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Adjuvant Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for patients at High-Risk of Peritoneal Metastases

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ABSTRACT

Background: Selection of patients for hyperthermic intraperitoneal chemotherapy (HIPEC) continues to evolve. We hypothesized that adjuvant HIPEC for patients at high-risk of peritoneal progression is safe and associated with favorable outcomes.

Methods: The institutional database of a high-volume center was queried for patients with high-risk disease undergoing HIPEC with a peritoneal carcinomatosis index (PCI) of 0. High-risk patients were defined as those with ruptured primary tumors or locally advanced (T_4) disease.

Results: 37 patients underwent adjuvant HIPEC, with a median follow-up of 5.2 years. 54% had low-grade (LG) tumors while 46% had high-grade (HG) tumors. No patients underwent neoadjuvant chemotherapy, while eleven patients (32.4%) received adjuvant chemotherapy. There were no perioperative mortalities, and the overall complication rate was 43%. For the entire cohort, five year recurrence-free survival (RFS) and overall survival (OS) were 77% and 100%, respectively. Five year RFS and OS were 75% and 100% for LG patients and 81% and 100% for HG patients, respectively.

Conclusions: Adjuvant HIPEC for patients at high-risk of peritoneal progression, with PCI 0, is safe and associated with favorable long-term survival. Additional prospective investigation is needed to identify patient populations who may benefit most from HIPEC.

1. Introduction

With primary and secondary peritoneal-based malignancies becoming increasingly recognized for their complexity and heterogeneous behavior, optimal treatment strategies for these challenging cases continue to evolve [1–4]. Variations in management and outcomes are due to biologic differences, increasing effectiveness of systemic therapy and broader application of peritoneal-directed therapy including cytoreduction with hyperthermic intraperitoneal chemotherapy [HIPEC] [5–9]. Due to a paucity of clinical trials and this variability, improving patient outcomes after HIPEC requires ongoing evaluation of our collective experiences in specific clinical scenarios.

The relative rarity of peritoneal carcinomatosis (PC) and heterogeneity in affected patient populations make large-scale randomized trials difficult. Some level-one evidence exists to guide management of malignant peritoneal disease [10–13]. Cytoreduction followed by early post-operative intraperitoneal chemotherapy (EPIC) with carboplatinum and paclitaxel was shown to improve survival in women with stage IIIC ovarian cancer [10]. Additionally, a randomized European trial demonstrated that cytoreduction with HIPEC followed by systemic chemotherapy, as opposed to systemic therapy alone, leads to improved survival in PC of colorectal origin [10,11]. While these studies have helped guide current therapeutic decisions, ongoing and future trials are needed to further identify patient populations that may benefit from HIPEC.

Contemporary debates regarding HIPEC utilization are based on key disease-specific characteristics. Tumor grade (generally low versus high) is one consideration. Second, the completeness of cytoreduction (CCR; 0/1 vs 2) prior to HIPEC is an important determinant of long-term prognosis [16]. Third, primary tumor type must be considered, with many practitioners arguing against the use of HIPEC in particularly aggressive malignancies [17–19].

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Significant uncertainty remains regarding the appropriate management of patients with high-risk of peritoneal progression, but no grossly visible disease [7,18–22]. For patients with ruptured primary lesions or T_4 disease, it remains unclear whether adjuvant HIPEC provides any clinical benefit. In this population, we must continue to risk stratify patients and study treatment strategies that prevent progression of microscopic peritoneal disease to grossly visible carcinomatosis. Available data from the colorectal literature suggest that adjuvant HIPEC for high-risk colon cancer yields lower rates of PC recurrence; however, more comprehensive analyses examining the impact of HIPEC on other tumor types—including appendiceal malignancies— have not been previously performed [19–23]. As a result, our group hypothesized that adjuvant HIPEC in patients with previously resected appendiceal and colon primary malignancies at high-risk for peritoneal progression would be associated with favorable long-term survival and an acceptable adverse effect profile.

2. Methods

2.1. Patient selection

After Institutional Review Board approval, a retrospective review of the University of Cincinnati HIPEC database (1999–2017) was undertaken. From the initial dataset (n = 332), 37 patients with a peritoneal carcinomatosis index (PCI) score of zero were identified. Most patients underwent cytoreduction and HIPEC at the time of their primary oncologic operation. However, four patients underwent HIPEC following colectomy and systemic therapy. These patients were defined as high risk due to ruptured primary tumors or locally advanced (T_4) disease. The PCI score of zero was confirmed intra-operatively at the time of HIPEC or on final pathology report. Most patients with an appendiceal primary underwent right colectomy and omentectomy to complete oncologic staging. The rationale for right colectomy/omentectomy has been that the right colon is at high risk of developing surface disease, not necessarily that nodal sampling is required. Furthermore, our practice patterns have evolved and do not always include right colectomy currently. It was some surgeons' practice to routinely remove ovaries due to a propensity for developing metastasis, and the gallbladder was also selectively removed depending on surgeon practice. All other operative interventions were performed for a variety of incidental findings and/or predetermined reasons (e.g. Meckel's diverticulum and adrenal incidentaloma). Hysterectomy was performed due to fibroids or other irregularities. Two skin/soft tissue resections were performed; one for recurrence in the subcutaneous tissue and the other a prophylactic resection of previous port sites. Liver, mesenteric and peritoneal/retroperitoneal nodules were excised due to concern for disease, but were negative for malignancy on final pathology.

Patient demographics, comorbidities, and previous abdominal operations were reviewed. Tumor and treatment-specific variables including origin of primary tumor, tumor grade, PCI, presence of ascites, chemotherapy type and timing, organs removed, operative time, postoperative complications, hospital length-of-stay (LOS), and site/date of recurrence, if applicable, were included for analysis. Adjuvant therapy was defined as any therapy given after primary oncologic resection. Additionally, patients were categorized into those with low-grade tumors (LG, n = 20) and those with high-grade tumors (HG, n = 17).

Recurrence-free and overall survival (RFS, OS) were defined as time to death/recurrence or last follow-up. Surveillance was performed with cross sectional imaging and tumor markers per National Cancer Care Network guidelines. RFS and OS were assessed with the Kaplan-Meier method, compared by log-rank analysis. RFS was defined as interval from date of HIPEC to any recurrence. Continuous variables were reported as medians with interquartile ranges (IQR) and categorical variables were reported as frequencies. A p-value < 0.05 was considered significant. Statistical analysis was performed using SAS software (Version 9.3; SAS Institute, Inc, Cary, NC).

2.2. Pathologic definitions

The classification of appendiceal mucinous neoplasms has been controversial and a uniform definition across centers is lacking. At the University of Cincinnati, we classified non-invasive mucinous neoplasms into low-grade appendiceal mucinous neoplasm (LAMN) or high-grade appendiceal mucinous neoplasm (HAMN). Both LAMN and HAMN tend to have 'pushing' interface but lack of true invasion; dissection of acellular mucin in the appendiceal wall is common. LAMN can also expand into surrounding tissues without causing destruction [22]. In addition to the histological features of LAMN, HAMNs have high-grade cytology. Mucinous adenocarcinoma was defined as having infiltrative destructive invasion and further classified into well, moderately or poorly differentiated (usually with signet ring cells) carcinoma. All pathologic specimens with intraperitoneal mucin were also evaluated for cellularity. A specialized gastrointestinal pathologist evaluated all colorectal specimens using standard era specific AJCC guidelines. However, we do acknowledge that the current, updated AJCC guidelines are different than the ones used during this study period. LAMNs and well-differentiated adenocarcinoma were defined as low-grade tumors. Goblet cell carcinoids, moderately differentiated and poorly differentiated adenocarcinoma were defined as high-grade tumors.

2.3. HIPEC technique

HIPEC techniques have been described extensively [19,26,27]. Our institutional practice is to perform HIPEC via open coliseum technique, using Silastic sheeting with a defect created for manual mixing of the chemotherapy perfusate. Standard perfusion duration was 90 min, with inflow and outflow temperatures of 44°C and 41–42°C, respectively. Our peritoneal chemotherapy dosing regimen was Mitomycin C (30 mg/m^2) for both appendiceal and colon carcinomas.

3. Results

Patient demographics, tumor characteristics, and treatment-specific variables are shown in Table 1. Median follow-up for the cohort was 5.2 years and 54% of patients (n = 20) had LG tumors. The median time from primary oncologic operation to HIPEC in the four patients who underwent colectomy followed by systemic therapy prior to HIPEC was

Table 1
Patient demographics, stratified by subgroups; A) patients with low-grade tumors, B) Patients with high-grade tumors.

Characteristic	Low Grade (n = 20)		High Grade (n = 17)		P value
	n	%/range	n	%/range	
Age (years)	49	(30–61)	53	(36–68)	0.39
Gender					0.75
Male	9	(45%)	9	(53%)	
Female	11	(55%)	8	(47.1%)	
Prior Abdominal Surgery	20	(100%)	17	(100%)	> 0.99
Neoadjuvant chemotherapy	0	(0%)	0	(0%)	> 0.99
Adjuvant chemotherapy	4	(22.2%)	7	(43.7%)	0.27
Primary Tumor Site					< 0.05
Appendix	19	(95%)	16	(94.1%)	
Adenocarcinoma	15	(75%)	7	(41.2%)	
Goblet Cell Carcinoma	0	(0%)	9	(52.9%)	
Low-grade Appendiceal Mucinous Neoplasm (LAMN)	4	(20%)	0	(0%)	
Colon	1	(5%)	1	(5.9%)	
Presence of Ascites	1	(5%)	0	(0%)	> 0.999

HIPEC, hyperthermic intraperitoneal chemotherapy.

Table 2
Operative characteristics of study cohort.

Characteristic	Low Grade (n = 20)		High Grade (n = 17)		P value
	n	%/range	n	%/range	
Operative Time (minutes)	335	(222–493)	334	(253–451)	0.78
Length of Stay (days)	9	(7–28)	8	(5–12)	0.11
Operative Intervention					
Right hemicolectomy	18	(90%)	15	(88.2%)	> 0.999
Sigmoid colectomy	1	(5%)	1	(5.9%)	> 0.999
Cholecystectomy	6	(30%)	8	(47.1%)	0.33
Oophorectomy	5	(25%)	4	(23.5%)	> 0.99
Hysterectomy	2	(10%)	1	(5.9%)	> 0.99
Small bowel resection	2	(10%)	2	(11.8%)	> 0.99
Omentectomy	19	(95%)	17	(100%)	> 0.99
Peritoneal/Retroperitoneal stripping	0	(0%)	1	(5.9%)	0.46
Adrenalectomy	1	(5%)	1	(5.9%)	> 0.999
Skin/Soft tissue/Port site	1	(5%)	1	(5.9%)	> 0.999
Liver resection/biopsy	0	(0%)	1	(5.9%)	0.46
Appendectomy	0	(0%)	1	(5.9%)	0.46

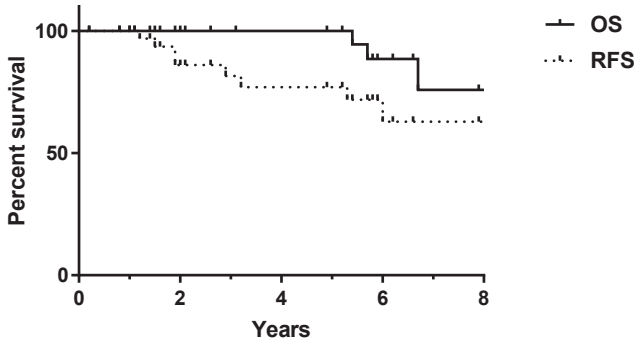
431.5 days (interquartile range 282.5–949 days). Age and gender were similar between groups. Neoadjuvant chemotherapy was administered to zero patients, while 22.2% (n = 4) of LG patients and 43.7% (n = 7) of HG patients received adjuvant systemic chemotherapy. Majority of tumors were appendiceal in origin (95%, n = 35) while the remaining two were colonic primary tumors. Of the 35 appendiceal malignancies, 63% were appendiceal adenocarcinoma, 26% were Goblet Cell Carcinoid (GCC), and 11% were LAMN. Thirty-five of the thirty-seven patients (95%) had mucinous characteristics. 89% of tumors (n = 33) were ruptured at the primary operation; neither colon primaries were ruptured (both had T4 disease only) and all but two appendiceal primaries were ruptured at appendectomy.

Operative characteristics are shown in Table 2. Median/IQR operative time and hospital length of stay were 5.5 (4.9–5.9) hours and 8 (7–9) days, respectively. The most common procedure performed was omentectomy (97%, n = 36) followed by colectomy (95%, n = 35). Cholecystectomy and oophorectomy were performed in 38% (n = 14) and 24% (n = 9) of patients, respectively. 89% of patients (n = 33) underwent a right hemicolectomy, and all of these patients had an appendiceal primary. Of the patients who underwent right colectomy, 15.2% (n = 5) had nodal disease.

There were no perioperative deaths in this series. 43% (n = 16) of patients had one or more complications, including deep venous thrombosis, pulmonary embolism and pneumonia. Thirty-five percent (n = 13) were grade 3 or 4 complications requiring additional operative procedures, and 8% (n = 3) were grade 1 or 2 complications. Two patients developed superficial surgical site infections. There were five instances of small bowel obstruction (SBO) and four required operative intervention; three occurred within the first year. There were two instances of enterocutaneous fistula formation, one patient with anastomotic leak (which required reoperation), one patient with post-operative bleeding requiring reoperation and one patient with fascial dehiscence that required reoperation. Four patients, in long-term follow up, developed incisional hernias.

Overall, 22% (n = 8) of patients developed recurrence after initial HIPEC. Specifically, 25% (n = 5) of LG patients and 17.6% (n = 3) of HG patients developed recurrent disease. RFS and OS for the entire cohort, LG patients, and HG patients are shown in Figs. 1 and 2. For the entire cohort, five year RFS and OS were 77% and 100%, respectively. HG patients had five year RFS and OS of 81% and 100%, respectively. LG patients had five year RFS of 75% and OS of 100%. There were no differences found in median RFS and OS between LG and HG groups.

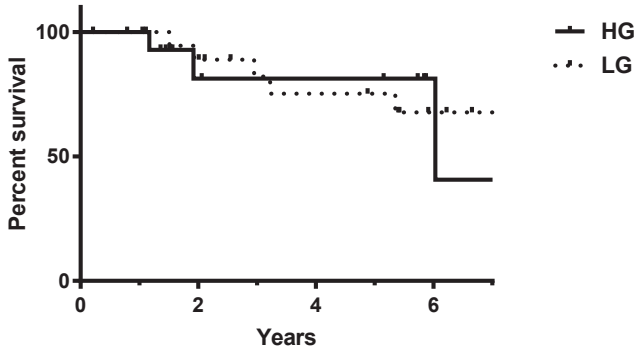
Subgroup analysis was also performed for patients with GCC (Fig. 3). In the GCC group 5 year RFS was 75% and OS was 100%. Patients who underwent right colectomy and omentectomy without other prophylactic resections were compared to patients who



Numbers at risk

RFS	35	23	19	18	17	8	
OS	35	26	23	21	20	12	7

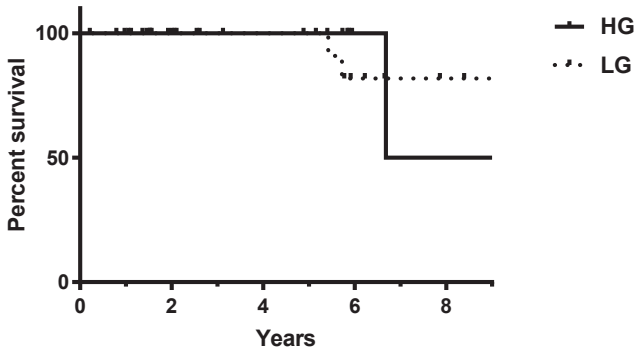
Fig. 1. Recurrence-free survival (RFS) and Overall survival (OS) for Entire Cohort. Five year RFS was 77% and OS was 100%.



Numbers at risk

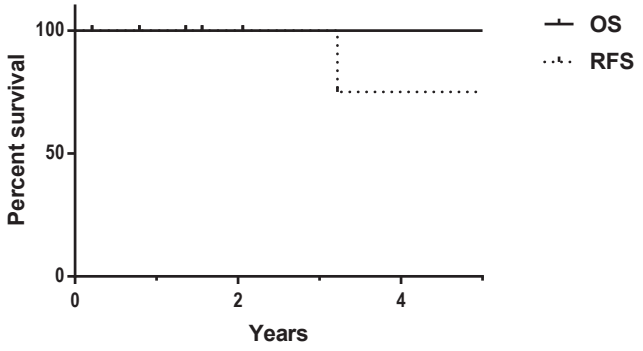
Low grade	20	17	13	12	11	7
High grade	16	8	7	7	6	3

Fig. 2. Recurrence-free survival (RFS) for low grade (LG) vs. high grade (HG). Five year RFS was 75% and 81%, respectively (p-value = 0.84).
(b). Overall survival (OS) for low grade (LG) vs. high grade (HG). Five year OS were 100% for both low grade and high grade lesions (p value = 0.99).



Numbers at risk						
Low grade	20	19	15	14	13	8
High grade	16	9	8	8	7	3

Fig. 2. (*continued*)



Numbers at risk					
RFS	8	6	5	4	4
OS	8	6	5	5	5

Fig. 3. Recurrence free survival (RFS) and Overall survival (OS) for the Goblet Cell Carcinoid (GCC) subgroup. Five year RFS and OS was 75% and 100%, respectively.

underwent other operative interventions (including prophylactic oophorectomy and cholecystectomy); this subgroup analysis was done to evaluate the influence of prophylactic visceral resections on RFS and OS. In patients who only underwent a right colectomy and omentectomy, five year RFS and OS were 87% and 100%, respectively. The comparison group's five year RFS and OS were 71% and 100%, respectively. Median RFS and OS were not reached and the two groups were not statistically different.

4. Discussion

The role of adjuvant HIPEC for patients at risk for progression of peritoneal carcinomatosis, without evidence of gross disease, is unclear. Here, data from a high-volume HIPEC program demonstrates long-term survival associated with adjuvant perfusion in a high-risk patient population. We found no difference in survival between patients with LG and HG tumors with a PCI of 0. Importantly, both patients with LG and HG tumors may achieve survival rates beyond a decade after adjuvant HIPEC.

A number of key findings require discussion. First, the overall survival of patients who underwent HIPEC on the basis of high-risk features (e.g. tumor perforation) is noteworthy; with a median follow up of 5.2 years, median overall survival and median recurrence free survival in the entire cohort was not reached. The 5-year RFS and OS for the entire cohort was favorable in both groups, but not different. Although previous data has demonstrated that HG peritoneal disease is associated with poorer long-term survival, our data did not confirm this. Perhaps the microscopic tumor burden (if present) is sufficient to mitigate the aggressive tumor biology of HG disease; this should be investigated in future studies.

One may argue that adjuvant perfusion is over-treatment for a population that has no evidence of active malignancy. However, five patients had evidence of nodal disease and the fact that over 20% of these patients recurred over time is evidence that this patient population is indeed at high risk for recurrence. These realities suggest that aggressive surgical intervention may be warranted, particularly as cytoreduction/HIPEC of more advanced disease is associated with poorer outcomes.

The concept of adjuvant perfusion is not new [25]. In 2011, Elias et al., reported their experience with planned second-look surgery over a ten-year period. Of 41 patients, 18 did not have evidence of peritoneal disease but underwent HIPEC anyway. At a median follow up of 30 months, only two of the 18 patients demonstrated peritoneal recurrence, and all 18 patients were alive [19]. In 2013, a review of second-look laparotomies and HIPEC for colorectal cancer by Brucher and colleagues emphasized that approximately 50% of patients with high-risk clinical and pathologic features and no radiographic evidence of disease did indeed have macroscopic disease at the time of surgery, supporting the practice of second-look surgery with HIPEC [23]. Taken together, these studies confirm that patients who may not have radiographically or visually evident disease are still at risk for disease progression, and HIPEC may well be a useful adjuvant therapeutic modality.

Previous literature suggests that patients with high-risk colon primaries (e.g. perforated or T4 disease) have a 14–58% risk of peritoneal recurrence [28–31]. Our study cohort had a recurrence rate of 22%, although this number reflects both solid organ and peritoneal recurrences; our peritoneal-only recurrence rate was 6% (n = 2). This low peritoneal-only recurrence rate demonstrates the potential value of adjuvant HIPEC in this population; most interventions are not associated with such favorable DFS. Conversely, other reports have shown that peritoneal disease can develop in greater than 50% of patients with perforated appendiceal cancer (without evidence of peritoneal disease) who underwent cytoreduction only [32]. Although we cannot make strong conclusions about therapeutic efficacy without a direct comparison group, our results suggest that adjuvant HIPEC may reduce the rate of peritoneal recurrence.

Discussion would be incomplete without acknowledging PROPHYLOCHIP, a multicenter randomized phase 3 trial performed to evaluate the benefit of second-look surgery and HIPEC in patients at high risk of developing peritoneal metastases of colorectal origin. While the investigators discovered peritoneal recurrence in roughly half of the patients who underwent second-look laparotomy, overall and disease free survival were similar between the second-look laparotomy and the surveillance groups. Most importantly, our series reports on a slightly different cohort—those without gross disease and generally with no delay to HIPEC for observation or systemic therapy. If we believe that HIPEC is particularly beneficial for micro-metastatic disease, this earlier peritoneal administration of chemotherapy may be more valuable. Additionally, it should be noted that our complication rate was similar to the PROPHYLOCHIP study [12].

Particular discussion about GCC of the appendix, known for its aggressive nature and poor outcomes, is warranted. Nine patients in our series, with GCC and PCI of 0, underwent HIPEC. These patients had 5 year RFS and OS of 75% and 100%, respectively, with no deaths and one recurrence. These findings are consistent with previously published reports by Madsen et al., who showed prolonged survival in patients

who had minimal disease or deemed at risk of peritoneal spread [33].

Given the high risk of ovarian recurrence and gallbladder stasis following HIPEC, it is the common practice in our group to remove the ovaries and gallbladder at the time of HIPEC. We attempted to identify whether patients who did not undergo prophylactic cholecystectomy or oophorectomy at the time of surgery were at a higher likelihood of recurrence or death. The patients who only underwent right colectomy and omentectomy with HIPEC had 5 year RFS and OS that were not different than those patients who underwent cholecystectomy or oophorectomy. Although prophylactic organ resection was not associated with worse survival, these data are not sufficient to make definitive recommendations.

Morbidity for any adjuvant treatment is of particular importance. In our series, there were no peri-operative deaths but 43% of patients (n = 16) had one or more complications. Major complications (grade 3 or 4 morbidity) occurred in 35% (n = 13) of patients. These patients required a return to the operating room or additional procedures for various reasons (small bowel obstructions, anastomotic leak, post-op bleeding and fascial dehiscence). Though these did not result in mortality, they certainly affected quality-of-life and discussion of these realities is a critical component of shared preoperative decision-making. This morbidity could possibly be ameliorated by a laparoscopic approach and should be investigated in future studies.

The most obvious limitation of this study is the inability to discern which patients would actually progress to develop PC, and more importantly those who would not. This uncertainty, and the question of whether to intervene when potentially only microscopic disease is present versus waiting for development of gross disease, is debatable. While disseminated peritoneal adenomucinosis (DPAM) or peritoneal mucinous carcinomatosis (PMCA) are commonly used classification schemes to stratify tumors according to clinicopathologic characteristics, these cohorts represent tumors that may ultimately behave differently. In the current study, we aimed to evaluate the impact of adjuvant HIPEC specifically in patients who may harbor microscopic disease, in both high and low grade malignancies. Secondly, as with essentially all other retrospective HIPEC studies, lack of a comparable control group limits the power of any assertion about an oncologic benefit from adjuvant perfusion with regard to either RFS or OS as these patients may have equivalently prolonged survival without HIPEC. Finally, consideration must be given to the relative impact on quality of life as well as short and long-term outcomes. We believe that our data is hypothesis generating and suggests that adjuvant HIPEC should be evaluated in a larger multi-institutional setting. Currently, there is a multi-institutional effort to open such a trial, which is being carefully designed and planned.

In summary, the role of adjuvant HIPEC in patients with PCI 0 is controversial. We have identified a subset of patients with high-risk disease (tumor perforation or T_4) that may benefit from adjuvant HIPEC. In particular, our data demonstrate that patients with high-risk of microscopic peritoneal disease demonstrate excellent long-term peritoneal recurrence free and overall survival after adjuvant perfusion and supports the use of tumor grade as a prognostic marker. Although only descriptive, this study highlights that adjuvant HIPEC demonstrates long-term recurrence free and overall survival.

Conflicts of interest

None.

Synopsis

The role of HIPEC in patients at high-risk for peritoneal carcinomatosis, but without macroscopic disease, remains controversial. We identified a subset of patients with high-risk disease that may benefit from adjuvant HIPEC, demonstrating long-term survival after adjuvant perfusion.

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