Diagnostic Laparoscopy in the Pre-operative Assessment of Patients Undergoing Cytoreductive Surgery and HIPEC for Peritoneal Surface Malignancies

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Abstract The introduction of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has led to an improvement in the survival of select patients with peritoneal surface malignancies (PSM). However, it is important to carefully identify patients who will benefit from this procedure and to avoid an unnecessary laparotomy in those who will not. The currently available imaging modalities are unable to accurately predict the peritoneal cancer index (PCI) score or the completeness of cytoreduction. In this article, we review the current status of staging laparoscopy in the assessment of patients with PSM who are planned for CRS & HIPEC. We discuss the patient selection, techniques, complications and efficacy of staging laparoscopy. To summarise, staging laparoscopy is a safe and feasible method of pre-operative assessment of patients with PSM. It has a high sensitivity and positive predictive value in identifying patients who can undergo a complete cytoreduction, thereby preventing many patients from undergoing an unnecessary laparotomy. With the exception of pseudomyxoma peritonei, it should be considered as a part of the routine assessment of patients with PSM who are being considered for CRS & HIPEC.

Keywords Cytoreductive surgery · Hyperthermic intraperitoneal chemotherapy · Staging · Laparoscopy · Peritoneal metastasis · Pseudomyxoma peritonei

Introduction

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is now being increasingly used in the management of peritoneal surface malignancies (PSM). This has led to a long-term survival in a select group of patients with PSM [1]: 10-year survival of 63 % in pseudomyxoma peritonei (PMP) [2], 5-year survival rates of 47 % in peritoneal mesothelioma (PM) [3], 27 %–42 % in peritoneal metastasis from colorectal cancer [4–6] and 6.7 %–13 % in peritoneal metastasis from gastric cancers [7, 8].

However, CRS & HIPEC is not only expensive and resource consuming, but is also associated with a morbidity and mortality ranging from 12 % to 67 % and 0 % to 9 % respectively [9, 10]. Further, not all patients with PSM benefit from this procedure. The two most important factors that predict good outcomes after CRS & HIPEC are the extent of peritoneal disease and the ability to completely remove all macroscopic disease surgically [11–14]. Although various scoring systems have been described to assess the extent of peritoneal disease, currently the most commonly used method is the Peritoneal Cancer Index (PCI), proposed by Sugarbaker et al. [15]. The PCI score is used as a selection criterion for performing CRS and HIPEC [16] and is usually calculated intra-operatively after releasing all adhesions and a thorough examination of the abdomen. In PMP, two large studies have shown that even though a 5 year survival of >50 % was observed in patients with a PCI score of >19, it was still significantly less than the survival of patients who had a PCI score of <19 [2, 17]. Each additional point of PCI increased the relative risk of death by 4.2 % [17]. Similarly, a PCI score of >20 in colorectal cancers and >10 in gastric cancers has been identified as an independent poor prognostic factor in patients undergoing CRS and HIPEC [8, 18]. A multi-institutional

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study of peritoneal mesothelioma reported that a PCI >20 was a significant factor predicting 5-year survival after CRS and HIPEC in univariate analysis, but not in multivariate analysis [3].

The adequacy of the cytoreduction can be assessed only at the completion of surgery by the completeness of cytoreduction score (CCR). Accordingly, CCR-0 indicates the absence of any macroscopic residual disease, whereas CCR-1, CCR-2 and CCR-3 indicate the presence of residual nodules ≤ 2.5 mm, 2.5 mm to 2.5 cm and >2.5 cm respectively [19]. HIPEC is useful only when complete macroscopic cytoreduction is achieved [20]. A CCR score of 0/1 has been shown to be an independent prognostic factor in PMP [2, 17], PM [3], colorectal cancer [21] and gastric cancer [7, 8]. Besides, the PCI score is also associated with the ability to achieve a CCR0 resection. Yonemura et al. reported complete cytoreduction in 86 %, 39 % and 7 % of patients with GCPC if the PCI score was ≤ 6 , >7 and >13 respectively [22].

Although the CCR score cannot be reliably estimated pre-operatively, it is logical that the ability to achieve a complete cytoreduction depends primarily on the distribution of disease within the peritoneal cavity [23]. The most important factor that would preclude the ability to achieve a complete cytoreduction is massive involvement of the small bowel or its mesentery which would require extensive resection of the small bowel [24]. In addition, in colorectal peritoneal carcinomatosis, presence of biliary or ureteric obstruction or large volume disease in the gastrohepatic ligament is generally associated with inability to achieve complete cytoreduction [16]. Hence, pre-operative assessment becomes crucial in choosing patients for CRS and HIPEC [25].

Pre-operative Assessment

A consensus statement from the Peritoneal Surface Oncology Group International considered computerised tomography (CT) scan as the primary imaging modality in peritoneal surface malignancy [26]. However, a CT scan cannot accurately predict the ability to achieve a complete cytoreduction, except in patients with PM, where a > 5 cm mass in the epigastric region and loss of normal architecture of the small bowel and its mesentery on CT scan has been shown to accurately predict an incomplete cytoreduction [27]. In general, the sensitivity of a CT scan in detecting peritoneal disease varies from 60 %–93 % [28]. This depends on the size of the peritoneal nodule and its location. While CT scan can detect a nodule >5 cm in 59 %–94 % cases, the sensitivity in detecting a lesion <1 cm is only 9 %–28 % and for identifying lesions <0.5 cm is only 11 % to 28 % [29–31]. A CT scan underestimates the size of a peritoneal deposit in 33 % of patients [31]. In one report, there was a statistically significant difference in the lesion size score estimated on CT and during surgery in most compartments within the abdomen except epigastrium, left upper and left

flank regions [31]. The sensitivity of a CT scan in detecting small bowel involvement and mesenteric involvement is low and ranged between 8 %–17 % in one series [31] and 18 % to 55 % in another [30]. In a prospective multi-institutional study using PCI calculated on the basis of pre-operative CT scan (CT-PCI), significant inaccuracies of the CT based assessment of the size of the peritoneal lesion was observed in all 13 regions of the abdomen, with the least sensitivity in the distal jejunum and distal ileum (64 % and 59 % respectively).

The clinical accuracy of a CT scan in estimating the true PCI is reported to be around 88 %, whereas it underestimates the true PCI in nearly 33 % of patients [32]. In a multi-institutional study, Esquivel et al. observed that CT scan underestimated a true PCI score of >20 in 12 % of patients with colorectal cancer who would therefore have had an unnecessary laparotomy [32]. Koh et al. reported that the mean intra-operative PCI was almost double the PCI estimated by a CT scan [31].

Although an MRI scan has been reported to have a sensitivity of 87 % and a negative predictive value of 73 % in detecting peritoneal carcinomatosis per segment of the abdominal cavity [33], it is not uniformly available, is costly and is highly operator dependent and therefore not commonly used for evaluating peritoneal carcinomatosis [34]. An [^{18}F]FDG positron emission tomography scan (PET-CT) has been reported to have a sensitivity of 58 %–100 % in detecting peritoneal metastasis [34, 35]. However, it may not be sensitive in small tumors, mucinous tumors or in gastric cancers. The positive predictive value of a PET-CT to assess completeness of cytoreduction is around 27 % [36].

The best method to assess the PCI and thereby assess resectability is by direct visualisation intra-operatively [23, 32, 37]. However, 20 %–40 % of patients who are operated with the intent of CRS and HIPEC are finally declared inoperable at laparotomy [37, 38]. An unsuccessful laparotomy for abdominal malignancies has been reported to have a morbidity of 12 % to 23 % and mortality of 20 to 36 % [39]. An unnecessary laparotomy is not only a financial burden on the patient, but also strains the resources of the hospital, delays institution of other methods of treatment, not to mention the psychological impact on the patient and their care givers. Therefore, careful patient selection for CRS and HIPEC is necessary to achieve good results both in terms of reduced postop complications and improved survival, thus avoiding an unnecessary laparotomy [40].

Role of Staging Laparoscopy

A staging laparoscopy has been shown to reduce the number of unnecessary laparotomies in intra-abdominal malignancies [41]. A prospective comparison of laparoscopy and CT scan showed that in a series of patients in whom a CT scan identified peritoneal disease in only 47.8 %, subsequent

laparoscopy detected peritoneal spread in 100 % of the patients [42]. Diagnostic laparoscopy was generally considered unfeasible in PSM due to various factors including incomplete assessment due to previous surgical adhesions or hostile abdomen due to large peritoneal disease and port site recurrence [26, 43]. In an expert consensus statement at the Fifth international workshop on peritoneal surface malignancies, less than 10 % of the voters considered laparoscopy to be a fundamental investigative modality in the preoperative evaluation of a patient with peritoneal malignancy whereas 78 % felt that it was useful but not a fundamental method [26]. In a multi-institutional study comprising over 1200 patients treated by CRS and HIPEC, a laparoscopy was used to diagnose/stage the disease in only 8.8 % of the subjects [1]. The earliest series assessing the feasibility of laparoscopic assessment for PSM in 48 patients was reported by Garofalo et al. in 2003 [44]. Since then, there have been only a handful of reports describing the usefulness of a staging laparoscopy in identifying patients who will benefit from CRS and HIPEC [37, 38, 40, 43, 45–49]. While one series performed a staging laparoscopy on all consecutive patients who were planned for CRS and HIPEC except for PMP with massive mucinous ascites [37], others excluded patients from a staging laparoscopy if a recent surgical evaluation was done before referral and the disease appeared amenable to CRS according to the referral notes and imaging [38, 48]. All the series had a mix of PSM like ovarian, gastric and colorectal and appendiceal PC, PMP, mesothelioma etc. except two in which only patients with either mesothelioma [46] or PMP [47] were included.

Success and Complications of Staging Laparoscopy

The operative details and complications are shown in Table 1. Most published series report a high rate of successful laparoscopic evaluation of PC even though a majority of patients in these series had undergone at least one prior laparotomy. The reasons for an unsuccessful laparoscopic assessment included extensive adhesions or massive peritoneal thickness [37, 40, 48]. Laparoscopic evaluation could be done in a short time and with minimal complications. No mortality was reported in any series. None of the reported complications including perforation of the bowel or diaphragm necessitated a conversion to laparotomy. A port site recurrence was not reported in any series except in one patient with a PMP [47] which was subsequently resected.

Technique

The technique of staging laparoscopy varied slightly in these series. Pneumoperitoneum was created either using the optical trocar, the Veress needle or an open Hasson's technique. The site of placement of the first trocar also varied. Although the general tendency was to avoid previous scars, some authors

Table 1 Published series on laparoscopic staging for peritoneal surface malignancies

Author, Year	No. of patients	Prior laparotomy	Timing of laparoscopy	Median interval between laparoscopy and CRS (weeks)	No. of successful laparoscopic assessments	Median operating time (min)	Median hospital stay after laparoscopy	No. of complications	No. of port site recurrences
Pomel et al. 2005	11	Yes	Separate	12.7 (range 4–21)	11 (100 %)	38 (range 23–75)	1.7 days	2 (1.8 %)	NS
Valle et al. 2006	97	Yes (100 %)	Separate	NS	96 (98.9 %)	30 (range 15–45)	NS	2 (2.06 %)	Nil
Garofalo A et al. 2009	197	Yes (71.5 %)	Separate	NS	196 (99.4 %)	30 (range 15–45)		4 (2.04 %)	Nil
Laterza et al. 2009	33	NS	Separate	NS	33 ^a (100 %)	40 (range 20–60)	NS	Nil	Nil
Iversen et al. 2013	45		Separate	4 (0–13)	43 ^b (95.5 %)	NS	1 day (range 1–2 days)	1 (2.2 %)	NS
Valle M et al. 2012	351	Yes	Separate	NS	350 (99.7 %)	30 (range 15–45)	NS	5 (1.4 %)	Nil
Jayakrishnan TT et al. 2014	70	Yes	Concurrent/separate	NS	63 (86.3 %)	NS	NS	NS	Nil
Tabrizian P et al. 2015	217	Yes	Concurrent 89 % Separate 11 %	NS	211 (92.6 %)	NS	NS	1 (0.4 %)	Nil

NS not specified

^a Patients with incomplete laparoscopic evaluation excluded

^b In 10/43 patients, all regions could not be assessed

reported an umbilical [38, 46] or a midline entry [37], while others used the right or left iliac fossa [43, 45], right or left upper quadrants [49] or a left subcostal entry [48]. While most preferred a 30° scope, Pomel et al. used a 0° scope [38]. An additional 1 to 3 ports (5 mm or 10 mm) were used according to the surgeon's discretion inserted either in the flanks [43, 46] or in the midline [37, 38]. While placing all ports in the midline ensures excision of the port sites by a midline incision thus eliminating port site recurrences, placing the ports laterally helps to avoid iatrogenic bowel injury during entry, especially if there are extensive adhesions from a previous surgery or massive tumor infiltration of the midline [40, 43]. In case of a massive omental cake, placing the ports in the iliac fossa can give a better visualisation. An ultrasound imaging may also help to guide placement of the ports [40, 43].

The ascitic fluid is suctioned out to enable better visualisation and sent for cytological examination. Adhesiolysis is kept to a minimum to avoid bowel injury, but at the same time adequate to perform a complete assessment [40, 46]. A biopsy is taken for confirming the diagnosis if this has not been done so previously. Diaphragmatic biopsies that may cause perforation and provoke infiltration of the muscular wall should be avoided [40, 43]. In order to make a complete assessment of all regions of the peritoneal cavity, the table is tilted to 4 positions- steep left and right Trendelenburg and steep left and right reverse Trendelenburg [37, 38, 40]. In case of dense midline adhesions, two separate access may be made on either side of the midline [40]. A laparoscopic ultrasound may be useful in assessing the depth of diaphragmatic involvement, pancreatic involvement and evaluation of suspicious liver metastasis or suprahepatic vein involvement. The PCI should be scored for each region and the total PCI calculated.

Outcomes

The reliability and efficacy of laparoscopic staging is shown in Table 2. Laparoscopic staging helped to exclude 7 %–41 %

patients with disease not amenable for CRS from an unnecessary laparotomy. The reasons for excluding patients from CRS by laparoscopic assessment included extensive infiltration of the small bowel (>1/3rd length) or its mesentery [37, 38, 45, 46, 48, 49], a high PCI or no evidence of carcinomatosis [48, 49]. Only one study has compared the PCI scored at laparoscopy (median 13, range 4–21) to that scored at laparotomy for the CRS (median 20, range 11–27) [38]. This underestimation of the PCI could have been due to the median delay of nearly 3 months between the two procedures, although it did not contribute to unresectability. In another study comprising of patients with PMP, the mean PCI at laparoscopy was 16.5 ± 6.4 in 11 patients. At the time of second look laparotomy after a mean interval of 97 ± 40 days, the mean intraoperative PCI was 12.9 ± 7.1 . However, these patients had a laparoscopic HIPEC at the time of the preliminary laparoscopy and the discordance between the two PCI values could have been due to the effect of HIPEC [47]. The positive predictive value of laparoscopy (percentage of patients predicted to undergo a complete cytoreduction by laparoscopy who actually underwent a complete cytoreduction) ranged from 63 % to 98 % whereas the sensitivity (percentage of patients undergoing complete cytoreduction who were correctly predicted by laparoscopy) was 100 %. Only one series reported the ability of laparoscopy to correctly identify patients who could not undergo a complete cytoreduction (negative predictive value of 100 %) [46]. The extent of PC was overstaged by a laparoscopy in 4.4 % of patients in one series [37] whereas it was understaged in 1.4 %–12.5 % of patients in most series, resulting in an incomplete cytoreduction in most of these patients. The reasons for understaging included deep diaphragmatic invasion, infiltration of the hepatic pedicle/celiac axis [37, 38], extensive small bowel involvement not recognised on laparoscopy [37, 38, 46], pancreatic infiltration [37, 45], invasive growth in the pelvic wall/ureter, extensive adhesions and involvement of 6/7 regions according to the Dutch score [37]. A high rate of understaging by laparoscopy (37 %) was reported in only one study, which

Table 2 Efficacy of laparoscopic staging before cytoreductive surgery

Author	No. of patients excluded from CRS	Positive predictive value	Sensitivity	Negative predictive value	Specificity	Accuracy	Understaging at laparoscopy
Pomel et al. 2005	3 (27 %)	87.5 %	100 %	NA	NA	NA	12.5 %
Valle et al. 2006	16 (16.4 %)	98 %	100 %	NA	NA		2.06 %
Garofalo A et al. 2009 ^a	67 (34 %)	NA	NA	NA	NA	NA	2 %
Laterza et al. 2009	3 (7 %)	97 %	100 %	100 %	75 %	97 %	3.3 %
Iversen et al. 2013 ^b	18 (41 %)	63 %	100 %	NA	NA	NA	37 %
Valle M et al. 2013	104 (29.6 %)	NA	NA	NA	NA	NA	1.4 %
Jayakrishnan TT et al. 2014	18 (27.7 %)	85.4 %	100 %	NA	NA	NA	NS
Tabrizian P et al. 2015	68 (31.3 %)	91.9 %	100 %	NA	NA	NA	NS

NA not available, PCI peritoneal cancer index

^a 82 % patients had PCI > 17, ^b Dutch score

was attributed to disease involvement in areas difficult to identify on routine laparoscopy [37].

The primary site of origin also seems to influence the ability of laparoscopy to accurately predict complete cytoreduction. Iversen et al. [37] reported that laparoscopy correctly predicted complete cytoreduction in only 29 % of patients with recurrent colorectal cancers, compared to 33 %, 80 % and 87.5 % of patients with mesothelioma, PMP and synchronous colorectal PC respectively. This has been attributed to the fact that recurrent CRC often tends to infiltrate retroperitoneal structures like the ureters or pancreas.

Advantages and Disadvantages

The advantages of a staging laparoscopy, therefore, include the ability to assess involvement of the small bowel and its mesentery, assess the PCI and need for a multi-organ resection, thus helping to determine if a complete cytoreduction is possible thereby avoiding an unnecessary laparotomy [40, 43]. In one report from Denmark, the rate of incomplete CRS decreased from 44 % before introducing laparoscopic assessment of the PC to only 30 % after its introduction as a part of routine pre-operative staging [37]. In addition, it can also identify the origin of the neoplasm by permitting biopsies [45]. It also allows for restaging after neoadjuvant treatment. The procedure is associated with minimal morbidity. The disadvantages of a staging laparoscopy include the inability to correctly assess involvement of the retroperitoneal structures like the ureter or the pancreas [37], the omental bursa near the celiac axis [38] and the depth of involvement of the hepatic pedicle or diaphragm [37]. However, these may be overcome to a large extent by the use of a laparoscopic ultrasound [40].

There is still no consensus on who should perform the staging laparoscopy, when it should be performed and in which patients it could be avoided. While it is generally believed that the laparoscopy should be done by the same team who will be performing the CRS [45], Laterza et al. [46] reported that exploratory laparoscopy can be done even by general surgeons without experience in CRS and HIPEC as long as the recorded tapes are reviewed by the surgeon who will perform the CRS. The staging laparoscopy can be performed as a separate procedure or concurrent with the planned CRS procedure. While the former involves additional cost, it allows time to plan the logistics involved in a major procedure like CRS and HIPEC.

It is logical to assume that the maximum impact of a staging laparoscopy would be in colorectal and gastric PC where the PCI is an important criterion to decide on CRS and HIPEC. Laparoscopy would have a lesser impact in PMP (especially in the diffuse peritoneal adenomucinosis variant) and in PM where CRS and HIPEC is possible even if the PCI is high and in recurrent colorectal cancer where involvement of the retroperitoneal structures may be difficult to identify.

Conclusion

Staging laparoscopy is an invaluable tool in the pre-operative assessment of patients with PSM. It should be used in conjunction with routine imaging modalities in selecting patients who will benefit the most from CRS and HIPEC.

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