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CONTINUING EDUCATION– PERITONEAL SURFACE MALIGNANCY

The Landmark Series: Appendiceal Primary Peritoneal Surface Malignancy

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ABSTRACT Appendiceal primary peritoneal surface malignancies are rare and include a broad spectrum of pathologies ranging from indolent disease to aggressive disease. As such, the data that drive the management of appendiceal peritoneal surface malignancies is generally not based on prospective clinical trial data, but rather consists of level 1 data based on retrospective studies and high-volume institutional experiences. Complete surgical debulking typically offers the best chance for long-term survival. This review highlights the landmark articles on which management of primary appendiceal peritoneal surface malignancies are based.

Appendiceal neoplasms are rare and involve a spectrum of diseases that can be either low grade with fairly slow growth rates or high grade with aggressive features. Broadly, appendiceal neoplasms account for only 1–2 % of intestinal malignancies.[1,2] Appendiceal malignancies may present with acute appendicitis, or more frequently, with progressive abdominal discomfort. Patients with appendiceal cancers may also be asymptomatic, and diagnosed secondary to identification of an abnormality noted on cross-sectional imaging, at the time of colonoscopy with an abnormal-appearing appendiceal orifice or at the time of surgery for another indication.

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Typically, when symptoms are present, the malignancy is advanced and usually indicates peritoneal dissemination. Importantly, the appendix can yield a number of diverse morphologic tumor types including mucinous neoplasms, adenocarcinoma, neuroendocrine tumors, and goblet cell cancers. The median survival time for perforated malignant appendiceal tumors can vary from 6 months for patients with adenocarcinoma to longer than 8 years for patients with low-grade mucinous neoplasms. The management of appendix cancers is dependent on the primary histologic subtype and may include a combination of surgical debulking or cytoreductive surgery (CRS), heated intraperitoneal chemotherapy (HIPEC), and systemic therapy.

The focus of this article is on the management of disseminated appendiceal cancers, defined by the primary tumor histologic subtype. Due to the low incidence of primary appendiceal neoplasms, randomized controlled trials (RCTs) addressing the various aspects of its management are currently lacking, so this study reviews high-impact retrospective studies that guide current practice.

SURGICAL PRINCIPLES

In brief, patients who have localized disease to the appendix should undergo appendiceal resection, and depending on the pathology, may require a right hemicolectomy for assessment of regional lymph nodes (i.e., for adenocarcinoma). Patients who have disseminated disease to the peritoneum should be managed based on histologic subtype and current available guidelines. Additional information on appropriate patient selection based on pathologic subtype is discussed later.

PERITONEAL SCORING SYSTEMS

In an effort to select optimal candidates for CRS and HIPEC, a number of preoperative scoring systems have been developed.[3–6] The primary purpose of these systems is to determine the likelihood that a complete cytoreductive operation can be performed.

The most frequently used scoring system is known as the Peritoneal Cancer Index (PCI). The PCI was developed by Jacquet and Sugarbaker and first described in 1996. The PCI evaluates the tumor burden and distribution in nine predefined abdominopelvic regions (regions 0–8) and four segments of the small intestine (regions 9–12). Each region is then assigned a score from 0 to 3 based on tumor size in that location. In the presence of optimal cytoreduction for primary appendiceal malignancies, the prognosis may still be excellent despite high PCI scores, especially in patients with low-grade disease.[7,8] For other types of malignancies, such as colorectal cancer, the PCI may be more predictive of the possibility of complete cytoreduction, and ultimately, the patient's long-term survival.[9]

The peritoneal surface disease severity score (PSDSS) is another scoring system described by Sugarbaker in 1998 that assigns patients to prognostic groups based on the volume of peritoneal disease, tumor histology, and clinical symptoms (Table 1). The disease burden used to calculate the PSDSS score is derived from preoperative imaging, which has frequently been described as suboptimal.[10–12] The PSDSS has been shown to be valuable in predicting resectability for mucinous appendiceal neoplasms.[6,13]

Another scoring system, the simplified preoperative assessment for appendix tumor (SPAAT) score, was described in 2015. The SPAAT score described by Dineen et al.[3] provides a radiologic scoring of five anatomic regions for volume of disease in low-grade appendiceal mucinous neoplasms. Based on radiologic assessment, a score of 0 or 1 is given for the absence or presence of scalloping of the liver, spleen, pancreas, or portal vein, and a score of 0 or 3 is given for "mesenteric foreshortening," yielding a maximum score of 7. In this study, 42 patients had a SPAAT score lower than 3, and 28 patients had a SPAAT score of 3 or higher. Using a SPAAT score lower than 3 to determine which patients could undergo complete cytoreduction, the study demonstrated an accuracy of 97.14 %, suggesting that based on imaging alone, patients could be appropriately selected for CRS.[3]

ROLE OF SYSTEMIC THERAPY

The role of systemic chemotherapy in appendiceal neoplasms is fairly sparse, and the current evidence is suggestive of limited efficacy for the most common subtypes. Low-grade mucinous neoplasms are typically considered to be slow-growing and fairly indolent, with limited, if any, response to systemic chemotherapy. The mainstay of treatment is therefore surgical. Patients who have low-grade mucinous carcinoma peritonei are treated with CRS and HIPEC. Patients who may experience progressive or recurrent disease or those deemed to be non-surgical candidates can be considered for systemic therapy using regimens that are currently used to treat mucinous colorectal adenocarcinomas.[14–16]

Retrospective evidence suggests that systemic chemotherapy after CRS has the greatest benefit for moderate- and high-grade tumors and tumors with signet ring cell morphology, with limited benefit for well-differentiated appendiceal cancers.[16,17]

For patients with peritoneal metastases from appendiceal adenocarcinoma, especially with high-grade histology, systemic therapy is used in a multimodality approach together with CRS-HIPEC, similar to colorectal cancer.[14] Some argue that patients who receive systemic chemotherapy before CRS and HIPEC may have worse outcomes, possibly due to tumor progressing through ineffective systemic therapy, and that this may lead to ineligibility for potentially curative cytoreduction and that patients may be so debilitated that they are no longer candidates for surgery. Proponents for neoadjuvant chemotherapy counter this argument with "testing" of the biology and selecting patients who may truly benefit from a local treatment (i.e., CRS-HIPEC) after receiving systemic therapy, especially for histologies carrying a high risk for systemic disease. However, the evidence supporting administration of systemic chemotherapy at a specific time in relation to surgery (neoadjuvant, adjuvant, or perioperative) is lacking.

TABLE 1 Peritoneal surface disease severity score (PSDSS) calculation factors. Adapted from Esquivel et al.[13]

Primary tumor pathology	Clinical symptoms	Extent of carcinomatosis
Low-grade mucinous neoplasm (1 point)	None (0 points)	PCI <10 (1 point)
Mucinous adenocarcinoma (3 points)	Mild (1 point)	PCI 10–21 (3 points)
High-grade mixed adenocarcinoma and goblet cell carcinoid (9 points)	Severe (6 points)	PCI >20 (7 points)

PCI, Peritoneal Cancer Index

In a retrospective review from the MD Anderson Cancer Center evaluating patients who received perioperative systemic chemotherapy for poorly differentiated and signet ring cell appendiceal adenocarcinoma consisting of 142 patients with peritoneal metastases, 78 patients received systemic chemotherapy. The overall response rate to chemotherapy was 44 %, with stable disease noted in 42 % and disease progression noted in 14 % of the patients. In a multivariate analysis, the response to chemotherapy (hazard ratio [HR], 0.5; $P = 0.02$] predicted improved progression-free survival (PFS), and complete CRS (HR, 0.3; $P = 0.004$) predicted improved overall survival (OS). The patients who underwent complete CRS ($n = 26$) had a median relapse-free survival (RFS) of 1.2 years and a median OS of 4.2 years. A complete cytoreduction was associated with improved RFS and OS.[18]

In another single-institution retrospective study by Milovanov et al.,[19] 30 of 72 patients received systemic therapy before CRS-HIPEC, and 42 of the 72 patients did not. At a median follow-up period of 3.2 years, with comparable rates of lymph node positivity, postoperative systemic therapy, and rates of complete cytoreduction, the OS rate after CRS-HIPEC was 93 % at 1 year, 68 % at 2 years, and 51 % at 3 years in the neoadjuvant chemotherapy cohort and 82 %, 64 %, and 60 % respectively in the upfront surgery group ($p = 0.74$). However, among the patients with signet ring cell histology, the survival rate was 94 % at 1 year, 67 % at 2 years, and 22 % at 3 years in the neoadjuvant chemotherapy cohort and 43 %, 14%, and 14 % respectively in the upfront surgery cohort ($p = 0.028$).

The optimal timing for the use of systemic chemotherapy for appendiceal cancer patients is not absolute, and patients can be treated neoadjuvantly, adjuvantly, or with a combination of the two. Current standards support treatment for a total of 6 months or 12 cycles.[16,20]

APPENDICEAL MUCINOUS NEOPLASMS

A majority of primary appendiceal adenocarcinomas are of the appendiceal mucinous neoplasm subtype, with mucin identified in more than 50 % of the appendiceal mass. They generally arise from low-grade appendiceal neoplasms (LAMNs), which stem from adenoma development within the mucosa. The data suggest that mucinous and non-mucinous epithelial appendiceal adenocarcinomas behave differently, with the latter having a significantly worse prognosis.

Histologically, LAMNs are characterized by mucinous epithelium with low-grade cytologic atypia, and the affected patient's clinical course is highly dependent on the degree of disease involvement at the time of diagnosis.[21,22] Patients who have disease confined to the appendix can be managed with an appendectomy with negative margins and have minimal risk of disease recurrence or progression. Patients who have a perforated LAMN leading to the development of mucinous implants and mucinous ascites known as pseudomyxoma peritonei (PMP) typically have slowly progressive disease and good OS with complete surgical debulking.[23–25] In PMP, mucin is ectopically secreted and increasingly deposited in the peritoneal cavity, where, unable to degrade or drain away, it forms voluminous gels over months and years. Most of the tumor cells are surrounded by the mucin coat, which allows them to move freely, disseminate, and redistribute within the peritoneal cavity.[26] Patients with PMP, depending on the extent of disease and histologic appearance of the tumor, may warrant CRS-HIPEC.

PATHOLOGIC CLASSIFICATION

Different classification systems for appendiceal neoplasms have been used over the years, leading up to the current classification developed by consensus from the Peritoneal Surface Oncology Group (PSOGI), which divides appendiceal tumors into mucinous epithelial neoplasms (LAMNs, high-grade appendiceal mucinous neoplasms [HAMNs], mucinous adenocarcinomas), non-mucinous epithelial neoplasms (adenocarcinoma), epithelial neoplasms with neuroendocrine features (neuroendocrine tumors, goblet cell carcinoids), and mesenchymal neoplasms.

LAMNs are mucinous tumors with low-grade cytology and any of the following features: loss of muscularis mucosae, submucosal fibrosis, "pushing" or diverticular-like growth into the wall, dissecting acellular mucin, undulating or flattened epithelial growth, and mucin or neoplastic cells outside the appendix.[21] Essentially, the PSOGI consensus guideline suggests that mucinous adenocarcinoma would be reserved for tumors demonstrating infiltrating invasion, with LAMN reserved for no infiltrating invasion and minimal cytologic atypia, and high-grade appendiceal mucinous neoplasm (HAMN) reserved for lesions without infiltrative invasion but with high-grade cytologic atypia. Additionally, PMP was classified as low grade, high grade, and high grade with signet ring cells.

Ronnett et al.[27] initially described the following three-tier classification for disseminated appendiceal mucinous neoplasms: disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA), and PMCA of indeterminate or discordant features (PMCA I/D). This classification predicted differences in OS between the three groups. While DPAM patients had an

indolent clinical course without distant spread, PMCA patients had a higher potential for metastasis to lymph nodes and extra-peritoneal locations.

In 2005, the Ronnett classification was revised and simplified into low- and high-grade carcinoma, with invasion beyond the muscularis mucosa strongly suggestive of invasive high-grade disease.[28] Additionally, acellular mucin is classified separately, and published literature suggests a significant difference in patient outcomes based on whether acellular or cellular mucin is found.[22,29] The PSOGI expert panel suggests that PMP classification be determined by histology of the peritoneal disease rather than by the primary tumor. The categories currently used for PMP grading include acellular mucin, low-grade mucinous carcinoma peritonei (previously DPAM), high-grade mucinous carcinoma peritonei (previously PMCA), and high-grade mucinous carcinoma peritonei with signet ring cells (previously PMCA-S).[21]

The 2019 World Health Organization (WHO) update for primary neoplasms of the appendix classified appendiceal mucinous neoplasms as low- and high-grade appendiceal mucinous neoplasms (LAMN and HAMN, respectively). Furthermore, a three-tier grading scheme was included for primary appendiceal tumors and their respective peritoneal metastases. Tumors demonstrating low-grade cytology without infiltrative invasion and LAMNs were classified as grade 1. Grades 2 and 3 tumors, however, demonstrate high-grade cytology, with presence of signet rings and infiltrative invasion. In addition, for cases with discordance, two grades should be reported. Additionally, with respect to neoplasms previously denoted as goblet cell carcinoid and adenocarcinoma ex-goblet cell carcinoid, per the WHO classification, the preferred terminology is "goblet cell adenocarcinoma." This classification reflects the histology of these tumors which are typically composed primarily of mucin-secreting cells with a limited component of neuroendocrine cells. Furthermore, it elucidates their character, which is more typical of appendiceal adenocarcinoma.

Currently, the PSOGI consensus definition is the most widely adopted classification system used for mucinous neoplasms of the appendix.

MOLECULAR SUBTYPES OF MUCINOUS NEOPLASMS OF THE APPENDIX

For patients with peritoneal dissemination from mucinous neoplasms of the appendix, CRS with HIPEC represents the primary treatment modality. In addition to the traditional prognostic indicators (histologic grade, completeness of cytoreduction, patient's performance status), heterogeneity at a molecular level may explain differences in tumor aggressiveness, treatment response and prognosis. In appendiceal mucinous neoplasms, KRAS and GNAS mutations are common, while BRAF mutations are rarely found.[30,31]

For patients with pseudomyxoma peritonei, prognosis was noted to be associated with expression of p53,[32] carbonic anhydrase II,[33] and SMAD4[34] in small patient series. Additionally, gene expression-profiling has been used to identify gene clusters of prognostic significance for low-grade appendiceal tumors.[35] Using a 148-gene panel, Su et al.[36] identified three molecular subtypes of appendiceal mucinous neoplasms by the expression patterns of 17 genes with roles in cancer progression or anti-tumor immunity. These subtypes were termed "immune-enriched" (IE), "oncogene-enriched" (OE), and "mixed" (M), as evidenced by their gene expression patterns, and exhibited significantly different post-treatment survival outcomes.

Future work focusing on the molecular subtypes would help clinicians identify specific management algorithms that will potentially be more efficacious while also determining prognosis.

RANDOMIZED CLINICAL TRIALS

Due to the low incidence of appendiceal mucinous neoplasms and PMP, RCTs addressing the various aspects of their management with a large number of participants are currently lacking and unlikely to be performed in the near future. We discuss the RCT performed to evaluate the role of CRS-HIPEC for colorectal cancer that included a small cohort of patients with appendiceal tumors.

RETROSPECTIVE EVIDENCE

The therapeutic rationale for cytoreduction and HIPEC for metastatic appendiceal mucinous neoplasms stems from retrospective evidence. For patients with low-grade mucinous neoplasms, CRS-HIPEC with successful complete cytoreduction leads to excellent long-term survival for a majority of patients.[37–41] Sugarbaker and Chang[42] first described outcomes for 385 patients with primary appendiceal tumors treated with CRS-HIPEC and concluded that completeness of cytoreduction and primary tumor histology were of paramount importance.

Subsequently, in 2006, Stewart et al.[39] published data on 110 patients with PMP who underwent CRS-HIPEC, of which 55 patients had low-grade mucinous carcinoma peritonei, 47 patients had high-grade mucinous carcinoma peritonei, and 8 patients had high-grade non-mucinous tumors. Evaluation on the basis of histology showed that patients with low-grade mucinous tumors had better 3-year

survival rates (77 % for low-grade mucinous tumors vs 35 % for high-grade mucinous tumors and 15 % for high-grade non-mucinous tumors).

Similarly, Smeenk et al.[37] evaluated 103 patients with PMP and found that pathologic subtype was the main prognostic factor independently associated with OS after CRS-HIPEC. Likewise, 10-year data from Australia for patients who had PMP treated with CRS-HIPEC, including both low- and high-grade pathologies, demonstrated a median OS survival of 104 months, with 5-year OS rates of 75 %. Again, histopathology and completeness of cytoreduction were thought to influence OS for this cohort.[40]

In 2010, Elias et al.[43] reported on the French experience of CRS-HIPEC for PMP. The study included 301 patients with a mean follow-up period of 88 months. For 91 % of the patients, PMP was known to originate from the appendix, and most of the patients were found to have PMP secondary to unexplained ascites (32 %) or abdominal pain (27 %). The median PCI for the evaluated patients was 18, and most of the patients underwent complete cytoreduction (CC0 for 73 % and CC1 for 20 % of the patients). In this study, a small subset of patients ($n = 46$, 15 %) were treated with early postoperative intraperitoneal chemotherapy (EPIC). The overall 3- and 5-year survival rates were 84.8 % and 72.6 % respectively, with a disease-free survival (DFS) rate of 56 % at 5 years. The patients with PCI values greater than 19 had significantly worse 3- and 5-year survival rates compared to patients with PCI values of 1 to 6, 7 to 12, and 13 to 19 ($p < 0.001$; Fig. 1). Additionally, the patients with CC1 and CC2 cytoreduction had worse OS than the CC0 patients, and incomplete CRS was observed only for the patients with a PCI greater than 20. Similar to previous studies, the patients with DPAM and intermediate PMCA had a better OS than the patients who had high-grade PMCA, with a 5-year OS of 85 % vs 84 % and 47 %, respectively, again suggesting that pathology was a main driver of survival benefit. Finally, the patients treated with HIPEC had a better OS the than patients treated with EPIC, with a 5-year OS of 79 % and 54 %, respectively ($p < 0.001$). Overall, this large study supports the view that for patients with PMP, PCI and the CC score have a greater impact on OS after CRS-HIPEC than pathology alone.

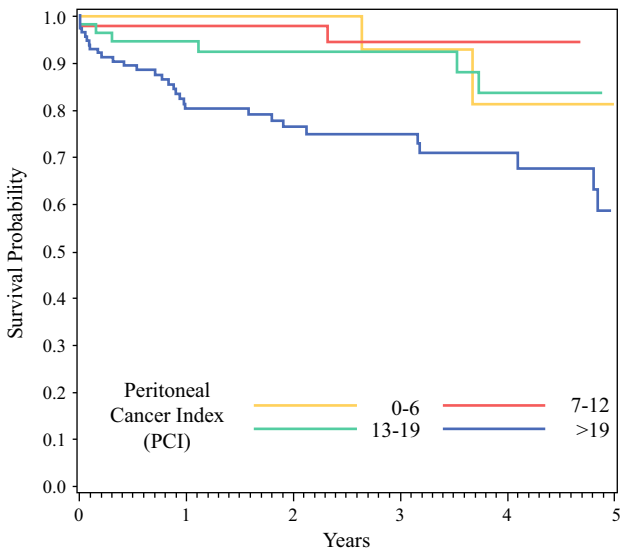

FIG. 1 Overall survival according to the Peritoneal Cancer Index (PCI) of patients undergoing CRS/HIPEC for pseudomyxoma peritonei (PMP). CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy. Elias et al.[43]

In 2015, Moran et al.[44] published their experience with 1200 patients treated at a single institution during a 20-year period. A total of 956 patients (79.7 %) had primary appendiceal cancers. The 5-year OS was 84 % for the 636 appendiceal cancer patients who underwent complete CRS with HIPEC.

Based on available data, CRS-HIPEC is an appropriate therapy for patients with PMP. Factors such as primary tumor, disseminated peritoneal disease histology, and PCI should be considered in the selection of patients for surgical debulking, but even in the setting of more aggressive disease, it appears that CRS-HIPEC allows for improved survival for appropriately selected patients.

PERITONECTOMY TECHNIQUE

In 1995, Sugarbaker[45] first described a complete peritonectomy to remove all tumors implanted in the peritoneal cavity. Essentially, a complete peritonectomy includes greater omentectomy with splenectomy, left upper-quadrant peritonectomy, right upper-quadrant peritonectomy, lesser omentectomy with cholecystectomy and omental bursa peritonectomy, pelvic peritonectomy with resection of the sigmoid colon, and antrectomy. Since then, the procedure has evolved with the addition of Glisson's capsulectomy of the liver, posterior lesser sac peritonectomy, and total mesenteric peritonectomy.[46–50] The details concerning the individual components of the cytoreduction and HIPEC procedure are beyond the scope of this article, but key components that have an impact on survival are highlighted.

COMPLETENESS OF CYTOREDUCTION

One of the key prognostic factors that has an impact on survival after cytoreduction and HIPEC is an optimal cytoreduction.[51,52] To standardize the method of quantifying residual disease after CRS, Sugarbaker proposed the completeness of cytoreduction (CC) score (Fig. 2).[53] This score ranges from 0 to 3, with a score of 0 to 1 suggesting

residual tumors smaller than 2.5 mm and a score of 2 or 3 suggesting residual tumor nodules larger than 2.5 mm. A CC score of 0 or 1 suggests a complete cytoreduction, whereas a score of 2 or 3 suggests an incomplete cytoreduction.[54] Patients with incomplete cytoreduction have a shorter PFS and worse a OS than patients with CC scores of 0 or 1.[25,40]

An alternate scoring system has been described by Levine et al.[51,55] In their cohort of 1000 patients treated at a single institution, completeness of CRS was classified as follows: R0 (complete removal of all visible tumor and negative cytologic findings or microscopic margins), R1 (complete removal of all visible tumor and positive post-perfusion cytologic findings or microscopic margins), R2a (minimal residual tumor, nodule(s) measuring <0.5 cm), R2b (gross residual tumor, nodule >0.5 cm but <2 cm), and R2c (extensive disease remaining, nodules >2 cm). The resection status (R score) was a significant predictor of survival, with a considerable survival advantage for R0/R1 resection compared with R2 resection. ($p < 0.0001$; Fig. 3). Irrespective of the scoring system used to assess the volume of residual disease, it is clear that an optimal cytoreduction is one of the main prognostic indicator impacting survival in these patients.

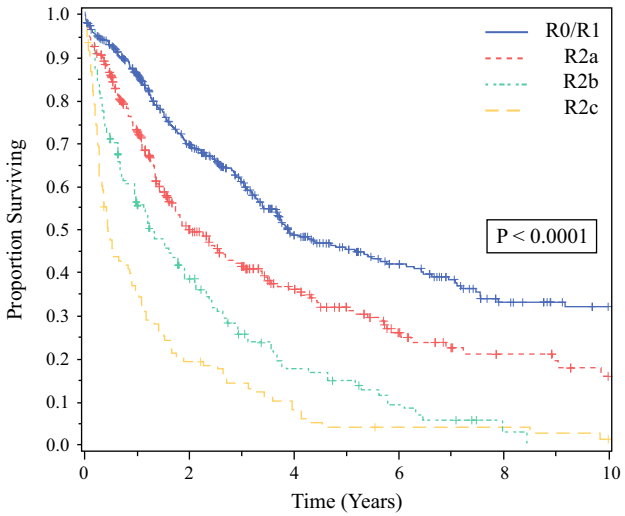

FIG. 3 Overall survival by resection status.[51]

OPEN VERSUS CLOSED TECHNIQUE

Various methods for delivery of intraperitoneal chemotherapy are available. After optimal cytoreduction (CC0/CC1 or R0/R1), heated chemotherapy can be delivered via open or closed abdominal technique. The open technique, often termed "the coliseum technique," was described by Sugarbaker.[45] With the coliseum technique, after placement of closed suction drains for inflow and outflow, the skin edges of the abdominal wall are elevated with a retractor, and the abdominal contents are manually agitated. With the closed technique, which is more commonly practiced, the skin is closed temporarily with a watertight closure after placement of the inflow and outflow catheters, preventing the escape of perfusate from the abdominal cavity. This is accompanied by manual agitation of the abdomen externally to promote uniform distribution of the perfusate.

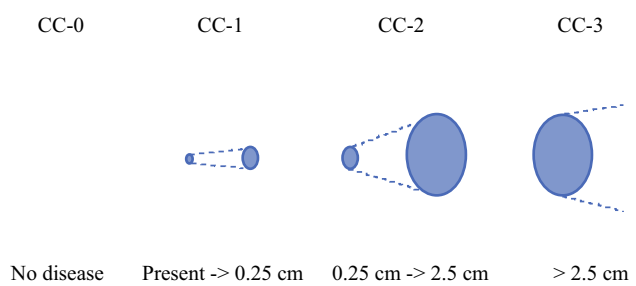

FIG. 2 Completeness of cytoreduction score (CC score). Adapted from Sugarbaker.[53]

There have been no prospective trials evaluating the superiority of one technique over the other. Ortega-Deballon et al.[56] performed a comparative analysis in pigs using both techniques and demonstrated that although both techniques achieved similar hyperthermia, the open technique had higher systemic absorption and abdominal tissue penetration. The United States HIPEC Collaborative performed a retrospective review of 1812 patients who underwent curative-intent CRS-HIPEC, with 372 patients (21 %) undergoing open HIPEC and 1440 patients (79 %) undergoing closed HIPEC. In the multivariable analysis, regardless of histologic subtype, the closed HIPEC technique was not a significant predictor for OS (HR, 0.75; 95 % confidence interval [CI], 0.51–1.10; $p = 0.14$) or RFS (HR, 1.39; 95 % CI, 1.00–1.93; $p = 0.05$). This study concluded that the HIPEC method is not independently associated with postoperative or survival outcomes and may be left to the discretion of the operating surgeon.[57] Currently, the closed technique seems to be the most commonly used technique for delivering intraperitoneal chemotherapy at most centers.

CHOICE OF INTRAPERITONEAL DRUG

An area of ongoing study is the use of optimal intraperitoneal chemotherapy. The intent of administration of heated chemotherapy directly to the peritoneal cavity is to maximize the chemotherapeutic dose to the peritoneal cavity while minimizing systemic toxicity, taking advantage of the plasma-peritoneal barrier.

Mitomycin C (MMC) and oxaliplatin are the two agents most commonly used for HIPEC in patients with appendiceal neoplasms (low- and high-grade/adenocarcinomas). Several characteristics of MMC make it an appealing intraperitoneal agent: it is a large molecule that is not rapidly absorbed systemically; it maintains stability at high temperatures, making it ideal for use with hyperthermia; and it has a satisfactory area-under-the-curve (AUC) ratio of intraperitoneal concentration and plasma concentration. Table 2 summarizes some studies evaluating the use of MMC, oxaliplatin, and cisplatin in the treatment of appendiceal tumors.[58]

A multi-center RCT was performed by Levine et al.[63] to evaluate the hematologic toxicity profile of mitomycin C and oxaliplatin in patients undergoing CRS for appendiceal tumors. Retrospective analyses had reached differing conclusions on which agent was superior.[59–62] The primary objective was to assess hematologic toxicity, while the secondary objectives of this trial were to compare complications, quality of life, survival, and time to progression. In this RCT, 121 patients at multiple centers were randomized to either oxaliplatin (200 mg/m^2) or MMC (40 mg) for 120 min (Fig. 4A). Resection (R) scores were similar between the groups, with 54 % achieving R0/1 and 46 % achieving R2 resections in the MMC group versus 51 % and 49 %, respectively, in the oxaliplatin group. The rate of preoperative chemotherapy administration did not differ significantly between the two groups (10 % for MMC and 20 % for oxaliplatin; $p = 0.26$). More patients in the MMC group were leukopenic during the immediate postoperative period (days 5 to 30), and G-CSF was needed for 13 % of the oxaliplatin group and 21 % of the MMC group ($p = 0.072$). The overall toxicity for any level of leukopenia differed significantly between the two groups ($p = 0.036$), with the mitomycin group having more leukopenia (predominantly grade 1). However, when only grades 3 and 4 toxicity was considered, the difference between the groups was not significant ($p = 0.67$).[63] In terms of OS and PFS, the two groups were similar (Fig. 4B and C).

This trial was the first RCT of its kind with a sizable cohort to compare these two commonly used agents. The data from this trial helped to identify that patients with baseline thrombocytopenia might be better treated with oxaliplatin and that those with preoperative leucopenia might be better treated with MMC. Mitomycin C continues to be the most widely used chemotherapeutic agent for HIPEC currently in the United States for appendiceal neoplasms.

APPENDICEAL ADENOCARCINOMA

The role for CRS-HIPEC for patients with high-grade histologies (moderately, poorly differentiated and signet ring cell histology) is controversial. Verwaal et al.[64] conducted a RCT evaluating the role of CRS with HIPEC for colorectal cancer and included 18 patients with primary appendiceal adenocarcinoma in their cohort of 105 patients. Overall, the trial showed an improvement in OS for patients who underwent CRS with HIPEC. However, because no subgroup analysis was performed for appendiceal adenocarcinoma, we cannot derive any definitive inferences about the role of CRS-HIPEC in this subgroup from the trial. The remainder of the studies reviewed in this report are retrospective series.

Grotz et al.[65] published their 10-year experience in patients with moderately and poorly differentiated appendiceal adenocarcinoma. Of the 178 consecutive patients who had appendiceal adenocarcinoma with suspected peritoneal metastases, 118 (66 %) had imaging showing evidence for metastatic disease. The 60 patients (34 %) with no disease identified on imaging underwent a diagnostic laparoscopy, and a majority ($n = 35$, 58 %) had no evidence of disease.

After the study excluded the patients with a negative diagnostic laparoscopy and the patients with extensive disease (based on extensive small bowel serosal or mesenteric involvement, high PCI, and rapid disease progression from the time of last imaging to diagnostic laparoscopy), 116 patients who underwent CRS with HIPEC remained to be analyzed. The median DFS for the 83 patients who underwent a CC0 or CC1 cytoreduction was 23 months, and the DFS was 86.4 % at 1 year, 29.0 % at 3 years, and 16.8 % at 5 years.

On multivariate analysis, the only independent predictors of DFS were mucinous histology (HR, 0.52; 95 % CI, 0.28–0.98; $p = 0.04$) and PCI (HR, 1.054; 95 % CI, 1.01–1.10; $p = 0.02$). The median OS for all the patients undergoing CRS and HIPEC was 48 months, and the OS estimates were 95.7 % at 1 year, 65.1 % at 3 years, and 40.7 % at 5 years. The patients who had an improved OS were those with mucinous histology (HR, 0.352; 95 % CI, 0.15–0.84; $p = 0.018$) and positive peritoneal cytology only (HR, 0.081; 95 % CI, 0.007–0.890; $p = 0.04$). However, signet ring cells (HR, 3.34; 95 % CI, 1.21–9.21; $p = 0.02$) and elevated PCI (HR, 1.076; 95 % CI, 1.023–1.31; $p = 0.004$) were independently associated with worse OS. Notably, a PCI < 20 was associated with an improved median OS of 65 months, compared with 28 months for a PCI > 20 ($p < 0.001$; Fig. 5). This study defined the importance of intraoperative PCI for appendiceal cancers,

TABLE 2 Studies evaluating CRS-HIPEC in the treatment of pseudomyxoma peritonei and appendiceal cancers. Adapted from Goodman et al.[58]

Study	Pathology	Patients (*n*)	Chemotherapeutic drug (temperature and duration)	Survival
Sugarbaker & Chang (1999)[42]	Appendiceal	385	HIPEC MMC 12.5 mg/m^2 (males), MMC 10 mg/m^2 (females) (n = 205); EPIC 5-FU/MMC + IP 5-FU + IV MMC ×3 cycles (n = 156); EPIC + IP 5-FU/MMC ×3 cycles (n = 21); EPIC 5-FU ×12 cycles (n = 3)	5-year OS (adenomucinosis), 86 %; 5-year OS (hybrid pathology), 50 %; 5-year OS (CC2), 20 %
Deraco et al. (2004)[83]	PMP	31	CIS 25 mg/m^2/L + MMC 3.3 mg/m^2/L (42.5 °C, 60 min)	5-year OS, 97 %; 5-year PFS, 43 %; 5-year LR-PFS, 59 %
Loungnarath et al.[84] (2005)	PMP	27	CIS 0.7 mg/kg + MMC 0.5 mg/kg (42–42.5 °C, 90 min)	Median OS not reached (median follow-up, 23 months; range, 3–82). Actuarial 1-year survival, 100 %; actuarial 5-year survival, 52 %
Stewart et al. (2006)[39]	Appendiceal	110	MMC 30 mg, 10 mg added after 60 min (38.5–42 °C, 60–120 min)	1-year OS, 79.9 %; 5-year OS, 53.4 %
Smeenk et al. (2007)[37]	PMP	103	MMC 35 mg/m^2 (40–41 °C, 90 min), adjuvant IV 5-FU/leucovorin ×6 months (n = 30)	Median DFS, 25.6 months; 3-year DFSP, 43.6 %; 5-year DFSP, 37.4 %
Cioppa et al. (2008)[85]	PMP	53	CIS 100 mg/m^2 + MMC 16 mg/m^2 (41.5 °C, 60 min), 2 patients with MMC only due to preoperative platinum toxicity	5-year OS, 94 %; 10-year OS, 84.6 %; 5-year DFS, 80 %; 10-year DFS, 70 %
Marcotte et al. (2008)[86]	Appendiceal	38 23 HIPEC	Oxaliplatin 460 mg/m^2 (30 °C, 30 min)	3-year OS (HIPEC), 86 %; 3-year DFS (HIPEC), 49 %
Elias et al. (2010)[43]	PMP	301 255 HIPEC	HIPEC MMC (41–42 °C, 60–120 min) + oxaliplatin (43 °C, 30 min) (n = 255); EPIC MMC, day 1 + 5-FU, days 2–5 (n = 46)	1-year OS, 89.4 %; 5-year OS, 72.6 %; 10-year OS, 54.8 %; 5-year DFS, 56 %. In CC0 group: 5-year OS, 84 %; 10-year OS, 61 %

CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; MMC, mitomycin C; OS, overall survival; EPIC, early postoperative intraperitoneal chemotherapy; 5-FU, 5-fluorouracil; CC-0, complete cytoreduction; CC-2, incomplete cytoreduction; PMP, pseudomyxoma peritonei; CIS, cisplatin; PFS, progression-free survival; LR, locoregional; DFSP, disease-free survival probability

which previously had been extrapolated from data in colorectal peritoneal metastases, suggesting that CRS-HIPEC for patients with a high PCI (>20) did not improve OS.

Notably, most of the patients (73.3 %) in this study received four to six cycles of chemotherapy with FOLFOX (± bevacizumab). The patients treated with neoadjuvant chemotherapy were significantly more likely to have poorly differentiated tumors ($p < 0.001$), nonmucinous tumors ($p = 0.001$), signet ring cells ($p = 0.019$), lymphovascular invasion ($p = 0.001$), and lymph node involvement ($p = 0.008$). No difference in OS was observed between those treated with neoadjuvant chemotherapy and those managed with a surgery-first approach. However, about 90 % of the patients in this study had stability (36/85) or improvement (40/85) of disease with neoadjuvant systemic chemotherapy, while nine patients (10.6 %) had progression of disease. The patients showing progressive disease on restaging imaging after neoadjuvant chemotherapy had a significantly worse OS than the patients with radiographic evidence of stable or responsive disease ($p = 0.01$).

In another retrospective study by El Halabi et al.,[66] among 77 patients with peritoneal mucinous carcinomatosis (PMCA) of appendiceal origin who underwent CRS-HIPEC, 52 (68 %) had a PCI > 20. Complete cytoreduction was achieved in 65 % of the group with a PCI > 20 and 96 % of the group with a PCI < 20 ($p = 0.004$). The 5-year OS was 45 % for the patients with a PCI > 20 and 66 % for the patients with a PCI < 20 when a complete cytoreduction was achieved ($p = 0.14$). The authors concluded that a PCI > 20 should not be used as a criterion for excluding the use of CRS-HIPEC as long a complete cytoreduction was possible.

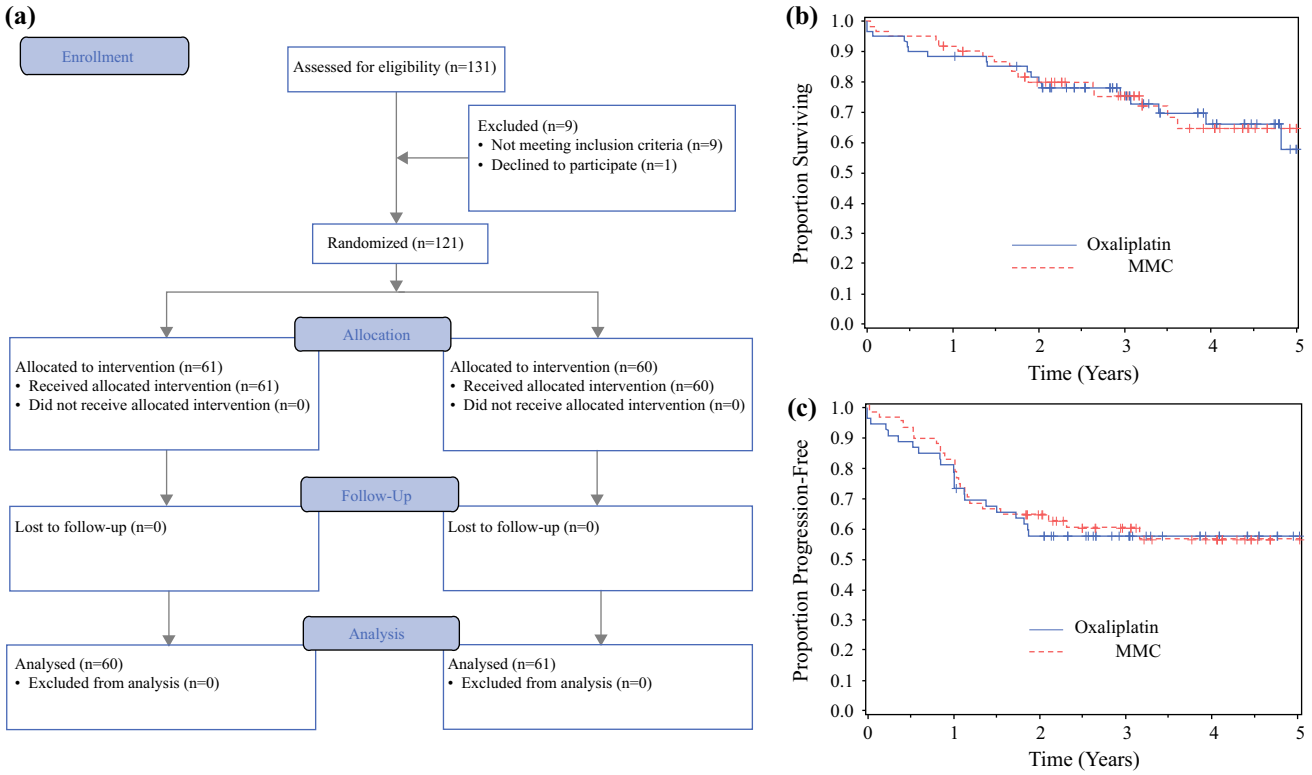

FIG. 4 (**a**) Consort flow diagram, (**b**) overall survival (OS), and (**c**) progression-free survival (PFS) from the Levine et al. randomized control trial evaluating mitomycin C versus oxaliplatin for treatment of appendiceal tumors.[63]

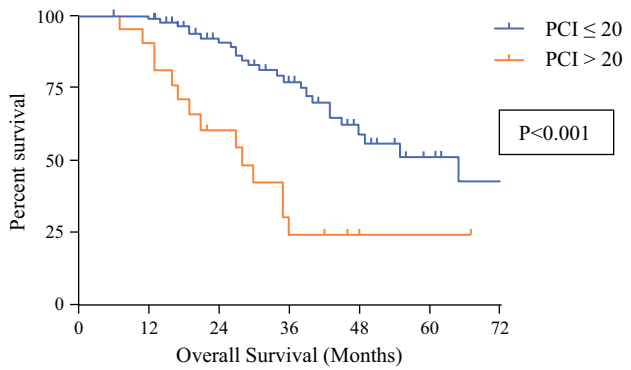

FIG. 5 Kaplan-Meier overall survival (OS) for patients with moderately or poorly differentiated appendiceal adenocarcinoma undergoing CRS/HIPEC based on a Peritoneal Cancer Index (PCI) score of 20 or less or more than 20.[65] CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy

The current practice patterns for the management of appendiceal adenocarcinoma at most institutions seem to mirror those for colorectal cancer peritoneal metastases, especially when considering factors such as a PCI cutoff for performance of a CRS with HIPEC.

Adenocarcinoma With Signet Ring Cell Morphology

Signet ring cell morphology is another high-grade histology for which the role of CRS-HIPEC is discussed. To help answer this question, the US HIPEC Collaborative conducted a retrospective review of 514 patients undergoing CRS-HIPEC for appendiceal adenocarcinoma, 125 (24 %) of whom had signet cell morphology. The presence of signet ring cells conferred a worse median OS (32.0 vs 91.4 months; $p < 0.001$) and a worse median RFS (17.7 vs 32.4 months; $p < 0.001$) compared to patients without signet ring cells after CRS-HIPEC. The factors independently associated with decreased OS in the multivariate analysis were age (HR, 1.03; 95 % CI, 1.01–1.05; $p < 0.01$), treatment with systemic chemotherapy (HR, 1.98; 95 % CI, 1.23–3.19; $p < 0.01$), incomplete cytoreduction (CC-2/3) (HR, 3.01; 95 % CI, 1.75–5.18; $p < 0.001$), poorly differentiated tumor (HR, 2.44; 95 % CI, 1.30–4.59; $p < 0.01$), and positive lymph nodes (HR, 1.10; 95 % CI, 1.02–1.18; $p < 0.01$). Interestingly, signet ring cell morphology was not associated with decreased OS (HR, 1.07; 95 % CI, 0.56–2.02; $p = 0.85$). When Cox proportional hazard regression was performed on signet cell cancers alone ($n = 125$), the only factors independently associated with decreased OS were poor differentiation (HR, 5.60; 95 % CI, 1.29–24.39; $p = 0.02$), positive lymph nodes (HR,

1.14; 95 % CI, 1.00–1.31; p = 0.04), and incomplete cytoreduction (HR, 4.90; 95 % CI, 1.11–12.70; p = 0.03). As such, although signet cells are a negative prognostic factor, they should not be a contraindication for CRS-HIPEC.[67] Based on the currently available data, CRS-HIPEC is a viable option for the management of peritoneal surface disease from appendiceal adenocarcinoma with signet ring cell features for appropriately selected patients.

GOBLET CELL ADENOCARCINOMA/MIXED ADENONEUROENDOCRINE CARCINOMA

Goblet cell carcinoids (GCCs), also known as adenocarcinoids or goblet cell adenocarcinoma (GCA), were first described in 1974. Together with mixed adenoneuroendocrine carcinomas (MANECs), GCAs share pathologic and biologic features of both adenocarcinomas and neuroendocrine neoplasms. The most common site of metastatic spread from GCA of the appendix is to the peritoneum via trans-celomic spread, with 40 % of patients presenting with peritoneal metastases at the time of diagnosis and 77 % in the case of recurrence.[68]

Given the propensity of these tumors to spread locoregionally without hematogenous spread, CRS with HIPEC becomes an appealing treatment modality. The evidence to support the role of CRS with HIPEC for this disease entity primarily consists of small, non-comparative, retrospective studies.[68,69] The Tang classification that separates tumors into typical GCA (Tang group A), signet ring cell type (Tang group B), or poorly differentiated carcinoma type (Tang group C) is useful for determining the sequencing of therapy and patient prognosis.[14,70]

A recent propensity-matched cohort study of patients with MANECs and GCAs from centers in Netherlands and Belgium compared OS as the primary outcome measure between patients treated with CRS-HIPEC and those managed with surgery alone. The control group was composed of 30 of 569 patients identified in the national tumor registry who were treated with CRS alone. The treatment group was composed of 45 patients, of whom 29 had GCA and 10 had MANEC. The HIPEC treatment was performed using intraperitoneal oxaliplatin with a target temperature of 41 °C with simultaneous intravenous 5-fluorouracil or MMC for 30 or 90 min. Propensity-matching then was performed, creating a 1:1 ratio of GCA and MANEC patients treated with CRS-HIPEC to patients treated with surgery alone (total n = 60). A subgroup analysis of the GCA patients also was performed. After matching for sex, tumor stage, lymph node stage, and liver metastases, CRS-HIPEC was associated with improved median OS in both the GCA/MANEC group (HR, 4.27; 95 % CI, 1.88–9.66; p = 0.001) and the GCA-alone group (HR, 2.77; 95 % CI, 1.06–7.26; p = 0.038).[71] This together with other smaller studies have shown that CRS with HIPEC may be considered for select patients with peritoneal metastases from GCA.[68,72,73]

QUALITY OF LIFE AFTER CRS-HIPEC

The potential survival benefits of CRS-HIPEC should be carefully weighed against the substantial risk of treatment-related morbidity and mortality as well as potentially diminished quality of life (QoL) and functional status. Numerous retrospective studies have shown that the QoL for these patients dropped after surgery but returned to baseline by 6 months.[74–78]

In a prospective study that used the Functional Assessment of Cancer Therapy (FACT) and the Medical Outcomes Study Health Survey, Short-Form questionnaires (SF-36) showed an impairment in the QoL up to 3 months after surgery, with recovery to near or above baseline by 12 months.[79] Another prospective study by Chia et al.[80] administered the European Organization for the Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) and the colorectal module (QLQ-CR29) before surgery and then 3, 6, and 12 months after surgery. Their study evaluated 23 patients undergoing CRS-HIPEC for peritoneal carcinomatosis from colorectal cancer. They noted that physical and functional recovery scores decreased at 3 months but returned to baseline at 6 months. They also reported significant increases in emotional and social functioning scores at 6 to 12 months and improvements in all symptom scores at 6 to 12 months, especially the fatigue and appetite scores. A worse QoL was associated with a higher PCI score, a longer surgery, the presence of a stoma, and recurrence within 3 months.

A recent systematic review of 14 studies that used 12 different questionnaires evaluating QoL data for 1556 patients, showed a diminished QoL within 3 months after surgery and a return to baseline by 12 months. The authors did note that QoL was negatively influenced by older age, female sex, prolonged operation time, extensive disease, residual disease, adjuvant chemotherapy, complications, stoma placement, and recurrent disease.[81]

Additionally, a recent retrospective cohort analysis comparing outcomes of 34,114 patients included in the American College of Surgeons National Surgical Quality Improvement Project (NSQIP) database who underwent CRS-HIPEC, right hepatic lobectomy, trisegmental hepatectomy, pancreaticoduodenectomy, and esophagectomy found that patients undergoing CRS-HIPEC had lower morbidity and mortality and a shorter hospital stay than patients undergoing similar-risk oncologic procedures.[82]

In addition to discussing the anticipated postoperative clinical course with patients scheduled to undergo CRS-HIPEC, surgeons should consider patients' perspective regarding QoL and counsel them about these outcomes.

CONCLUSIONS

Despite the lack of randomized clinical trials evaluating outcomes of CRS-HIPEC for primary mucinous appendiceal malignancies, retrospective data support CRS-HIPEC as the mainstay of therapy for patients with peritoneal dissemination. As is the case for a majority of gastrointestinal malignancies, appropriate patient selection is of paramount importance and contributes to positive outcomes. These decisions about patient selection should be made in a multidisciplinary setting at expert centers.

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