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Laparoscopic cytoreductive surgery and HIPEC: a comparative matched analysis

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Abstract

Background Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) is a procedure that has had encouraging results for peritoneal metastases (PM) from diverse tumour origins, but it is not exempt from high morbidity. Recently, the important role of laparoscopy in oncologic surgeries and its benefits have been evaluated for CRS + HIPEC in selected patients, which has yielded promising results. The aim of our study is to analyse the use of laparoscopy for CRS + HIPEC in patients with limited peritoneal disease.

Methods We have conducted a retrospective study from a prospective database in our tertiary referral hospital within the period of January 2009 to July 2019, which includes 825 patients who had PM from varying tumour origins. We have compared the patients treated with the laparoscopic approach (L-CRS-HIPEC) to a matched population who have undergone the open approach (O-CRS-HIPEC) and fulfil the same selection criteria. We have analysed the postoperative outcomes and survival results.

Results We have confirmed the homogeneity between the sample of the O-CRS + HIPEC ($n = 42$) and the L-CRS + HIPEC ($n = 18$) regarding preoperative and intraoperative features. The L-CRS + HIPEC group had shorter hospital stays, (median of 4 [2–10] days versus 9 [2–19] days) and reduced wait time to return to chemotherapy (median of 4 [3–7] weeks and a median of 8 [4–36] weeks) than the O-CRS + HIPEC group. No differences were found regarding the need for perioperative blood transfusion, surgery time or postoperative morbi-mortality. No early locoregional relapse occurred in the L-CRS + HIPEC group and short term disease-free survival did not differ between groups.

Conclusions Laparoscopy for CRS + HIPEC is feasible and safe in highly selected patients, with no significant differences concerning postoperative morbi-mortality or early oncological results. We have found that patients who have undergone laparoscopic operations have shorter hospital stays and that they return to adjuvant chemotherapy sooner. Further investigation is required to confirm the benefits of minimally invasive procedures for the management of PM.

Keywords Cytoreductive surgery · HIPEC · Laparoscopy · Minimally invasive surgery

Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) is a procedure that has been demonstrated to significantly improve the survival of patients affected by peritoneal metastases of differing originations. It has become the main option for the treatment of pseudomyxoma peritonei, peritoneal mesothelioma and ovarian cancer with peritoneal metastases [1–3]. Currently, the benefits of HIPEC are also being evaluated for colorectal, gastric and endometrial cancer with metastatic disease when limited to the abdominal cavity [4–6].

In recent decades, the laparoscopy has become the gold standard approach for several abdominal tumours, providing patients with similar oncological outcomes to the open approach but with minimized morbidity and faster recovery [7–11]. In the field of peritoneal metastases, it has been widely considered as a useful tool for diagnosis, determining the burden of disease and for palliative treatment [12, 13], reducing the need for large midline laparotomies.

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A major abdominal cytoreductive surgery often implies several aggressive procedures that are associated to a high rate of major complications. The current, encouraging, results of the laparoscopic approach for CRS + HIPEC have shown less morbidity and length of hospital stay in highly selected patients with a Peritoneal Carcinomatosis Index (PCI) of 10 or less and, ideally, with borderline or low-grade tumours [14].

The aim of this study is to evaluate the postoperative outcomes using a minimally invasive approach for CRS and HIPEC in patients with limited peritoneal metastasis and compare those outcomes to a matched population who have undergone the standard open approach.

Methods

Patients

We have conducted a single institution retrospective study from a prospective database (Fig. 1). From January 2009 to July 2019, 825 patients who had a peritoneal disease from ovary, endometrium and colon carcinomas, or pseudomixoma peritoneii and peritoneal mesothelioma were treated through cytoreductive surgery plus HIPEC in our tertiary referral hospital by either an open (O-CRS + HIPEC) or laparoscopic approach (L-CRS + HIPEC).

The patient selection for the laparoscopic CRS + HIPEC surgery is based on the current experience of the diverse centres that perform this novel procedure [2, 14]. The criteria for an initial laparoscopic approach were: an intraoperative peritoneal carcinomatosis index (PCI) lower than 10, no major prior surgery (PSS ≤ 2), no large abdominal masses, no gross diaphragmatic involvement and no multifocal mesenteric lesions.

In order to acquire two comparable groups, a matched sample of patients from the open group who would have been suitable for a laparoscopic approach were selected. The postoperative management of both groups did not differ from a clinical point of view, although oral intake and mobilization tended to occur earlier in the laparoscopic group. Both groups received epidural anaesthesia combined with general anaesthesia for a better control of the postoperative pain. The drug selection for the epidural analgesia and its duration were decided by the anaesthesiology team (usually, for 2–4 postoperative days). All patients were extensively informed and signed a consent form. The study protocol was approved by our Hospital Committee for Ethics and Research.

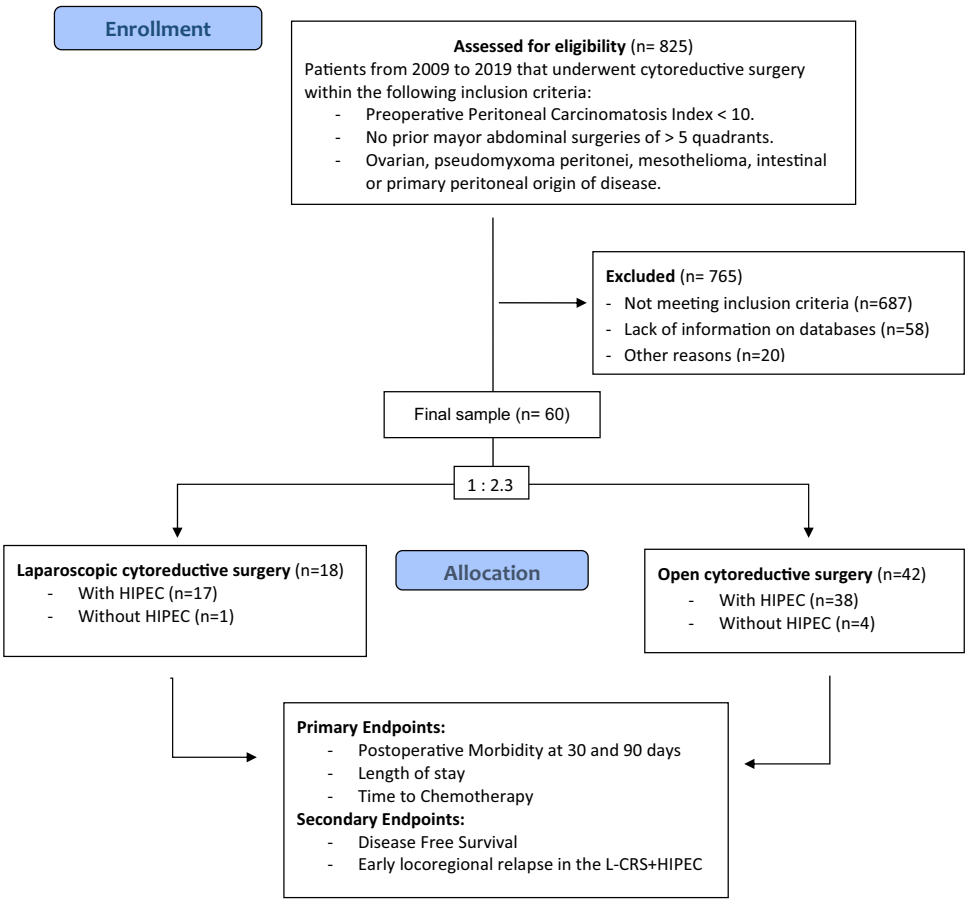

Fig. 1 Flowchart

Description of the surgical technique

All cytoreductive surgeries have been performed by the same team of proficient surgeons at a tertiary referral hospital for locally advanced abdominal cancer.

Open procedure

In brief, CRS + HIPEC is performed as described in previous publications (l). PCI is always assessed to decide whether an optimal resection could be achieved and is based on completeness of the cytoreduction score (CCS). Cytoreductive surgery includes the resection of all visible tumour deposits, with excision of affected organs if necessary, and electrofulguration of millimetric implants on mesenteric and small bowel surfaces. A peritonectomy of the affected serous surfaces is also performed. For malignant gynaecological tumours, a pelvic peritonectomy, hysterectomy plus bilateral adnexectomy are always performed. The total omentectomy is accomplished with a total splenic and hepatic colonic flexure mobilization and the gastroepiploic vessels are preserved as long as they are not involved with the tumour.

The classification of the six peritonectomy procedures was defined by Sugarbaker (Table 1). They have been used for the description of the surgical resections performed.

HIPEC was performed in our centre using the semi-open coliseum technique until 2017, since then we have used the closed technique. Intra-abdominal chemotherapy is administered for 60 min at a temperature of 42 °C. Mitomycin C is used for intestinal tumours with a dose of 30 mg/m^2, for ovarian carcinomatosis, paclitaxel 120 mg/m^2 is the drug of choice, and cisplatin 100 mg/m^2 plus doxorubicin 30 mg/m^2 diluted in 4 L of 1.5% dextrose solution is used for mesothelioma.

Laparoscopic procedure

Patients are placed in the modified Lloyd-Davis position and trocars usually follow the pattern shown in Fig. 2. The patient is carefully fixed to the operating table and soft foams

Fig. 2 Trocars placement for laparoscopic CRS + HIPEC procedure

are used to protect the patient from pressure injuries as full mobilization of the table is needed for complete access.

As with the open approach, we routinely begin with an exhaustive abdominal cavity exploration to calculate the PCI, making use of the operating table's mobilization and of the 30 or 45 degree laparoscope. The decision to continue with the procedure is made only if the PCI is equal or inferior to 10 and if the implants are completely removable by the minimally invasive procedure. No gross diaphragmatic infiltration or multifocal mesenteric implants are considered for this approach. HIPEC is administrated with a closed technique with CO_2 infusion (Biosurgical®). The catheters are introduced by laparoscopic ports with two inflow catheters and two outflow catheters with a continuous flow of 1 L/min. The intra-abdominal level is tested using a transparent device placed in the umbilical port and an intra-abdominal thermometer is also introduced to control the temperature (Fig. 3).

Variables

The primary outcomes analysed were postoperative morbidity at 30 and 90 days, defined by the Dindo-Clavien score, length of hospital stay and wait time to return to the adjuvant systemic chemotherapy (TTC). The secondary outcomes were disease-free survival (time from surgery to the date of documented pathologic or radiographic recurrence of

Table 1 Peritonectomy procedures and visceral resections required to achieve a complete cytoreduction

Peritonectomy	Resections
Left upper quadrant peritonectomy	Greater omentectomy and spleen
Right upper quadrant peritonectomy	Tumour on Glisson's capsule of the liver, round ligament
Anterior parietal peritonectomy	Old abdominal incisions, umbilicus and epigastric fat pad
Pelvic peritonectomy	Uterus, ovaries and rectosigmoid colon
Mesenteric peritonectomy	Right colon and terminal ileum, appendectomy
Omental Bursectomy	Gallbladder and lesser omentum

Adaptation of Sugarbaker's cytoreductive procedures described on Cytoreductive Surgery & Perioperative Chemotherapy for Peritoneal Surface Malignancy: Textbook and Video Atlas

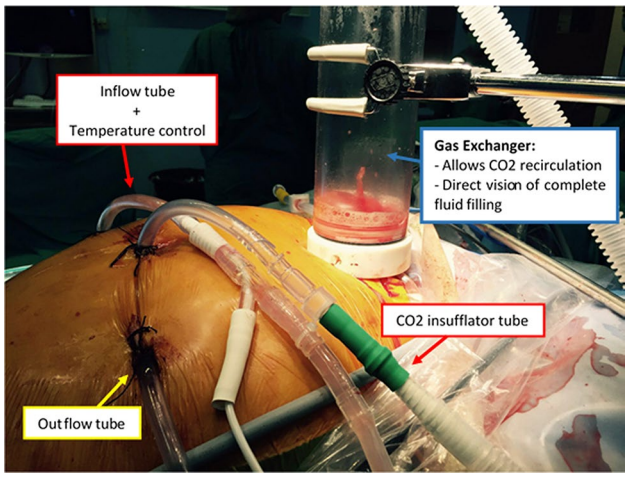

Fig. 3 HIPEC administration by closed technique

disease) and early loco-regional relapse of disease (during the first 12 months after CRS + HIPEC).

Statistical analysis

The normality criteria were tested on the cohort according to the Kolmogorov–Smirnov test. Due to non-normal distribution, we applied the non-parametric Mann–Whitney U test for comparisons of quantitative variables and the Chi Square test for qualitative variables between the L-CRS + HIPEC and the O-CRS + HIPEC. Disease-free survival was estimated using the Kaplan–Meier method. Patients, living or lost to follow-up at data cut, were censored at last contact as per this methodology and the log rank test was used for group comparisons. A p value < 0.05 was considered statistically significative. All statistical analyses were performed with SPSS version 24.0 (SPSS Inc., IBM Corp).

Results

No statistically significant differences were found regarding preoperative and intraoperative features that were considered to assess the homogeneity between both groups (Table 2).

While intraoperative PCI seems to have a higher tendency towards the O-CRS + HIPEC, the number of peritonectomy procedures performed in each group was similar, with a median of 2 procedures in both groups. Three patients, one from the laparoscopy group (L-CRS + HIPEC) and two from the open group (O-CRS + HIPEC), with peritoneal metastasis from endometrial origin in our sample did not receive HIPEC according to the institutional protocol for treatment.

The L-CRS + HIPEC patients had a shorter hospital stay compared to the O-CRS + HIPEC patients, with a median of 4 [2–10] days versus 9 [2–19] days, respectively. We also found significant differences in TTC after surgery, with a median of 4 [3–7] weeks for the laparoscopic patients and a median of 8 [4–36] weeks for the open surgery patients. No differences were found regarding the need for perioperative blood transfusions nor for surgery duration (Table 3).

Morbidity

Postoperative morbi-mortality did not differ between groups. Regarding major morbidities, in the L-CRS + HIPEC group, one patient suffered an obstructive ileus due to a trocar hernia which was resolved with manual reduction plus a primary closure of the fascia using loco-regional anaesthesia. In the O-CRS + HIPEC group, during the first 30 postoperative days, three IIIa-complications had occurred, a wound infection that required surgical debridement, a hydropneumothorax that was treated via thoracentesis and an intra-abdominal abscess that was treated via percutaneous drainage. Two IIIb-complications also occurred in this group, one hemoperitoneum and one evisceration that caused a perforation of the transverse colon.

Considering the cumulative morbidity within 90 postoperative days, no additional morbidity was found in the L-CRS-HIPEC group. In the O-CRS + HIPEC group however, in addition to the previously mentioned, two patients had IIIa-complications: both developed hydroureteronephrosis secondary to postoperative fibrosis that needed ureteral catheterization. Two patients suffered IIIb-morbidities: an enterocutaneous fistulae from an ileum stump and a colovesical fistulae.

Survival

Short term survival rates were similar for the O-CRS + HIPEC group and L-CRS + HIPEC group. After discarding borderline tumours from each group (benign mesothelioma and pseudomixoma, both with considerably better prognosis), disease free survival (DFS) showed no significant differences, with 63.7% of the patients free of relapse at 24 months in the O-CRS + HIPEC group and 71.4% in the L-CRS + HIPEC group. No deaths were registered during the follow-up of the L-CRS + HIPEC patients. In the O-CRS + HIPEC group, 97.3% of the patients were living at 24 months after surgery.

No early loco-regional relapse (< 12 months) occurred in the L-CRS-HIPEC group. However, three patients had disease relapse after the L-CRS + HIPEC. Patient one had lymphatic metastases 13 months later with ovarian carcinoma origins. Patient two had an intra-abdominal recurrence after 19 months of follow-up (also with ovarian carcinoma origins), which was a splenic intraparenchymatous lesion treated by a splenectomy using the laparoscopic approach as

Table 2 Clinical characteristics of patients treated with laparoscopic vs. open cytoreductive surgery

Variables	Laparoscopy surgery ($n=18$)	Open surgery ($n=42$)	p value
Age (years)			
Median (IQR)	56 (51–61)	61.50 (55.5–68.8)	0.176
Body Mass Index [kg/m^2]			
Median (IQR)	26.11 (22.7–29.5)	27.70 (24.68–32.76)	0.15
Histopathology *n*(%)			
Ovarian	6 (35.3)	15 (36.6)	0.904
Endometrial	1 (5.9)	4 (9.8)	
Colorectal	6 (35.3)	13 (31.7)	
Mesothelioma	2 (11.8)	2 (4.9)	
Signet ring cell	0	1 (2.4)	
Pseudomyxoma	2 (11.8)	6 (14.6)	
Previous surgeries *n*(%)			
No	7 (36.8)	18 (42.9)	0.288
1 Region	8 (42.1)	21 (50)	
2–5 Regions	4 (21.1)	3 (7.1)	
> 5 Regions	0	0	
Number of neoadjuvant systemic chemotherapy			0.12
Cycles	[8/18 patients]	[30/42 patients]	
Median (IQR)	4 (3–4)	5 (4–6)	
Radiological PCI			
Median (IQR)	3 (1–3)	2.5 (2–5)	0.076
Intraoperative PCI			
Median (IQR)	3 (2.75–4)	5 (3–7.25)	0.00*
Number of peritonectomy procedures			
Median (IQR)	2 (2–2.25)	2 (2–3)	0.341
Anastomosis *n* (%)			
No	14 (73.7)	20 (47.6)	0.94
1	5 (26.3)	22 (52.4)	
HIPEC *n* (%)			
Paclitaxel	7 (38.9)	17 (40.5)	0.97
Mitomicin C	8 (44.4)	18 (42.9)	
Doxorrubicin + Cisplatin	2 (11.1)	3 (7.1)	
No	1 (20)	4 (9.5)	

IQR interquartile range, *PCI* Peritoneal Carcinomatosis Index

well. Patient three had a hematogenous liver recurrence with colon carcinoma origins that was resected by laparoscopic segmentectomy.

Discussion

In this study we present a comparative analysis evaluating the feasibility and postoperative benefits of L-CRS-HIPEC on selected patients with limited peritoneal disease from varying originations including aggressive histologies. We have found that L-CRS + HIPEC allows the patients to have shorter hospital stays and a quicker return to systemic chemotherapy treatment while maintaining similar oncological outcomes.

The postoperative recovery after a laparoscopy procedure is widely known to be significantly faster, with reduced postoperative pain and postoperative ileus, earlier resumption of solid food and hence, shorter hospital stays. Having become a standardized technique for many major abdominal surgeries, interest continues to grow as high-quality studies have illuminated the feasibility of laparoscopy for proper oncological resections all the while showing no differences regarding port sites, wounds, regional or distant recurrences, or survival rates when compared to open procedures [7–9] and demonstrating a significant decrease in postoperative complications [10, 11]. In our study, no differences in the

Table 3 Postoperative morbidity and oncological results

Variables	Laparoscopy surgery ($n=18$)	Open surgery ($n=42$)	p value
Postoperative morbidity at 30 days			
[Dindo-Clavien ≥ IIIa] *n* (%)	IIIa 1 (5.6)	IIIa 3 (7.1) IIIb 2 (4.7)	0.48
Cumulative postoperative morbidity at 90 days*			
[Dindo-Clavien ≥ IIIa] *n* (%)	IIIa 1 (5.6)	IIIa 5 (11.8) IIIb 4 (9.5)	0.344
Hospital stay (days)			
Median (IQR)	4.5 (4–6)	8 (7–9.5)	< 0.05*
Surgery time (hours)			
Median (IQR)	7 (4.8–8)	5.1 (4.13–6.4)	2.67
Time to chemotherapy (weeks)			
Median (IQR)	4 (3.8–6)	7 (4.8–8)	< 0.05*
Disease free survival (months)			
Median (IQR)	15.5 (8.75–23)	33.5 (12–94.5)	0.53
Perioperative blood transfusion *n* (%)			
Yes	2 (11.1)	5 (23.8)	0.38
No	8 (44.4)	8 (38.1)	
CRP at 4th postop day			
Median (IQR)	103.5 (48.4–161)	143.7 (89–207.9)	0.12
Lactic acid after HIPEC			
Median (IQR)	2.4 (3.5–1.65)	1.9 (4.5–1.1)	0.92

IQR interquartile range, *CRP* C-reactive protein

*Cumulative morbidity at 90 days includes all the complications during the first three postoperative months

postoperative complications or surgical time were identified. However, a tendency for a higher number of complications was identified in the O-CRS + HIPEC.

The benefits of the minimally invasive approach have already been described in the context of cytoreductive surgery when peritoneal metastases are present. Several publications, Esquivel et al. [15, 16], Passot et al. [17] and Parks et al. [18], have reported the feasibility and reliability of laparoscopic cytoreductive surgery in terms of complete resection for locally advanced plus limited peritoneal metastases, initially from low-grade neoplasm such as pseudomyxoma peritonei and benign multicystic mesothelioma. Furthermore, more extensive experience on the satisfactory oncological results of the minimal approach on more prevalent and aggressive originating tumours, like ovarian and colon cancer, continues to come forth [19, 20].

Even though we would initially only consider benign or low-grade tumours for a minimally invasive approach of CRS + HIPEC procedures at our institution, we have improved our understanding and our learning curve for the laparoscopic peritonectomy procedures. The malignant tumour histology is no longer an absolute contraindication for the laparoscopy at our institution. Nevertheless, we lean on the conservative side when determining the indication, especially in the more aggressive varieties.

A remarkable aspect of the laparoscopy approach that we have found in our study is that the faster recovery allows the oncological patients to receive adjuvant systemic chemotherapy treatment sooner than if they had been operated via a xypho-pubic laparotomy. This shorter period to return to chemotherapy treatment is a fundamental tool that has been reported to provide better survival rates as there are no delays after surgery [20–22].

One fundamental criterion when considering the laparoscopic approach, that is shared by most teams, is a limited extension of the peritoneal disease, measured by the PCI. A PCI lower than 10 is the commonly chosen cut-off value [14, 17, 23]. In our study, the PCI comparison between the open and the minimally invasive group resulted in a higher PCI for the open group. In order to reflect comparable operative complexity, we have selected patients for the O-CRS + HIPEC cohort with a PCI lower than 10. Nevertheless, after the analysis of the number of procedures performed in each group, according to the description of Sugarbaker [24], no difference was found.

We are acutely aware that the short follow-up time for the L-CRS + HIPEC is a limitation in our study, as we have first introduced this approach in 2016. However, we would like to point out some preliminary considerations regarding our data.

We have found that no early loco-regional relapse of disease (< 12 months) was identified in the L-CRS + HIPEC patients, which is remarkably suggestive of satisfactory oncological results for laparoscopic procedures in well selected patients, and this is, likewise, supported by publications from other institutions [20, 23, 25].

Intra-abdominal chemotherapy administration with a closed technique has been widely used in open and laparoscopic procedures and its efficacy and benefits are well recognized, allowing better heat preservation, a more homogeneous drug distribution over the surfaces obtained by the CO2 insufflation and higher tissue penetration as a consequence of the elevated intraabdominal pressure induced by pneumoperitoneum [26]. Another novel example of the advantages of the gas pressure is the use of aerosolized chemotherapy sprayed in the carbon dioxide pneumoperitoneum, known as pressurized intraperitoneal aerosol chemotherapy (PIPAC), as a current locally enhanced therapy in the unresectable disease [27].

Our study has methodological limitations. This is a retrospective analysis based on a prospective database. We have followed the same criteria that we currently use to indicate the laparoscopic approach to select similar control patients from our database to design the O-CRS + HIPEC group with a resulting 1:2.3 matching. Furthermore, as inherent to any new technique, our L-CRS + HIPEC sample size is small and the follow-up time is still very short for reliable conclusions about survival. Accordingly, additional large population studies are needed to back up our results.

Conclusions

According to our results, the L-CRS-HIPEC offers patients with limited peritoneal metastasis a shorter hospital stay and a quicker return to systemic chemotherapy when compared with O-CRS-HIPEC. Similar morbidity and survival outcomes have been demonstrated. Our data merit further research into the role of the minimally invasive approach to confirm its benefit in the setting of CRS and HIPEC for peritoneal metastases.

Compliance with ethical standards

Disclosures Drs. Rodríguez, Arjona, Ibañez, Sánchez, Casado, Rufián and Briceño have no conflicts of interest or financial ties to disclose.

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