



The robotic future of minimally invasive cytoreduction and hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancies

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Abstract: Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) has been increasingly utilized for peritoneal surface malignancies. This has been commonly utilized for a variety of neoplasms, but, especially mucinous neoplasms of the appendix, ovarian cancer, gastric cancer, colorectal cancer and mesothelioma. Traditionally, CRS/HIPEC has been performed as an open, extensive operation associated with prolonged hospitalization. However, when the peritoneal carcinomatosis index (PCI) is small (<10), minimally invasive approaches can be considered. Such less invasive approaches may be associated with improved postoperative recovery, less complications while preserving oncologic outcomes. The robotic platform offers distinct advantages over laparoscopy with superior visualization and ergonomics which account for its increased utilization in oncologic surgery. Herein, we review available data on minimally invasive approaches to CRS/HIPEC procedures, focusing on patient selection and comparative studies to open CRS/HIPEC. We summarize the existing initial studies on robotically assisted CRS/HIPEC and provide technical insights about our approach to robotically assisted CRS/HIPEC. Current data suggests that treatment of peritoneal surface malignancies with minimally invasive CRS/HIPEC is feasible in selected cases and is associated with improved postoperative recovery. The robotically assisted platform for CRS/HIPEC deserves further investigation and may improve outcomes after this procedure in the future for carefully selected patients with low PCI.

Keywords: Peritoneal surface malignancies; minimally invasive surgery; robotic surgery; cytoreduction and hyperthermic intraperitoneal chemotherapy (cytoreduction and HIPEC); peritoneal carcinomatosis index (PCI)

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Introduction

Background

Peritoneal metastases are common event for intra-abdominal malignancies and have been traditionally associated with a dismal prognosis (1-4). Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/

HIPEC) (5) is the treatment of choice for pseudomyxoma peritonei and peritoneal mesothelioma (2-4,6,7) and utilized selectively for gastric, colorectal, ovarian and other malignancies (2,8-10). The most important prognostic factors after CRS/HIPEC are the type of primary cancer, completeness of cytoreduction and the performance status of the patient (2,10).

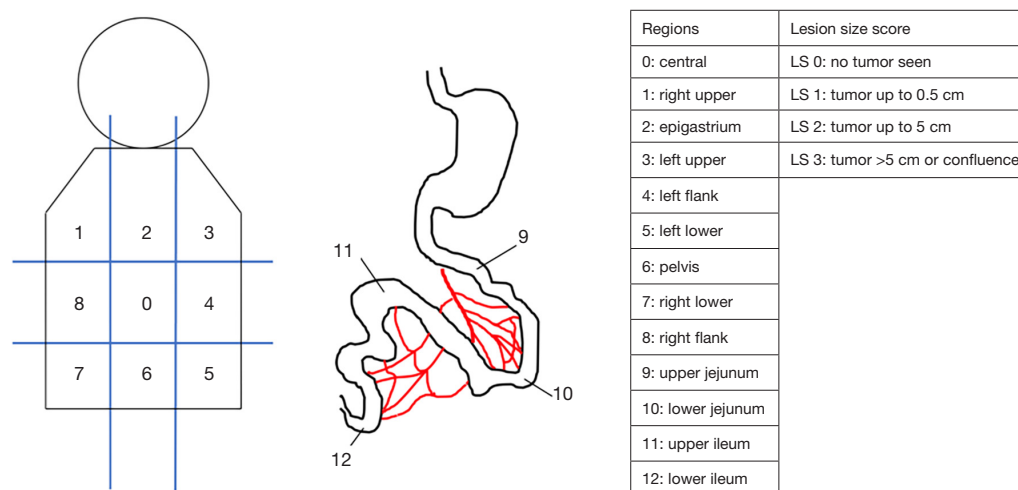


Figure 1 PCI (17). The original figure is available under a Creative Commons Attribution License 4.0. LS, lesion size; PCI, peritoneal carcinomatosis index.

CRS/HIPEC has traditionally been performed via large midline laparotomy incisions. However, the potential for less invasive approaches to this procedure have been explored. Minimally invasive oncologic surgery has been documented in multiple studies to be associated with improved postoperative outcomes versus open surgery (11,12). A logical extension of laparoscopic CRS and HIPEC are robotic assisted oncological surgeries for gastrointestinal malignancy (13). The advantages of the robotic platform with enhanced visualization and ergonomics make it an ideal platform for long, technically demanding surgeries. Initial reports on outcomes of robotic CRS/HIPEC have started to emerge (14–16).

Rationale and knowledge gap

In this review, we summarize important current evidence of minimally invasive CRS/HIPEC, we discuss technical considerations for the robotic approach, and give future perspectives for the treatment of peritoneal surface malignancies.

Methods

A literature search was conducted using PubMed and the most recent literature regarding minimally invasive approaches for CRS/HIPEC was reviewed. Selected studies for this review were chosen based on their quality, innovation and patient size by 3 of the authors (JO, TO,

IK). The peritoneal carcinomatosis index (PCI) (*Figure 1*) is widely utilized to quantify peritoneal tumor burden and ranges from 0 to 39 (17).

Minimally invasive CRS/HIPEC: patient selection and outcomes

Table 1 summarizes the largest series on laparoscopic HIPEC. No large series utilizing robotic assisted CRS/HIPEC have yet been published. In these initial reports, patients are selected based on low-volume disease and favorable histology mainly low-grade pseudomyxoma peritonei (PMP) and benign multicystic mesothelioma. The PCI in these series was typically <10 (18–21).

In the study conducted by Mercier *et al.* (21), 32 patients with low-grade PMP and multicystic peritoneal mesothelioma who underwent laparoscopic CRS/HIPEC were retrospectively analyzed over a period of 8 years. Their results demonstrated a median PCI score of 2.5 and median length of hospital stay of 11 days. Overall, they reported zero major morbidity and mortality, and 5-year overall survival and disease-free survival rates of 100% and 91% respectively. The study also discussed the results of 11 patients with similar clinical characteristics who underwent conversion to open CRS/HIPEC. This group had a higher median PCI score of 7, longer median length of hospital stay of 13 days, and increased rate of major surgical complications of 9.1%. Their 5-year overall survival was 100%, whereas disease-free survival was 62.5%.

Table 1 Largest retrospective series on laparoscopic HIPEC

First author, year, country	Number of patients	Primary cancers	PCI	Length of stay, days	Postoperative mortality (%)	Grade III or higher morbidity (%)
Arjona-Sanchez, 2019 (18), International	90	Appendiceal, colorectal, gallbladder, ovarian	4.1	7.4	N/A	9.9
Arjona-Sanchez, 2021 (19), International	143	PMP, mesothelioma, colorectal, ovarian	3	6	0.7	8.3
Abudeeb, 2020 (20), UK	55	PMP	0	6	0	3.6
Mercier, 2020 (21), France	32	PMP, mesothelioma	2.5	11	0	0

PCI, peritoneal carcinomatosis index; PMP, pseudomyxoma peritonei; HIPEC, hyperthermic intraperitoneal chemotherapy; N/A, not applicable.

The authors concluded that the long-term outcomes of laparoscopic CRS-HIPEC are favorable.

Arjona-Sanchez *et al.* conducted two separate international retrospective studies on laparoscopic CRS/HIPEC. Their first study in 2019 included 90 patients with PCI score of 10 or less (18). The majority of patients in their study had low grade appendiceal cancers and pseudomyxoma. The remaining pathologies consisted of colon adenocarcinoma, benign multicystic mesothelioma, cholangiocarcinoma, goblet cell carcinoid, and ovarian carcinoma. Their mean PCI score was 4.1, mean length of hospital stay was 7.4 days, and grade 3 or higher morbidity 9.9%. The 5-year overall survival was noted to be 100% for patients with low-grade tumors (low grade PMP, benign multicystic mesothelioma, and ovarian) and 64% for patients with colon and high-grade appendiceal tumors. Their second study in 2021 included 143 patients and only involved centers performing at least 30 CRS/HIPEC procedures per year (19). They found a median PCI score of 3, median length of hospital stay of 6 days, and major morbidity of 8.3%. The primary pathologies in this patient population, similar to their previous study, consisted mostly of low-grade pseudomyxoma from appendiceal neoplasms (55.2%), followed by multicystic peritoneal mesothelioma, colorectal cancer, and ovarian peritoneal metastasis. The 5-year overall survival was similar to their prior study with PMP low-grade and benign multicystic mesothelioma reaching 100%, colorectal cancer reaching 54%, and ovarian reaching 78%.

These results demonstrate the excellent feasibility and safety of minimally invasive CRS/HIPEC in highly selected patients with major morbidity below 10%. The long-term oncologic outcomes are preserved and comparable to open CRS/HIPEC for the same pathologies and volume of disease.

Open versus minimally invasive cytoreduction with HIPEC

The advantages of minimally invasive oncological surgery over open are associated with decreased length of stay, faster return of bowel function, decreased wound infection rates, less postoperative adhesions (18,21). There are currently only a handful small retrospective studies supporting the above for CRS/HIPEC. To date there have been no prospective randomized trials comparing open with minimally invasive CRS/HIPEC.

Passot *et al.* were among the first to compare the outcomes of laparoscopic versus open CRS/HIPEC (22). Their study included 16 patients with low-grade PMP and multicystic mesothelioma and limited peritoneal disease who underwent CRS/HIPEC either via open (n=8) or laparoscopic (n=8) approach. The median length of hospital stay was shorter in the laparoscopic group (12 days) versus the open group (19 days) ($P=0.01$). Though, it is important to note that the median PCI score was higher in the open cases (8 *vs.* 2.5; $P=0.001$) and statistically significant. The authors noted no differences in the recurrence and death rates at a short follow-up of 192 days.

A comparative matched analysis of open (n=42) versus laparoscopic (n=18) CRS/HIPEC also found no significant differences in morbidity or mortality (23). Disease free survival was equivalent with 63.7% of the patients free of relapse at 24 months in the open group and 71.4% in the laparoscopic group ($P=0.53$). Patients who underwent laparoscopic CRS/HIPEC had shorter hospital stays and returned to adjuvant chemotherapy sooner.

Another comparative matched analysis by Abudeeb *et al.* noted no statically significant differences in morbidity and mortality between laparoscopic (n=55) and open (n=29) groups ($PCI \leq 7$) (20). Groups were matched for age, gender and extent of surgery. They found the median operative

time was longer in the laparoscopic group when compared to the open group (8.8 *vs.* 7.3 h; $P < 0.001$); however, the median length of stay remained shorter in the patients undergoing laparoscopic CRS/HIPEC (6 *vs.* 10 days; $P < 0.001$). Patients who underwent laparoscopic CRS/HIPEC required less admissions to high dependency units. Clavien-Dindo Grade 1–4 complications were similar between the groups with no postoperative mortality.

These three studies are among the few that directly compare open to minimally invasive CRS/HIPEC. They reinforce that the improved patient outcomes of laparoscopic surgery can be applied to selected CRS/HIPEC procedures with low predicted PCI.

Robotic assisted cytoreduction with HIPEC (RCRS/HIPEC): initial reports

Initial reports on robotically assisted CRS/HIPEC have started to emerge. These studies and their findings are outlined below, and their results are promising. To date there have been no prospective randomized trials comparing robotically assisted with laparoscopic or open CRS/HIPEC.

Koti *et al.* described their experience with open and minimally invasive CRS/HIPEC for appendiceal, colon and gastric primaries over a period of 4.5 years. The minimally invasive group comprised of 7 patients who underwent robotic assisted and 2 patients who underwent laparoscopic procedures. The minimally invasive group had a mean PCI of 5.6, despite longer operative time, the time to return bowel function was shorter, the analgesic requirements were reduced and the hospitalizations were shorter (16).

Fagotti *et al.* similarly compared open and minimally invasive cytoreduction (SCS)/HIPEC in isolated platinum-sensitive recurrent ovarian cancer (14). The PCI score for all patients included in the study was 2. In the minimally invasive group, there were 3 patients that underwent robotic assisted SCS while the remaining 8 patients underwent laparoscopic SCS. Overall, their results demonstrated shorter operative time, decreased blood loss, and shorter length of hospital stay for the MIS in comparison to the open group. Though the number of robotic cases in this study is small ($n=3$), the findings remain promising in patients with extremely limited PCI.

Gabriel *et al.* described their technique of RCRS/HIPEC for a patient with pseudomyxoma and a PCI of 1 (15). They found this technique particularly useful to minimize surgeon fatigue in patients with increased BMI undergoing long surgeries.

Chen *et al.* demonstrated their approach to RCRS/HIPEC in a patient with advanced rectosigmoid cancer involving pelvic peritoneal metastases and PCI score of 2 (24). Though the patient's length of hospital stay was long (40 days), she remained disease-free at 40 months and regained urinary and bowel function. Clearly with a 40-day hospital stay and a PCI of 2, this points out that even a robotic platform can be associated with substantial postoperative complications even in patients with very low PCI.

RCRS/HIPEC: technical aspects

With regards to our technical approach to RCRS/HIPEC, at Texas Tech, we utilize the Xi robotic platform (Intuitive Surgical, Sunnyvale, CA, USA) for these procedures. Patients typically have disease which is radiologically confined in 1 or 2 quadrants or only found in diagnostic laparoscopy. We do not use an absolute PCI cutoff excluding patients from RCRS/HIPEC.

Insufflation of the abdomen is performed with Veress needle at the left upper quadrant. Entry into the abdomen is performed with an 8 mm robotic trocar near the umbilicus with optiview technique. If the findings of initial abdominal inspection do not preclude robotic CRS/HIPEC, we use 4 robotic ports (8 mm each) in a straight line at the level of the umbilicus and a 12 mm assist port at the left upper quadrant which is later used for the inflow perfusion catheter during the perfusion step. A symmetrical incision at the right upper quadrant is made for the outflow perfusion catheter during the perfusion step (Figure 2).

We start with cytoreduction in the upper abdomen with the patient in 20° reverse Trendelenburg. A greater omentectomy is typically performed in all patients and this specimen is left above the right liver lobe until the specimen extraction phase. We redock the robot and target towards the pelvis in order to resect disease from the lower abdomen with the patient in Trendelenburg position. The robotic platform allows for easy docking and re-docking to allow disease clearance from the upper and lower abdomen. If a right hemicolectomy needs to be performed, we place additional robotic ports in a diagonal configuration at the right abdomen and conclude this step as a typical robotic right hemicolectomy. Utilization of indocyanine green (ICG) technology allows for identification of the biliary anatomy and assessment of the bowel perfusion before anastomosis which is typically performed after the perfusion step. HIPEC is given using Mitomycin C for 90 minutes



Figure 2 Port configuration for robotic assisted CRS/HIPEC. CRS/HIPEC, cytoreductive surgery/hyperthermic intraperitoneal chemotherapy.

at 41–42 degrees Celsius, with a crystalloid prime via cannulas placed through the port sites. All anastomoses are completed at the conclusion of HIPEC. All ports are removed under direct vision, the incisions are closed, the patient extubated, aroused and taken to the recovery area.

Conclusions

The utilization of robotic assisted surgery for the resection of gastrointestinal malignancies is growing and will continue to expand. Peritoneal surface malignancies will be part of this trend. Even though the current reported experience on minimally invasive CRS/HIPEC represents mainly laparoscopic procedures, more reports utilizing the robotic platform are emerging. The advantages of the robotic platform for long, technically demanding patients and the ease of incorporating ancillary technologies such as the ICG to assess biliary anatomy or bowel perfusion will contribute to this, although the low PCI burden in current reports weaken this argument.

Open CRS/HIPEC will continue to be the mainstay of therapy for patients with diffuse disease involving the whole abdomen. There is obvious selection bias in the existing reports on minimally invasive CRS/HIPEC, mainly on selecting patients with very low PCI. However, with the evolution of robotic instruments and technology, minimally invasive approaches will be utilized more frequently and for higher PCI numbers in the future. The added benefit of the robotic platform to manipulate tissue, dissect and suture in

tight spaces will contribute to this.

The future of cytoreductive surgery and HIPEC for peritoneal surface malignancies is more minimally invasive, more multimodal and, certainly, very promising.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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