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A minimally invasive approach for peritonectomy procedures and hyperthermic intraperitoneal chemotherapy (HIPEC) in limited peritoneal carcinomatosis: The American Society of Peritoneal Surface Malignancies (ASPSM) multi-institution analysis

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Abstract

Background Minimally invasive surgery is playing an increasing role in the treatment of patients with gastrointestinal and gynaecological malignancies as the data show reduced morbidity, faster recovery and similar oncological outcome when compared to open procedures.

Materials and methods The American Society of Peritoneal Surface Malignancies (ASPSM) conducted a retrospective study to analyse peritonectomy procedures and HIPEC done via the laparoscopic route. A database with standard clinical and pathological parameters was set up and distributed amongst ASPSM members. Rate of relapse, morbidity and mortality were the primary endpoints of the study.

Results A total of 90 patients from 7 centres around the world were identified. Sixty percent were female. Mean age was 50 years. Peritoneal carcinomatosis from appendiceal origin was the most common diagnosis in a 64.9% of patients and colon origin was diagnosed in 16.5% of patients. Mean peritoneal cancer index (PCI) was 4.1 (0–10). Forty-one percent of patients had a bowel resection. Mean operative time was 4.7 h (2.5–8). All patients had a complete cytoreduction and HIPEC. Grade 3 and 4 morbidity was 3.0 and 6.5%, respectively. The most common reason for re-operation was an internal hernia in 2 out of 5 cases. Operative mortality and re-admission rates were 0 and 5%, respectively. Mean hospital stay was 7.4 days (1–18). At a mean follow-up of 31.6 months, 15/90 patients have a disease relapse but loco-regional relapse was identified in only five patients.

Conclusions Analysis of these data suggests that minimally invasive approach for peritonectomy procedures and HIPEC is feasible, safe and should be considered as part of the armamentarium for highly selected patients with peritoneal surface malignancies with limited tumour burden, defined as PCI of 10 or less and borderline tumours as low-grade pseudomyxoma and benign multicystic mesothelioma.

Keywords Hyperthermic intraperitoneal chemotherapy (HIPEC) · Cytoreductive surgery (CRS) · Laparoscopic surgery

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Over the past two decades, the role of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in the management of patients with peritoneal surface malignancies of gastrointestinal, gynaecological or peritoneal origin has continued to evolve, but this procedure is considered a major surgery with high morbidity and mortality rates. During this period, this multi-modality therapy has improved as a consequence of better patient selection, better systemic chemotherapy and a deeper understanding of the natural history of this particular route of dissemination [1]. These improved outcomes have changed the patterns of referral from community-based medical oncologists to the surgical oncologists with a growing number of patients with limited peritoneal metastases being referred to centres that perform cytoreductive surgery and HIPEC.

Also, over the past two decades, surgeons' experience with advanced laparoscopic and robotic skills has been growing around the world. The application of minimally invasive approaches to the resection of benign and malignant tumours has become standard practice with numerous studies demonstrating that this approach is feasible and safe and, in many cases, associated with shorter hospital stays, reduced morbidity and similar oncological outcomes when compared to open procedures in colorectal [2], hepatic [3] and early stages of oesophageal–gastric malignancies [4].

When it comes to the field of peritoneal surface malignancies, studies have shown that laparoscopy is safe and accurate to evaluate peritoneal surface metastases prior to cytoreductive surgery, that the laparoscopic peritoneal cancer index (PCI) is similar to the PCI at laparotomy in advanced-stage ovarian cancer [5] and that the laparoscopic approach can be used for cytoreductive surgery to palliate metastatic disease [6, 7] and to provide staged HIPEC in patients that had an open cytoreductive surgery [8].

Park et al. [9] reported their experience with laparoscopic cytoreductive surgery and early postoperative intraperitoneal chemotherapy for patients with colorectal cancer peritoneal carcinomatosis with safety results. However, the experience with laparoscopic approach in cytoreductive surgery and HIPEC has been reported by Esquivel et al. [10, 11], Passot et al. [12] and Arjona-Sanchez et al. [13], and they have included patients with low-grade pseudomyxoma peritonei (PMP), benign multicystic mesothelioma (BMM) and limited ovarian and colon carcinomatosis.

The purpose of this manuscript is to report the results of a multi-institution retrospective study by The American Society of Peritoneal Surface Malignancies (ASPSM) evaluating the morbidity and mortality of cytoreductive surgery and HIPEC done via the laparoscopic route in patients with minimal peritoneal metastases, defined as a PCI of 10 or less.

Patients and methods

Patient selection

The American Society of Peritoneal Surface Malignancies (ASPSM) established a standard database for the retrospective collection of data on patients undergoing laparoscopic CRS and HIPEC for a variety of peritoneal surface malignancies. In addition to standard demographic, clinical and histopathological data, patients were analysed based on the peritoneal cancer index (PCI), the completeness of cytoreduction score and the agent used for the HIPEC therapy. Morbidity and mortality were the primary endpoints of the study. All data were collected following the established guidelines for data collection at each institution.

Cytoreductive surgery and HIPEC

Patients with the diagnosis of a peritoneal surface malignancy (PSM) and no evidence of gross peritoneal metastases on imaging studies went to the operating room for a diagnostic laparoscopy. All the patients have signed the informed consent. The procedures continued via the laparoscopic route only if the PCI at the time of exploration was 10 or less and the surgeon thought that the peritoneal metastases could be removed laparoscopically. The specifics of techniques for the laparoscopy, cytoreductive surgery and HIPEC delivery were according to each individual centre and some have been previously reported [10–13].

Completeness of cytoreduction score

The completeness of cytoreduction score constitutes a major prognostic indicator for survival in patients with PSM undergoing CRS and HIPEC. It is assessed at the completion of the cytoreductive surgery. A completeness of cytoreduction score of zero (CC-0) is assigned when there is no visualized peritoneal seeding within the operative field. CC-1 indicates peritoneal nodules < 2.5 mm persisting after cytoreduction. CC-2 indicates nodules between 2.5 and 2.5 cm, whereas a CC-3 score indicates nodules > 2.5 cm at any site within the abdomen or pelvis. CC-0 and CC-1 were each considered an optimal cytoreduction and CC-2 and CC-3 are designated as incomplete cytoreductions [10, 11].

HIPEC procedure

The technique for delivering intraperitoneal chemotherapy via the laparoscopic approach was done according to the protocol of each centre. Some of them have been described before [10–13]. All the HIPEC procedures were

carried out by closed technique introducing the cannulas through the laparoscopic ports. The perfusion machine was selected following the local protocol in each centre. The time of perfusion varied between 60 and 90 min. The intracavity temperature was 42–43 °C. The drugs used are described in Table 1.

Statistics

The data collected were analysed using SPSS for Windows (version 21.0). Patient characteristics were reported using frequency and descriptive analyses. The Kaplan–Meier method was used to analyse survival. Median time to death was defined as the time where 50% of patients have died. Follow-up was calculated from the date of CRS and HIPEC to the date of last follow-up. $P < 0.05$ was considered statistically significant.

Results

Only 7 centres belonging to ASPSM have initiated the minimally invasive approach for limited peritoneal carcinomatosis. A total of 90 patients from these centres were identified from January 2007 to December 2017. The demographic and clinical characteristics are shown in Table 2. The mean age was 50 (17–78) years. Median BMI was 26.7 kg/m^2 (16–54.2). Eighty-one of 90 patients (89.1%) had prior abdominal surgery with 65% of them having had a previous laparoscopic procedure and 24% a previous open procedure. Mean operative time was 4.7 h (2.5–8). Mean peritoneal cancer index (PCI) was 4.1 (0–10). All patients had a complete cytoreduction (CC0) and HIPEC completed via the laparoscopic route. Forty-one percent of patients had a bowel resection. Median blood loss was 94 ml (20–350). Mean length of hospital stay was 7.4 days (1–18). Mitomycin C as the major agent of HIPEC was used for 59 patients (64.9%). Oxaliplatin was given for 19 patients (21.1%). Combination chemotherapy was used for 10 patients (11%) and paclitaxel in 2 patients (2.2%) (Table 1).

Table 1 Cytostatics used in laparoscopic HIPEC procedures

Agent	Number	%
Mitomycin C	59	64.9
Oxaliplatin	19	21.1
Cisplatin + Doxorubicin	9	9.9
Cisplatin + Mitomycin C	1	1.1
Paclitaxel	2	2.2

Table 2 Demographic, clinical and perioperative features

Number of patients (*n*)	90
Mean age	50 (17–78)
Gender	
Male	34
Female	56
Previous surgery	
No	9
Yes	81
Mean body mass index (BMI)	26.7 (16–54)
Mean peritoneal cancer index (PCI)	4.1 (0–10)
Complete cytoreduction	
Yes	90
Complete HIPEC	
Yes	90
Bowel resection	
No	52
Yes	38
Type of resection	
Caecectomy	7
Colectomy	16
Ileo-colic anastomosis	3
Small bowel	2
Recto-sigmoidectomy	7
Partial gastrectomy	2
Splenectomy	1
Mean estimated blood loss	94 ml (32–152)
Mean blood transfused	0
Mean duration of surgery	4.7 h (2,5–8)
Grade 3 complications	
No	87
Yes	3
Grade 4 complications	
No	84
Yes	6
Mean length of hospital stay	7.4 days (1–18)
Mean follow-up	32 months
Mortality	0

Table 3 Re-operation reasons

Re-operation reasons	*N* = 5	5.5%
Drainage of pelvic haematoma	1	1.1%
Internal hernia	2	2.2%
Laparoscopic drainage of sub-hepatic abscess	1	1.1%
Trocar port hernia with obstruction	1	1.1%

Surgical morbidity

Grade 3 and 4 morbidity was 3.0 and 6.5%, respectively. The most common reason for re-operation was an internal hernia in 2 out of 5 cases (Table 3). Grade 3 complications were 2 pleural effusions with need of thoracic drainage and a pelvic abscess with need of percutaneous drainage. Operative mortality and re-admission rates were 0 and 5%, respectively.

Pathological findings

The number histology distribution was as follows: appendiceal cancer—59 (64.9%), 53/59 of appendiceal cancers were identified as low-grade pseudomyxoma from an appendiceal cystadenoma; colorectal cancer—15 (16.5%); BMM—10 (11%); cholangiocarcinoma—1 (1.1%); goblet cell carcinoid—1 (1.1%); goblet cell carcinoid—1 (1.1%) and ovarian carcinomatosis—4 (4.4%) (Table 4).

Table 4 Pathological findings

Event	Number	%
Appendiceal cancer	59	64.9
Low grade	53	58.3
High grade	4	4.4
Signed ring cell	2	2.2
Colon carcinoma	15	16.5
Benign multicystic mesothelioma	10	11
Cholangiocarcinoma	1	1.1
Goblet cell carcinoid	1	1.1
Ovarian carcinoma	4	4.4

Survival analysis

At a mean follow-up of 32 months, 15/90 (16.5%) patients have developed recurrent disease. One patient had a low-grade appendiceal tumour and experienced a local recurrence. The rest of the recurrences were in patients with invasive carcinomas: colon cancer in 8 of 15, high-grade appendiceal cancer 4/4, signet ring appendiceal tumour 1/2 and one cholangiocarcinoma. Eight patients out of 15 experienced a systemic recurrence and five had a loco-regional relapse (Table 5). Median survival has not been reached but the OS was 100% at 5 years in most of the patients except that for the colon carcinoma the 5-year OS was 64% and for the cholangiocarcinoma the survival was 12 months after HIPEC procedure (Fig. 1).

Discussion

Laparoscopic approach for abdominal neoplasms has gained in popularity in recent years and is now considered the gold standard approach in many cases. Earlier concerns included the hypothesis of greater risk of intraperitoneal dissemination of cancer cells during laparoscopic versus conventional technique. However, prospective randomized trials have shown that there are no differences in port site or wound recurrence, in distant recurrence related to tumour cell dissemination and seeding [14], and in survival in patients undergoing laparoscopic surgery for primary colon cancer [15].

Table 5 Descriptive information of the patients with disease relapse after cytoreductive surgery and peritonectomy plus HIPEC by laparoscopic approach

Patient	Tumour origin	PCI	Relapse	Follow-up (m)	Status
01	Colon carcinoma	9	Systemic recurrence	24	Death
02	Appendix low grade	6	Local recurrence	72	Alive
03	Colon carcinoma	7	Systemic recurrence	60	Alive
04	Colon carcinoma	6	Systemic recurrence	38	Death
05	Colon carcinoma	5	Systemic recurrence	39	Alive
06	Colon carcinoma	6	Systemic recurrence	30	Alive
07	Colon carcinoma	0	Local recurrence	34	Alive
08	Appendix signet ring core	2	Local recurrence	48	Alive
09	Appendix high grade	8	Local recurrence	46	Alive
10	Appendix high grade	5	Systemic recurrence	5	Alive
11	Colon carcinoma	3	Local recurrence	10	Alive
12	Cholangiocarcinoma	10	Systemic recurrence	12	Death
13	Colon	5	Systemic recurrence	13	Death
14	Appendix high grade	1	Local recurrence	7	Alive
15	Appendix high grade	6	Local recurrence	18	Alive

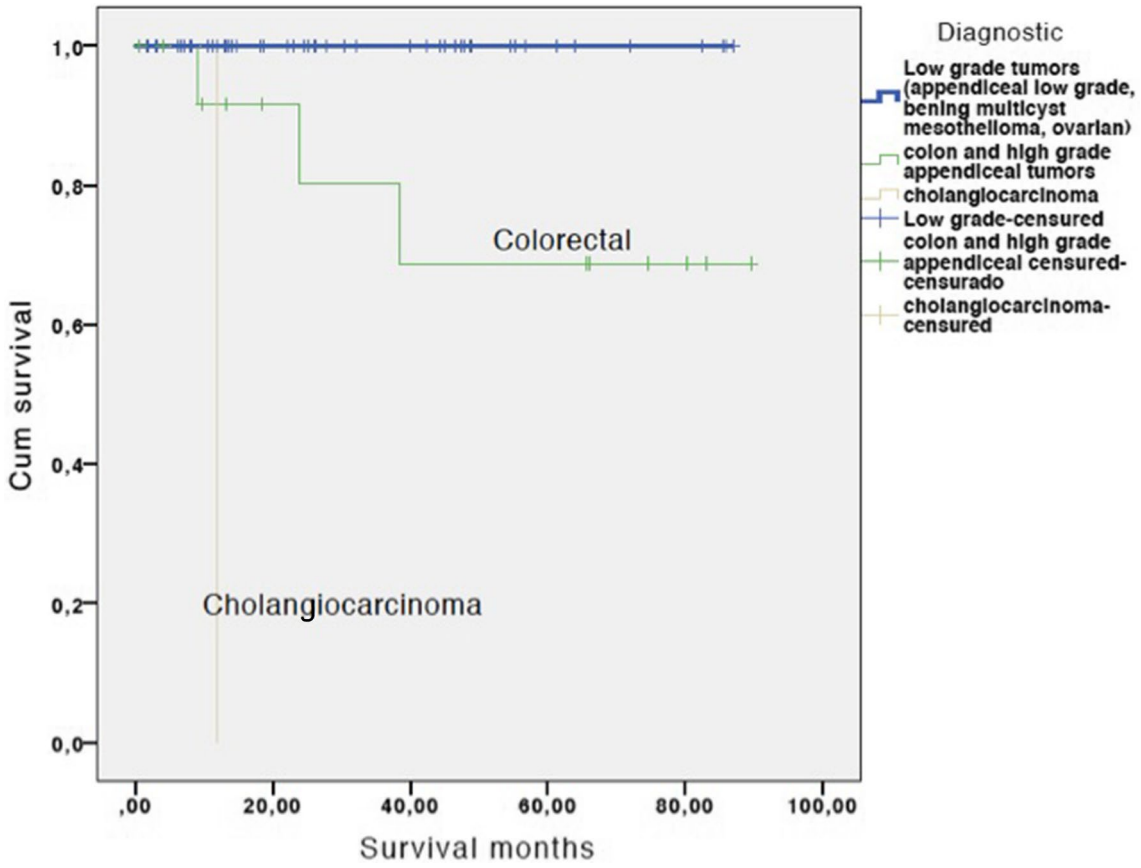

Fig. 1 Kaplan–Meier survival curve stratified by diagnostics in patients with cytoreductive surgery and HIPEC by laparoscopic approach

Laparoscopy and peritoneal surface malignancies

The role of laparoscopy in the field of peritoneal surface malignancies has had growing acceptance with some of the most common indications including palliation of intractable ascites, palliation of intestinal obstruction, evaluation of responses to neoadjuvant chemotherapy in patients with established high-grade carcinomatosis, and as a staging tool to determine if patients are candidates for CRS + HIPEC [5–7, 16]. Laparoscopy has also been performed in patients with unresectable PMP as a palliative therapy complementary to systemic chemotherapy. This approach allows for the introduction of proper suction devices that can assist with the evacuation of mucinous ascites, which is very difficult to drain with routine paracentesis because of the viscosity of the fluid. This technique is a feasible approach that results in significant, durable symptom control with minimal morbidity [17]. Neoadjuvant laparoscopic HIPEC has also been proven effective for ascites eradication and PCI reduction in ovarian carcinomatosis [18].

The first laparoscopic peritonectomies and HIPEC were tested in the pig model, reporting it to be technically feasible. Furthermore, the presence of the pneumoperitoneum penetration was shown to make the identification and dissection of the peritoneal layer easier [19]. Several studies have demonstrated increased drug penetration into the tissues with the laparoscopic HIPEC technique, supporting the hypothesis of the role of the increased intra-abdominal pressure induced by pneumoperitoneum on drug pharmacokinetics, with faster absorption and higher penetration of the chemotherapeutic agents [20–23]. Some others postulate a cytotoxic effect of CO_2 on malignant cells [24].

Laparoscopic cytoreductive surgery and HIPEC indications and safety

Although reports on the feasibility of combining laparoscopic cytoreductive surgery with HIPEC in humans remain limited, some experienced cytoreductive surgical groups have reported similar efficacy and safety using this technique when compared to the open approach. Esquivel et al. [10] and Passot et al. [12] have suggested that this minimally invasive approach should be reserved for patients with borderline malignancies like low-grade PMP and benign multicystic mesothelioma with limited peritoneal dissemination, PCI of 10 or less. In our study, the indications have been

more generalized and the only two absolute requirements were to have a PCI of 10 or less and to be able to achieve a complete cytoreduction, as Arjona-Sanchez et al. [13] suggested. Because of this methodology, 28% of the patients had a more aggressive, invasive peritoneal surface malignancy. Severe morbidity, defined as Grade 3 or higher, was 9.9% in this study. This rate compares favourably to reports from other high-volume tertiary centres doing an open approach and reporting rates of grade III/IV morbidity ranging from 12 to 58% and mortality rates of 0.9–5.8% [25]. These improved results from our study could be explained by the fact that only patients with limited PCI (10 or less) were considered for a laparoscopic approach. Similarly, when compared to the open approach with a large midline incision, laparoscopic surgery decreases wound morbidity and length of hospital stay and allows for an early recovery [12, 13]. In our study, the length of hospital stay was 7.4 days.

Recurrence and survival

The recurrence and survival rates reported in our study compare favourably to those reported by others utilizing the open approach for cytoreductive surgery and HIPEC. At a mean follow-up of 32 months, the rate of overall recurrence was 16.5%. Most of the recurrences were systemic and, as reported in Table 5, most of them occurred in patients with invasive peritoneal surface malignancies. Only one out of 62 patients with non-invasive disease (DPAM and BMM) had a local recurrence 72 months after the procedure and, at the end of the study, all 62 patients were alive. In patients with more aggressive and invasive peritoneal surface malignancies like colon cancer, the 5-year OS of 64% appears to be in accordance with other reports; Elias et al. [26] reported a 44% 5-year OS in patients with colon cancer with a PCI <6.

Limitations of laparoscopic approach in cytoreductive surgery and HIPEC

One of the most important limitations of laparoscopic cytoreductive surgery is the ability to perform a thorough exploration of the entire abdomen and pelvis to determine a true PCI [12]. Some areas like the root of the small bowel mesentery or the diaphragmatic peritoneum behind the liver and spleen could be difficult to explore. However, some studies have reported a similar efficacy between open and laparoscopic approaches in the PCI calculation [27, 28]. Despite these reports, we believe that the current stage regarding the experience with this minimally invasive approach allows us to recommend it only for patients with minimally invasive peritoneal surface malignancies. The consequences of missing small peritoneal tumour nodules in patients with more invasive malignancies can have a significant impact on the overall prognosis [29, 30]. For patients with low-grade tumours and previous limited and laparoscopic CRS, indolent recurrences can be detected with regular follow-up and could be treated with an iterative procedure with an open approach or a new laparoscopic approach.

Conclusions and future directions

There are limitations of the current study that are inherited to the retrospective nature of the study: the fact that there was no standardized method to deliver the HIPEC component and the small number of patients from different centres. The present study has collected the initial experience of laparoscopic cytoreductive surgery and HIPEC from seven centres belonging to the American Society of Peritoneal Surface Malignancies (ASPSM). The results demonstrate that this minimally invasive approach is feasible and safe in a highly selected group of patients with peritoneal surface malignancies that includes patients with low-grade tumours with limited peritoneal dissemination, defined as a PCI of 10 or less.

Further studies are needed to evaluate this approach in patients with high-grade tumours with limited peritoneal dissemination. We believe that genomic profile analysis and better understanding of the intracoelomic route of dissemination in patients with high-grade malignancies, coupled with improvements in the radiological and intraoperative detection of peritoneal tumour nodules, might benefit this group of patients with Stage IVB, from a minimally invasive approach with decreased morbidity and early recovery, allowing them to return to their improved systemic therapies that will maintain the complete surgical response achieved via a laparoscopic cytoreductive surgery with HIPEC.

Compliance with ethical standards

Disclosures Drs A. Arjona-Sanchez, J. Esquivel, O. Glehen, G. Passot, K. K. Turaga, D. Labow, S. Rufian-Peña, R. Morales and K. van der Speeten have no conflicts of interest or financial ties to disclose.

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