *Eur J Surg Oncol* 2006;32:614–18.
43. Mohamed F, Moran BJ. Morbidity and mortality with cytoreductive surgery and intraperitoneal chemotherapy: the importance of a learning curve. *Cancer J* 2009;15:196–9.
44. Moradi BN 3rd, Esquivel J. Learning curve in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Surg Oncol* 2009;100:293–6.

45. Yan TD, Links M, Fransi S, *et al.* Learning curve for cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal surface malignancy—a journey to becoming a nationally funded peritonectomy center. *Ann Surg Oncol* 2007;14:2270–80.
46. Chua TC, Esquivel J, Pelz JO, Morris DL. Critical analysis of treatment modality and impact on outcome in peritoneal metastases from colorectal cancer: a systematic review. *Ann Oncol* [in press].
47. Youssef H, Newman C, Chandrakumaran K, Mohamed F, Cecil TD, Moran BJ. Operative findings, early complications, and long-term survival in 456 patients with pseudomyxoma peritonei syndrome of appendiceal origin. *Dis Colon Rectum* 2011;54:293–9.
48. Chen CF, Huang CJ, Kang WY, Hsieh JS. Experience with adjuvant chemotherapy for pseudomyxoma peritonei secondary to mucinous adenocarcinoma of the appendix with oxaliplatin/fluorouracil/leucovorin (FOLFOX4). *World J Surg Oncol* 2008;6:118.
49. Sun WL, Hutarew G, Gradl J, Gratzl M, Denz H, Fiegl M. Successful antiangiogenic combination therapy for pseudomyxoma peritonei with bevacizumab and capecitabine. *Cancer Biol Ther* 2009;8:1459–62.
50. Farquharson AL, Pranesh N, Witham G, *et al.* A phase II study evaluating the use of concurrent mitomycin C and capecitabine in patients with advanced unresectable pseudomyxoma peritonei. *Br J Cancer* 2008;99:591–6.
51. Sugarbaker PH. New standard of care for appendiceal epithelial malignancies and pseudomyxoma peritonei syndrome. *Lancet Oncol* 2006;7:69–76.
52. Folprecht G, Kohne CH, Lutz MP. Systemic chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer. *Cancer Treat Res* 2007;134:425–40.
53. Folprecht G, Lutz MP, Schoffski P, *et al.* Cetuximab and irinotecan/5FU/folinic acid is a safe combination for the first-line treatment of patients with epidermal growth factor receptor expressing metastatic colorectal carcinoma. *Ann Oncol* 2006;17:450–6.
54. Hurwitz H, Fehrenbacher L, Novotny W, *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350:2335–42.
55. Goldberg RM, Sargent DJ, Morton RF, *et al.* Randomized controlled trial of reduced-dose bolus fluorouracil plus leucovorin and irinotecan or infused fluorouracil plus leucovorin and oxaliplatin in patients with previously untreated metastatic colorectal cancer: a North American Intergroup Trial. *J Clin Oncol* 2006;24:3347–53.
56. Sanoff HK, Sargent DJ, Campbell ME, *et al.* Five-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer: N9741. *J Clin Oncol* 2008;26:5721–7.
57. Kohne CH, Cunningham D, Di CF, *et al.* Clinical determinants of survival in patients with 5FU-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. *Ann Oncol* 2002;13:308–17.
58. Elias D, Lefevre JH, Chevalier J, *et al.* Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol* 2009;27:681–5.
59. Verwaal VJ, van Ruth S, de Bree E, *et al.* Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003;21:3737–43.
60. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-Year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* 2008;15:2426–32.
61. Verwaal VJ. Long-term results of cytoreduction and HIPEC followed by systemic chemotherapy. *Cancer* 2009;15:212–15.
62. Jackman DM. Current options for systemic therapy in mesothelioma. *Semin Thorac Cardiovasc Surg* 2009;21:154–8.
63. Garcia–Carbonero R, Paz–Ares L. Systemic chemotherapy in the management of malignant peritoneal mesothelioma. *Eur J Surg Oncol* 2006;32:676–81.
64. Janne PA, Wozniak AJ, Belani CP, *et al.* Open-label study of pemetrexed alone or in combination with cisplatin for the treatment of patients with peritoneal mesothelioma: outcomes of an expanded access program. *Clin Lung Cancer* 2005;7:40–6.
65. Brigand C, Monneuse O, Mohamed F, *et al.* Peritoneal mesothelioma treated by cytoreductive surgery and intraperitoneal hyperthermic chemotherapy: results of a prospective study. *Ann Surg Oncol* 2006;13:405–12.
66. Sugarbaker PH, Yan TD, Stuart OA, Yoo D. Comprehensive management of diffuse malignant peritoneal mesothelioma. *Eur J Surg Oncol* 2006;2:686–91.
67. Alexander HR, Hanna N, Pingpank JF. Clinical results of cytoreduction and HIPEC for malignant peritoneal mesothelioma. *Cancer Treat Res* 2007;134:343–55.
68. Elias D, Bedard V, Bouzid T, *et al.* Malignant peritoneal mesothelioma: treatment with maximal cytoreductive surgery plus intraperitoneal chemotherapy [French]. *Gastroenterol Clin Biol* 2007;31:784–8.
69. Chua TC, Yan TD, Morris DL. Outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal mesothelioma: the Australian experience. *J Surg Oncol* 2009;99:109–13.
70. Yano H, Moran BJ, Cecil TD, Murphy EM. Cytoreductive surgery and intraperitoneal chemotherapy for peritoneal mesothelioma. *Eur J Surg Oncol* 2009;35:980–5.
71. Baratti D, Kusamura S, Cabras AD, Laterza B, Balestra MR, Deraco M. Lymph node metastases in diffuse malignant peritoneal mesothelioma. *Ann Surg Oncol* 2010;17:45–53.
72. Adson MA, van Heerden JA, Adson MH, Wagner JS, Ilstrup DM. Resection of hepatic metastases from colorectal cancer. *Arch Surg* 1984;119:647–51.
73. Hughes KS, Rosenstein RB, Songhorabodi S, *et al.* Resection of the liver for colorectal carcinoma metastases. A multi-institutional study of long-term survivors. *Dis Colon Rectum* 1988;31:1–4.
74. Hughes KS, Simon R, Songhorabodi S, *et al.* Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of patterns of recurrence. *Surgery* 1986;100:278–84.
75. Kaido T, Uemoto S. Quality assessment of randomized controlled trials involving liver surgery. *Hepatogastroenterology* 2008;55:1678–80.

76. Hughes K, Scheele J, Sugarbaker PH. Surgery for colorectal cancer metastatic to the liver. Optimizing the results of treatment. *Surg Clin North Am* 1989;69:339–59.
77. Nordlinger B, Guiguet M, Vaillant JC, *et al.* Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. *Cancer* 1996;77:1254–62.
78. Gertsch P. A historical perspective on colorectal liver metastases and peritoneal carcinomatosis: similar results, different treatments. *Surg Oncol Clin N Am* 2003;12:531–41.
79. Shen P, Thai K, Stewart JH, *et al.* Peritoneal surface disease from colorectal cancer: comparison with the hepatic metastases surgical paradigm in optimally resected patients. *Ann Surg Oncol* 2008;15:3422–32.
80. Varban O, Levine EA, Stewart JH, McCoy TP, Shen P. Outcomes associated with cytoreductive surgery and intraperitoneal hyperthermic chemotherapy in colorectal cancer patients with peritoneal surface disease and hepatic metastases. *Cancer* 2009;115:3427–36.
81. Cao CQ, Yan TD, Liauw W, Morris DL. Comparison of optimally resected hepatectomy and peritonectomy patients with colorectal cancer metastasis. *J Surg Oncol* 2009;100:529–33.
82. Casarett D, Karlawish JH, Sugarman J. Determining when quality improvement initiatives should be considered research: proposed criteria and potential implications. *JAMA* 2000;283:2275–80.
83. Berwick DM. Developing and testing changes in delivery of care. *Ann Intern Med* 1998;128:651–6.
84. Van der Speeten, Stuart OA, Sugarbaker PH. Pharmacokinetics and pharmacodynamics of perioperative cancer chemotherapy in peritoneal surface malignancy. *Cancer J* 2009;15:216–24.

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