Data for HIPEC for Pseudomyxoma Peritonei/Tumors of the Appendix

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Introduction

Pseudomyxoma peritonei (PMP) is a condition of mucinous ascites and peritoneal nodules, typically originating from a mucinous appendiceal tumor. PMP has historically had various evolving definitions and variants; however, a consensus is emerging for standardized classification with defined pathologic criteria [1]. Under this classification, PMP can include low-grade mucinous peritoneal metastases, often known as diffuse peritoneal adenomucinosis (DPAM) or low-grade mucinous carcinoma peritonei (LGMCP), which arise from low-grade appendiceal mucinous neoplasms (LAMN) (Fig. 8.1). However, PMP can also include neoplastic cells with high-grade features, known as peritoneal mucinous carcinomatosis (PMCA) or high-grade mucinous carcinoma peritonei (HGMCP), typically arising from a high-grade appendiceal mucinous neoplasm (HAMN). Other PMP variants include acellular mucin from low-grade or high-grade appendiceal tumors, mucinous peritoneal tumors with signet ring cells, and mucinous adenocarcinoma.

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Carcinomatosis from non-mucinous tumors of the appendix is not considered PMP. These tumors are characterized by firm, invasive peritoneal implants that often appear as areas of peritoneal thickening and enhancement on imaging and are associated with serous ascites (Fig. 8.2). Non-mucinous adenocarcinoma of the appendix can arise de novo or in goblet cell neuroendocrine tumors of the appendix with mixed neuroendocrine/adenocarcinoma components. When carcinomatosis develops from these tumors, it is typically the adenocarcinoma component that gives rise to peritoneal disease. The aim of this chapter is to summarize existing data on CRS with HIPEC for appendiceal neoplasms with peritoneal dissemination, including both PMP from mucinous neoplasms and carcinomatosis from appendiceal adenocarcinoma.

Preclinical Data for Hipec

Hyperthermia has long been known to have greater cytotoxicity in tumor cells than in non-neoplastic cells [2, 3]. The mechanism of this cytotoxicity may include impaired damaged DNA repair, potentially sensitizing tumor cells to alkylating agents [4]. Intraperitoneal administration allows exposure of a higher dose of chemotherapy with theoretically less systemic effects than with systemic chemotherapy. A canine animal model has been used to demonstrate the

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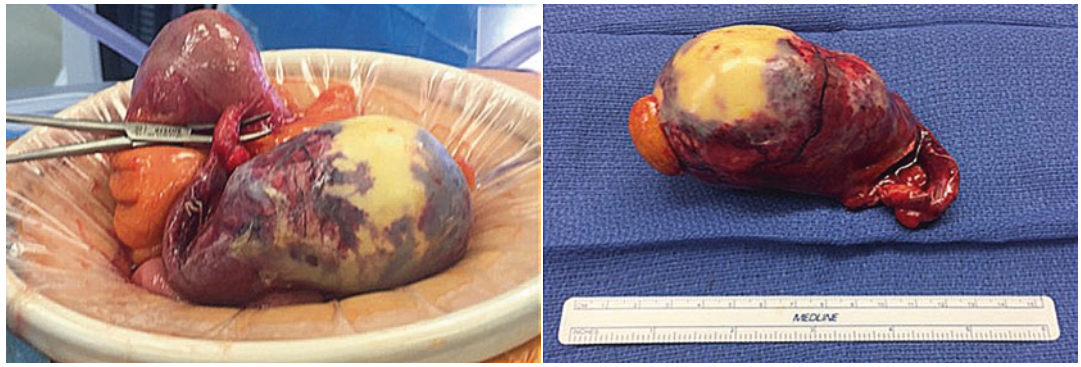

Fig. 8.1 Intact low-grade mucinous neoplasm of the appendix. This lesion is cured with appendectomy to negative margins with no need for HIPEC. When these lesions rupture, they can lead to the development of PMP

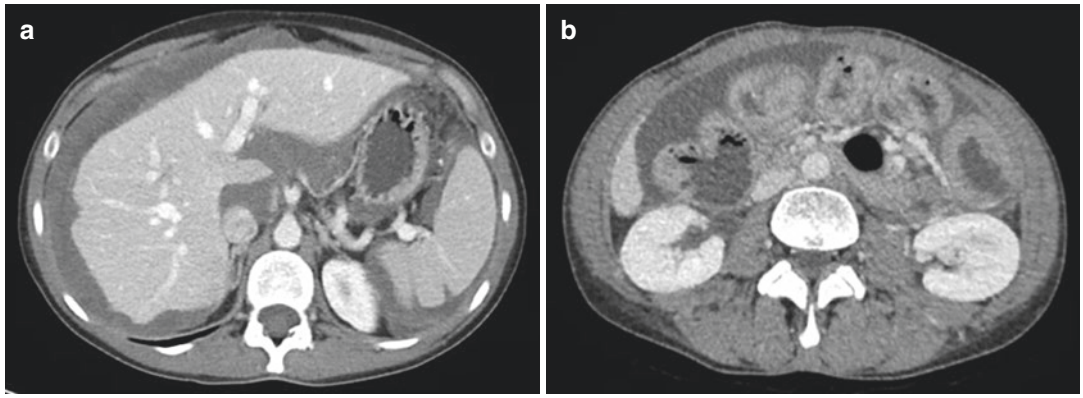

Fig. 8.2 Computed tomography scans of patients with (**a**) PMP with mucinous ascites showing characteristic scalloping of the liver edge and (**b**) carcinomatosis from non-mucinous appendiceal adenocarcinoma demonstrating thin, serous ascites and diffuse peritoneal thickening and enhancement

technical feasibility and safety of performing hyperthermic intraperitoneal chemotherapy administration [5].

Clinical Data for CRS/Hipec for PMP

Phase I Data

There have been three phase I studies of standard HIPEC agents in patients with appendiceal tumors. The first examined escalating doses of cisplatin with tumor necrosis factor under hyperthermia over 90 minutes after tumor debulking and identified a maximum tolerated cisplatin dose of 250 mg/m^2 [6]. The second examined escalating doses of oxaliplatin under hyperthermia over 120 minutes and found a maximum tolerated dose of 200 mg/m^2 [7]. This study included both patients with colorectal and appendiceal cancer, but the majority of patients (12 of 15) had the latter. The most recent study evaluated the use of intraperitoneal irinotecan, or CPT-11, in combination with a fixed dose of mitomycin C, delivered with a closed perfusion technique. The maximum tolerated dose of intraperitoneal irinotecan was found to be 100 mg/m^2 [8].

Case Reports and Small Clinical Series

PMP has been treated with extensive resection of gross peritoneal tumors (cytoreductive surgery,

CRS) since the 1970s when it was recognized that PMP had a low propensity for extraperitoneal spread. A single-institution series of 38 patients with PMP who underwent surgical resection with or without abdominal radiation and systemic chemotherapy reported a 54% actuarial 5-year survival [9]. Another series of CRS without HIPEC from Memorial Sloan Kettering Cancer Center included 97 patients, 52% of whom had low-grade disease, who underwent a mean of 2.2 cytoreductions (only 55% of which being complete gross cytoreductions) with a median overall survival of 9.8 years [10]. A case report describes the first human to receive hyperthermic intraperitoneal chemotherapy (HIPEC). This was a 35-year-old man with PMP of appendiceal origin. He was treated in 1979 and received intraperitoneal thiotepa [11].

Over subsequent years, HIPEC protocols and perfusion systems were optimized in patients with ovarian, appendiceal, colorectal, and gastric cancers. Sugarbaker et al. spearheaded the use of CRS with HIPEC for PMP in North America. Multiple studies from the late 1980s and early 1990s demonstrated favorable technical results and early disease control rates [12, 13]. In 2008, the Fifth International Workshop on Peritoneal Surface Malignancy took place in Milan, Italy. This workshop resulted in several consensus statements establishing CRS with HIPEC as the standard of care for appendiceal neoplasms. The HIPEC agents deemed appropriate for routine clinical use without need for further clinical trials for this disease included mitomycin C and cisplatin [14–16].

A study by Sardi and colleagues investigated the use of melphalan as an alternative agent for HIPEC in patients with peritoneal carcinomatosis from aggressive primary tumors. There were 25 total patients who underwent 31 CRS with HIPEC procedures, 19 of which were repeat procedures. Seventeen patients had primary appendiceal adenocarcinoma. In this study, the majority of patients had a peritoneal carcinomatosis index (PCI) >20. The rate of complete CRS was 88%. For those patients with appendiceal primary cancer, the 5-year overall survival (OS) following the melphalan HIPEC was 32.1%. The treatment was relatively well tolerated with a rate of postoperative grade III/IV morbidity of 22%. Myelosuppression was the most common complication. The authors concluded that melphalan is an efficacious agent for intraperitoneal therapy for patients with aggressive and recurrent peritoneal disease [17].

Another recent study evaluated the role of CRS with HIPEC for patients with high-grade appendix cancer and minimal peritoneal disease. Patients who were diagnosed incidentally by pathology after appendectomy were identified [18]. There were 62 total patients and 35 (57%) had gross peritoneal disease at the time of subsequent exploration for CRS with HIPEC. The mean peritoneal carcinomatosis index (PCI) for these patients was 5. All patients underwent right hemicolectomy as part of the CRS procedure and HIPEC was performed. Five-year disease-free and overall survival for these patients were excellent, at 83.2 and 76.0%, respectively. Additionally more recent small series have focused on CRS with HIPEC in unique patient populations, such as elderly patients, and those with particular comorbidities like obesity and cirrhosis [19]. These studies have shown that CRS with HIPEC is feasible and can be performed safely in selected patients with these conditions.

Large Retrospective Series

The strongest data on CRS with HIPEC for appendiceal neoplasms come from large retrospective studies. Table 8.1 summarizes the largest (each with greater than 200 patients) published series of CRS with HIPEC for appendiceal tumors. Each of these series included a combination of patients with low-grade and high-grade histologies, and concordance with the modern consensus pathologic classification is variable. The postoperative mortality ranges from 0 to 3%, and the postoperative major morbidity ranges from 15 to 34%. The 5-year overall survival is 53–87% and is variable by grade, with low-grade patients having an 81–83% 5-year survival and high-grade patients having a significantly lower 5-year survival at 41–59%.

Table 8.1 Largest published series of CRS with HIPEC for appendiceal neoplasms

Series	*n*	% LG	% CC-0/1	% 30d major morbidity[a]	% 30d mortality	Median PFS (yrs)	Median OS (yrs)	% 5 yr OS
Chua et al. [22]	2054[b]	62	83	22	2	Overall: 8.2 LG: NA HG: NA	Overall: 16.3 LG: NA HG: NA	Overall: 78[2] LG: 81 HG: 59
Votanopoulos et al. [23]	481	77.3	72.4[c]	27.8	2.7	NA	Overall: 14.6 (R0/1) HG: NA LG: NA	NA
Austin et al. [24]	282	64	82	23.7	1.1[d]	NA	Overall: 6.7 LG: NA HG: NA	Overall: 53 LG: NA HG: NA
Jimenez et al. [25]	202	38	85	15.8	0	Overall: 3.3 LG: NR HG: 2.2	Overall: 7.5 LG: NR HG: 3.9	Overall: 56 LG: 83 HG: 41
Ansari et al. [26]	738	80	100	15.2	0.8	Overall: 7.5 (mean) LG: NA HG: NA	Overall: 8.6 (mean) LG: NA HG: NA	Overall: 87.4 LG: NA HG: NA
Gonzalez-Moreno et al. [27]	501	NA	NA	NA	NA	NA	Overall: 13 LG: NA HG: NA	Overall: 72 LG: NA HG: NA
Kuijpers et al. [28]	300	47	80 (CC-0)[e]	34[e]	3[e]	Overall: 4.4 LG: NA HG: NA	Overall: 10.8 LG: NA HG: NA	Overall: 65 LG: NA HG: NA

LG low grade, *HG* high grade, *PFS* progression-free survival, *OS* overall survival, *NA* not available

[a]Clavien-Dindo Grade III–IV

[b]Those who received HIPEC, of 2298 total patients

[c]Included residual disease <5 mm

[d]60-day mortality

[e]Among all 960 CRS/HIPEC

Table 8.2 Summary of studies evaluating predictors of progression and death following CRS with HIPEC for appendiceal neoplasms

Study	Predictors of progression	Predictors of death
Low-grade disease		
Chua et al. [22]	–	Age > 53 CC-score > 1 Postoperative complications Preoperative systemic therapy
Votanopoulos et al. [23]	–	Positive lymph nodes CC-score > 0 Preoperative systemic therapy
Austin et al. [24]	–	Increasing age Preoperative systemic therapy High PCI
Jimenez et al. [29]	–	CC-score > 1
Reghunathan et al. [30]	Preoperative CEA ≥10 CC-score > 1	–
High-grade disease		
Halabi et al. [31]	–	Positive lymph nodes CC-score > 1 Increasing PCI
Jimenez et al. [29]	–	CC-score > 1 PCI ≥ 20 Positive lymph nodes
Votanopoulos et al. [23]	–	CC-score > 0 Preoperative systemic therapy
Baumgartner et al. 2015 [32]	Positive lymph nodes	–
Grotz et al. 2017 [33]	Non-mucinous histology Increasing PCI	Non-mucinous histology Gross peritoneal disease[a] Signet ring cells Increasing PCI

CEA carcinoembryonic antigen, *CC-Score* completeness of cytoreduction score, *PCI* peritoneal carcinomatosis index
[a]As opposed to positive peritoneal fluid cytology only

In addition to reporting survival data, these retrospective studies have also identified factors associated with recurrence and death after CRS with HIPEC for appendiceal neoplasms. Table 8.2 summarizes studies that have specifically reported independent predictors of progression and/or death following CRS with HIPEC for low- and high-grade appendiceal neoplasms. Consistently identified predictors of progression after CRS with HIPEC for low-grade disease include incomplete cytoreduction and elevated preoperative serum carcinoembryonic antigen (CEA) level. Predictors of progression in high-grade disease include positive lymph nodes, non-mucinous histology, and increasing PCI. Identified predictors of death or more variable across different studies, but those consistently identified in both low- and high-grade diseases include incomplete cytoreduction, advanced age, increasing PCI, incomplete cytoreduction, and receipt of systemic therapy prior to surgery.

Prospective Trials

There is a lack of prospective data available for CRS with HIPEC for appendiceal neoplasms. This is likely due to their overall low incidence, a problem compounded by the biologic heterogeneity of the different histologic subtypes. There are no randomized controlled trials comparing CRS alone versus CRS with HIPEC for appendiceal neoplasms. There has been one randomized controlled trial of CRS with HIPEC using mitomycin C versus systemic therapy with or without

palliative debulking. The majority of patients in this trial had colorectal primary tumors but 21% (n = 11) had appendiceal primary adenocarcinoma [20]. This study compared CRS with HIPEC with mitomycin C to systemic therapy with 5-fluorouracil (5-FU) and showed a survival benefit for CRS with HIPEC. The median OS for the CRS with HIPEC arm was 22.3 months compared to 12.6 months for the systemic therapy arm.

There has been one randomized controlled trial of CRS with HIPEC using mitomycin C versus oxaliplatin in 126 patients with mucinous appendiceal neoplasms with peritoneal dissemination [21]. This multicenter trial examined the hematologic toxicity of the two agents and found that mitomycin C resulted in lower white blood cell count from postoperative day 5 to 10, and oxaliplatin use led to slightly lower platelet count on postoperative day 5–6, with no differences in Clavien-Dindo complications between the two groups. There is an ongoing randomized phase II trial comparing complete CRS with HIPEC using mitomycin C to CRS with early postoperative intraperitoneal chemotherapy (EPIC) with floxuridine (FUDR) and leucovorin, which includes patients with appendiceal adenocarcinoma. This is a multicenter trial that is actively recruiting (https://clinicaltrials.gov/ct2/show/NCT01815359).

Conclusions

There are abundant retrospective data supporting the use of CRS with HIPEC for the treatment of appendiceal neoplasms with peritoneal dissemination showing favorable results in over 4500 patients. There have been no prospective trials comparing CRS versus CRS with HIPEC in this disease, in part because of the low incidence and due to the histologic and biologic heterogeneity, making prospective study difficult. CRS with HIPEC is currently the standard-of-care, with mitomycin C and cisplatin the most broadly applied and investigated agents for intraperitoneal perfusion.

Patient selection is critical for favorable outcomes. For patients with low-grade disease, complete cytoreduction can result in 5-year survival rates >80%. For patients with high-grade disease, long-term outcomes are poorer with 5-year survival on the order of 40%–60% for those with gross peritoneal disease. For those high-grade patients diagnosed early with minimal or no gross peritoneal disease, data suggest that long-term outcomes may be better. The rationale for current commonly used HIPEC agents is based on favorable pharmacokinetic profiles for intraperitoneal delivery, not on factors specific to appendiceal tumors. There is a need for a better understanding of the pathogenesis and molecular aberrations in this heterogenous disease, as well as development of more effective and potentially targeted intraperitoneal agents.

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