



Feasibility of hand-assisted laparoscopic cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancy

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Abstract

Background In light of the modern surgical trend towards minimally invasive surgery, we aim to assess the feasibility of hand-assisted laparoscopic (HAL) cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in peritoneal surface malignancy (PSM).

Methods Patients with PSM secondary to colorectal cancer or pseudomyxoma peritonei with peritoneal cancer index (PCI) of ≤ 10 were considered for HAL CRS and HIPEC. One patient had PCI of 15 but based on the disease distribution laparoscopic-assisted CRS and HIPEC was thought to be feasible, thus was also included. These patients were compared to matched controls who underwent open CRS and HIPEC for similar pathologies. Matching was performed on age and PCI to reflect a comparable complexity of the operation, and tumor grade for comparable risk of disease recurrence.

Results Eleven patients were included in each group. In both groups, mean PCI was 4.1, mean age was 58.5 years, and 81.8% were well-moderately differentiated tumors. Complete cytoreduction was achieved in all patients. Upon comparison, HAL patients had significantly less blood loss and 3-day shorter hospitalization. No difference was demonstrated in operative time, number of visceral resections, and rate of omentectomy/peritonectomy. Also, no difference was detected in morbidities and 30-day readmission rates. No intraperitoneal recurrences have been reported in the HAL group after a median follow-up of 11 months.

Conclusion HAL CRS and HIPEC is a feasible procedure and can be considered for PSM with low PCI. It offers very acceptable and comparable short-term outcomes to the conventional open approach.

Keywords CRS and HIPEC · Hand-assisted laparoscopy · Peritoneal surface malignancy

The surgical treatment of peritoneal surface malignancies (PSM) in the past was largely limited to palliation. With better understanding of the natural history of the disease, combining cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has been increasingly utilized. The procedure, however, is generally long,

technically challenging, and requires a long midline laparotomy incision.

Emphasis on the quality of life and limited morbidity are paramount for patients with PSM. In the past years, minimal access surgery showed a rapid expansion in the treatment of several intraabdominal malignancies. This frequently demonstrates superiority with respect to short-term safety and length-of-stay endpoints, and has shown similar oncologic outcomes, compared to laparotomy.

There is a rather limited experience with laparoscopic CRS and HIPEC. Esquivel et al. [1] reported their experience and showed a low morbidity and shorter hospital stay. They used a completely laparoscopic approach and, towards the end of the procedure, a mini-laparotomy was performed to extract the specimen. We modified this technique to use a hybrid hand-assisted approach. Hand-assisted laparoscopic (HAL) surgery was introduced in an attempt to expand the

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scope of laparoscopic abdominal surgery. This technique bridges the gap between open and pure laparoscopic surgery whereby the surgeon's hand is placed within the abdomen, and in concert, standard laparoscopic instrumentation is applied. This allows for retraction, tactile feedback, blunt dissection, and ease of bleeding control. Moreover, the hand port serves as the extraction site for the specimen at the end of the procedure.

On account of the above advantages, HAL may be more suitable than pure laparoscopy for complicated surgeries such as cytoreductive surgery. However, to the best of our knowledge, no previous study has described laparoscopic-assisted CRS and HIPEC.

Methods

Patient selection and case matching

The inclusion period for this study extended between 03/2015 through 8/2017. Patients undergoing planned CRS and HIPEC were retrospectively reviewed from a prospective database that is being updated and maintained under IRB approval. All the operations were performed by one surgeon (G.I.S.), already proficient in laparoscopy and cytoreductive surgery. A group of matched controls who underwent open CRS and HIPEC for similar histopathologies was identified from the database for comparison of outcomes. Matching was applied on age and extent of peritoneal disease as reported in the intraoperative peritoneal cancer index (PCI) to reflect a comparable operative complexity, and on tumor grade to reflect a comparable risk of disease recurrence.

After setting the matching variables, an automated search was conducted through the database. Tolerance level was set to 5% for continuous variables, and exact for categorical variables. The best match for each case was selected for the analysis. Two of our 11 cases had only one match, therefore higher rates of matching such as 1:2 or 1:3 could not be uniformly applied to the group.

Surgical technique of laparoscopic CRS and HIPEC

Patients were placed in lithotomy position. A periumbilical 6–7 cm incision was used for placement of the hand port. Two 12-mm trochars were placed on either side of the abdomen. Additional 5-mm trochars were placed as deemed necessary. The goal of cytoreductive surgery is the removal of all gross disease as previously described [2]. This consisted of the removal of gross tumor and involved organs and peritoneum, if any, as deemed safe. PCI was used to score the extent of peritoneal involvement at the time of surgery. The completeness of cytoreduction score was used to classify the resection status of patients as described by Dr. Sugarbaker

[3]. A total greater omentectomy was performed to include the omentum between the transverse colon and greater curvature of the stomach, which extends to the splenic hilum. In addition, a lesser omentectomy (between the liver and lesser curvature of the stomach) was performed in all cases.

Peritonectomy was limited to surfaces affected with gross visible disease. Anterior peritonectomy, upper quadrant peritonectomy, pelvic peritonectomy, subphrenic peritonectomy, and omental bursectomy were performed selectively depending on the site of peritoneal metastases.

HIPEC was performed using the closed-abdomen technique at 42–43 °C. At the completion of CRS, two inflow catheters were placed in the abdominal cavity at the 12-mm trochar sites. A looped outflow catheter was placed utilizing the midline incision and positioned anterior to the liver. The abdomen was then closed at the skin level using running sutures to prevent leakage of perfusate. Temperature probes were placed at the inflow and outflow catheters inside the abdomen. We used 3L Ringer's lactate as perfusate to establish a circuit with flow rates approximately 1600–1800 mL/min managed by the perfusionist.

Our postoperative protocol for oral intake is to remove the nasogastric tube once the output is < 300 mL in 24 h to introduce clear liquid diet with advancement as tolerated. Once patients tolerate a regular diet, ambulate without restrictions, and their pain is adequately controlled with oral medication, they are considered ready for discharge. This protocol is uniformly applied to all CRS and HIPEC patients regardless of the surgical approach.

We graded our postoperative complications based on the Clavien–Dindo classification system [4]; grade I represents any deviation from the normal postoperative course without surgical, endoscopic, or radiological intervention; grade II is a complication that requires pharmacological treatment (e.g., antibiotics beyond 24 h postoperatively) or blood transfusions; grade III is a complication requiring surgical, endoscopic, or radiological intervention; and grade IV is a life-threatening complication requiring any of the above in addition to critical care management (medical, surgical, or neurological). Grade V is reserved for death. Grades I and II are considered 'minor,' whereas grades III and higher are regarded as 'major.'

Follow-up

Our follow-up protocol includes physical examination, tumor markers (CEA, CA 19-9, and CA-125), abdomen/pelvis CT scan, and/or diffusion-weighted MRI every 3 months during the first 2 years and every 6 months thereafter. Chest imaging is dependent on tumor histopathology. Recurrence-free survival is defined by normal tumor markers and unremarkable imaging studies.

Statistical analysis

We used the standard statistical methods of Chi-square, Student's T-test, and Mann–Whitney U-test for inferential analysis of the study groups.

Results

Twelve patients submitted for laparoscopic CRS and HIPEC during the study period. One patient was noted to have a PCI of 19 at initial laparoscopy and was immediately converted to open procedure, otherwise there were no conversions. Thus, this analysis included the eleven patients who completed the planned HAL CRS and HIPEC. The primary pathologies were pseudomyxoma peritonei (PMP), appendiceal adenocarcinoma, or colon adenocarcinoma. Eleven patients matched on age, PCI, and tumor grade with similar histologies were included as a control group. Table 1 summarizes the preoperative characteristics of these patients.

Mean PCI was 4.1 ± 5.1 , mean age was 58.5 years, and 81.8% were well-moderately differentiated cancers. Of note, patients with colon adenocarcinomatosis underwent neoadjuvant chemotherapy, whereas patients with appendiceal adenocarcinomatosis or PMP did not.

There was no difference in the disease distribution between the study groups. Complete cytoreduction (CC-0) was achieved in all patients. Comparison of operative outcomes revealed that the HAL group had a significantly less intraoperative blood loss, and a 3-day shorter hospital stay. No difference was noted in the operative time, number of visceral resections, peritonectomy, or omentectomy. Of note, all peritonectomies that were performed in either group were partial peritonectomies. Moreover, there was no difference in the rates of postoperative morbidities (all of which were minor), or in 30-day readmission.

HAL patients had a mean follow-up period of 15.2 ± 11.7 months (median 11 months) during which no intraperitoneal recurrences were documented. One patient with colon carcinoma died of liver and brain metastases 5 months following HAL CRS and HIPEC while receiving systemic therapy. Table 2 demonstrates our surgical outcomes in this population. Figures 1, 2, and 3 demonstrate some technical and intraoperative details of HAL CRS and HIPEC.

Discussion

The major finding of this study is that HAL CRS and HIPEC for PSM is associated with acceptable perioperative outcomes and can be achieved with low rates of conversion and

Table 1 Summary of the demographics and preoperative characteristics of our laparoscopic-assisted vs. open CRS and HIPEC patients

	Laparo- scopic- assisted CRS and HIPEC (N=11)	Open CRS and HIPEC (N=11)	<i>p</i>
Sex			
Males	7 (63.6%)	8 (72.7%)	0.604
Females	4 (36.4%)	3 (27.3%)	
BMI	26.4 ± 4.6	29.02 ± 6.3	0.298
Charlson comorbidity index			
0	5 (45.4%)	5 (45.45%)	0.772
1	4 (36.4%)	5 (45.45%)	
≥ 2	2 (18.2%)	1 (9.1%)	
Primary malignancy			
Appendiceal adenocarcinoma	2 (18.2%)	4 (36.4%)	0.539
Colon adenocarcinoma	3 (27.3%)	3 (27.3%)	
Pseudomyxoma Peritonei	6 (54.6%)	4 (36.4%)	
Time from diagnosis to CRS and HIPEC (months)	15.9 ± 11.3	14.0 ± 9.2	0.312
Neoadjuvant chemotherapy	3 (27.3%)	3 (27.3%)	0.998
Disease distribution			
Malignant ascites only	3 (27.3%)	2 (18.2%)	NS
Adnexa/ovaries	3 (27.3%)	3 (27.3%)	
Appendix	4 (36.4%)	3 (27.3%)	
Right colon	1 (9.1%)	1 (9.1%)	
Transverse colon	0 (0.0%)	1 (9.1%)	
Descending colon	2 (18.2%)	3 (27.3%)	
Rectosigmoid	1 (9.1%)	1 (9.1%)	
Gallbladder	1 (9.1%)	3 (27.3%)	
Liver	2 (18.2%)	2 (18.2%)	
Small bowel	3 (27.3%)	2 (18.2%)	

morbidities. In fact, the one conversion occurred at the outset when the PCI was noted to be high. Thus, we currently consider HAL CRS and HIPEC in select patient with PSM.

Esquivel et al. [1] reported their experience with *pure* laparoscopic CRS and HIPEC and showed a low morbidity and shorter hospital stay. This, to our knowledge, is the only such experience reported. There was one grade III morbidity (10%), and one patient (10%) in the laparoscopy group experienced a grade IV complication, requiring a reoperation for an internal hernia. Mean length of hospital stay was 6 days for those completed laparoscopically, 8 days for those converted to an open procedure, and 8 days for a matched cohort of patients with an upfront open procedure. They concluded that it is feasible and safe to perform CRS and HIPEC via the laparoscopic approach in selected patients with low-tumor volume and no small bowel involvement mainly from appendiceal malignancies. Of note, they describe that “at

Table 2 Summary of the operative outcomes for patients who underwent HAL vs. open CRS and HIPEC

	Laparoscopic-assisted CRS and HIPEC (N=11)	Open CRS and HIPEC (N=11)	<i>p</i>
Estimated blood loss (mL)	70.5 ± 49.7	260.0 ± 110.8	0.021*
Operative time (min)	307 ± 82	298 ± 96	0.594
Omentectomy	11 (100%)	11 (100%)	0.999
Peritonectomy	4 (36.4%)	5 (45.45%)	0.713
<i>N</i> of visceral resections			
Median	1	1	0.682
Range	0–2	1–4	
Complete cytoreduction (CC-0)	11 (100%)	11 (100%)	0.999
Morbidity			
All	2 (18.2%)	4 (36.36%)	0.470
Major	0 (0.0%)	0 (0.0%)	
Time to oral intake (days)	3.1 ± 1.2	5.6 ± 2.2	0.097
Length of hospitalization (days)	6.5 ± 2.1	9.1 ± 1.44	0.009*
30-day readmission	2 (18.2%)	4 (36.36%)	0.470
One-year peritoneal recurrence	0 (0.0%)	0 (0.0%)	1.000

*Statistically significant

Fig. 1 Technical details of the operative setup for laparoscopic-assisted CRS and HIPEC. **A** periumbilical hand port incision (wound protector applied in the picture), and two 12-mm lateral ports. Additional 5-mm ports may be placed as needed. **B** Use of the periumbilical incision for placement of the outflow catheter, and the port incisions for placement of the inflow catheters, and application of the closed-abdomen technique of HIPEC. **C** Final appearance of the abdomen upon termination of laparoscopic-assisted CRS and HIPEC. Note the additional 5-mm epigastric trochar which was deemed necessary during the procedure. **D** Use of the periumbilical incision for bowel evisceration and inspection

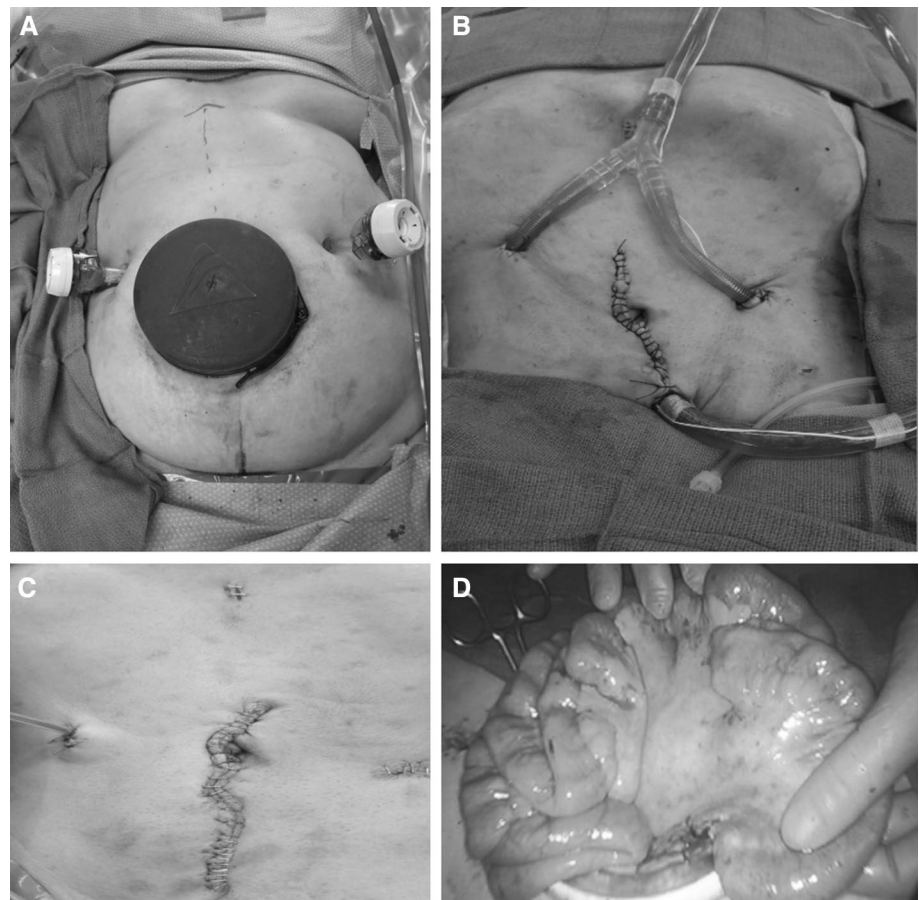


Fig. 2 Intraoperative images of laparoscopic-assisted CRS and HIPEC. **A** Evaluation of the right diaphragm and underneath surface of liver. **B** Palpation of the porta hepatis by passing a finger in the foramen of Winslow. **C** Evaluation of the left diaphragm. **D** Assessment of the small bowel involvement in the peritoneal disease

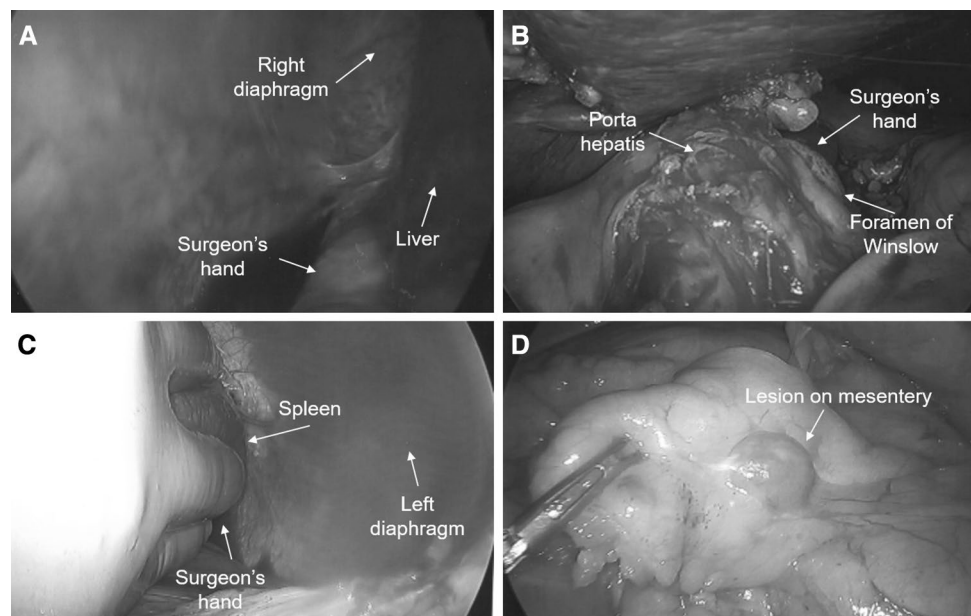
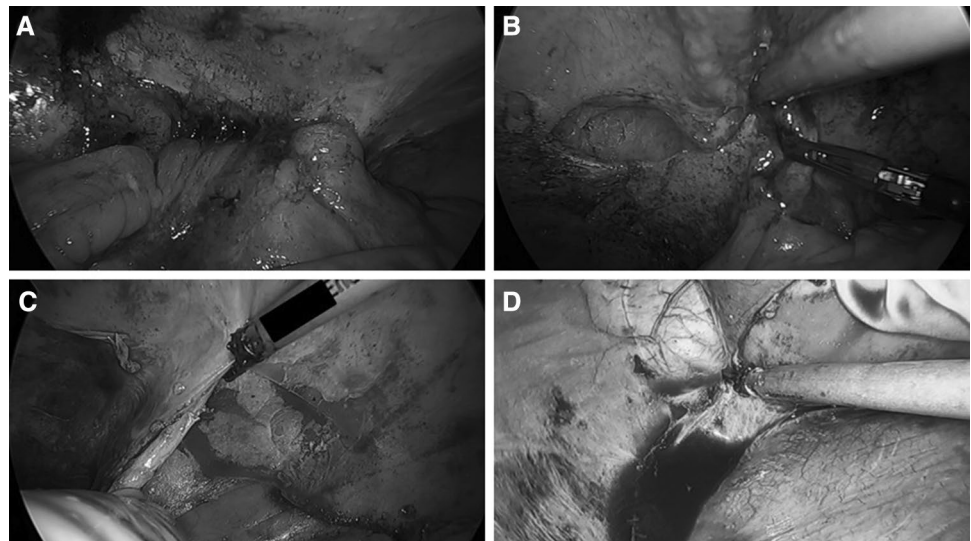


Fig. 3 Intraoperative images of laparoscopic-assisted peritonectomy. **A, B, C, D** Stepwise assessment and performance of limited right lower quadrant peritonectomy during laparoscopic-assisted CRS



the end of the laparoscopic stage of the procedure, a 6-cm periumbilical midline laparotomy was performed and the specimens were extracted.”

It is well known that a significant learning curve is associated with laparoscopic surgery. For example, in laparoscopic colectomy, a protracted learning curve has been demonstrated ranging from about 30 to 60 cases [5–7]. On the other hand, a report by Ozturk et al. showed that the learning curve for HAL colectomy is considerably faster (less than 10 cases) in comparison with pure laparoscopic approach [8]. We believe that HAL CRS and HIPEC can similarly speed up the learning curve.

The feasibility of laparoscopic cytoreductive surgery has been demonstrated in gynecology oncology literature [9]. In one study, ovarian cancer patients selected for laparoscopic

interval debulking surgery after neoadjuvant chemotherapy have comparable 3-year survival rates to women who undergo interval debulking by laparotomy [10]. However, there are certain anatomical and technical obstacles to the laparoscopic evaluation of several areas, such as the posterior aspect of the diaphragmatic leaves, the spleen, the pouch of Douglas, and the foramen of Winslow. In a study evaluating the diagnostic accuracy of HAL in predicting resectability of peritoneal carcinomatosis from gynecological malignancies, Varnoux and colleagues demonstrated that HAL was superior to standard laparoscopy for assessing the gastrosplenic ligament, spleen, lesser omental sac, pelvic nodes, and lumbo-aortic nodes [11].

Traditionally, an extended vertical midline abdominal incision is the recommended approach for patients

undergoing CRS and HIPEC. Our modified technique offers tactile feedback and the ability to feel nodules that the eyes do not see. In addition, it allows for evaluating small openings that may be challenging laparoscopically such as the foramen of Winslow. We were also able to eviscerate the small bowel to save operative time where no heroic laparoscopic completion at expense of time in this critical group of patients is warranted. We believe that our technique is reproducible considering the training and expertise in surgeons who are trained in oncology versus laparoscopy.

Several studies have advocated the use of HAL to minimize the need for conversion to open and to decrease operative time in complex cases [12, 13].

HAL was introduced as a viable alternative to straight laparoscopy offering a hybrid technique that allows surgeons to advance their laparoscopic skills. This approach also enables surgeons to incorporate the use of their hand for manual retraction, dissection, and prompt hemostasis, like an open operation [14], and has been advocated, at least in colectomies, as a useful bridging tool for surgeons between straight laparoscopy and open procedures [12].

Laparoscopic HIPEC without cytoreduction has also found applications in other clinical scenarios. It has been applied in PSM patients with refractory ascites in a study by Valle et al. They showed that this treatment modality is beneficial for the management and palliation of refractory malignant ascites and results in an excellent clinical and radiological resolution in patients with a complete resolution observed in their cohort of 12 patients [15]. More recently, a study from M.D. Anderson Cancer Center reported on patients with gastric or gastroesophageal adenocarcinoma and positive peritoneal cytology or radiologically occult peritoneal carcinomatosis after systemic chemotherapy. These patients received laparoscopic HIPEC, and, subsequently, patients whose peritoneal disease resolved were offered gastrectomy [16].

The current study may have some limitations, particularly surgeon bias and local extent of the tumor on preoperative imaging or previous laparoscopic surgery most likely played important roles in this selection. In addition, this is a retrospective analysis of prospective data in a small cohort of patients.

Oncologic equivalency or superiority may be of concern when a ‘new’ surgical technique for cancer is introduced. However, to date, there has been no evidence for peritoneal recurrence using our modified approach. One potential hurdle to the application of HAL CRS and HIPEC is the relatively low number of patients who may be selected for this approach.

In conclusion, our results show that HAL CRS and HIPEC is a safe and feasible option that yields a shorter hospitalization than that of open CRS and HIPEC, and comparable outcomes in other aspects of postoperative surgical care. We also believe

that this technique is reproducible and does add to the armamentarium of surgeons who offer CRS and HIPEC.

Compliance with ethical standards

Conflict of interest Dr. George I. Salti and Dr. Samer A. Naffouje have no conflicts of interest or financial ties to disclose.

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