

Accuracy and Clinical Relevance of Computed Tomography Scan Interpretation of Peritoneal Cancer Index in Colorectal Cancer Peritoneal Carcinomatosis: A Multi-Institutional Study

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Background: Evaluation of peritoneal metastases by computed tomography (CT) scans is challenging and has been reported to be inaccurate.

Methods: A multi-institutional prospective observational registry study of patients with peritoneal carcinomatosis from colorectal cancer was conducted and a subset analysis was performed to examine peritoneal cancer index (PCI) based on CT and intraoperative exploration.

Results: Fifty-two patients (mean age 52.6 ± 12.4 years) from 16 institutions were included in this study. Inaccuracies of CT-based assessment of lesion sizes were observed in the RUQ ($P = 0.004$), LLQ ($P < 0.0005$), RLQ ($P = 0.003$), distal jejunum ($P = 0.004$), and distal ileum ($P < 0.0005$). When CT-PCI was classified based on the extent of carcinomatosis, 17 cases (33%) were underestimations, of which, 11 cases (21%) were upstaged from low to moderate, 4 cases (8%) were upstaged from low to severe, and 2 cases (4%) were upstaged from moderate to severe. Relevant clinical discordance where an upstage occurred to severe carcinomatosis constituted a true inaccuracy and was observed in six cases (12%).

Conclusions: The actual clinical impact of inaccuracies of CT-PCI was modest. CT-PCI will remain as a mandatory imaging tool and may be supplemented with other tools including positron emission tomography scan or diagnostic laparoscopy, in the patient selection for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

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INTRODUCTION

The survival of patients with peritoneal carcinomatosis from colorectal cancer has significantly improved since the introduction of cytoreductive surgery (CRS), hyperthermic intraperitoneal chemotherapy (HIPEC), and modern systemic therapies [1]. Historically, this condition was regarded as the terminal phase of malignancy and was associated with a median survival of less than 7 months [2–4]. CRS and HIPEC have been shown to improve survival over systemic chemotherapy alone in a randomized clinical trial where a median survival of 22 months in the CRS and HIPEC arm significantly exceeded that of the control arm (13 months) [5]. Recent data have shown that long-term survival, with a median survival of 63 months and 5-year survival of 51%, is now achievable after a complete cytoreduction in carefully selected patients [1]. Improvements,

although to a lesser extent have also been demonstrated with modern multi-agent systemic chemotherapy without CRS [1]. To ensure that patients benefit from multi-modality treatment, it is imperative to select patients with limited peritoneal disease in whom a complete cytoreduction can be achieved [6].

The peritoneal cancer index (PCI) is a scale that combines the assessment of lesion sizes in nine abdominal and pelvic regions

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and four small bowel segments [7]. This index has been shown to be a prognostic factor in the survival of patients with colorectal cancer peritoneal carcinomatosis (CRCPC) who undergo CRS and HIPEC [5,8,9]. Current consensus among surgical oncologists have agreed that a PCI < 20 is a prerequisite for undergoing this treatment. In addition to the PCI, a recent selection criterion that combined various established prognostic factors into a scoring system known as the Peritoneal Surface Disease Severity (PSDS) Staging for Colon Cancer has been described to guide patient selection for CRS [10]. This staging system comprised a scoring protocol based on the patient's clinical symptoms, extent of carcinomatosis, and tumor histopathology. In this staging system, the extent of carcinomatosis is assessed based on CT interpretation of the PCI which differs to the originally described PCI assessment which was based on intraoperative exploration. If CT PCI were to be a surrogate of the intraoperative PCI, it would allow better treatment planning and patient selection, and avoid unnecessary surgical exploration.

Computed tomography (CT) scan is the most common imaging modality used during the preoperative assessment of patients with advanced colorectal cancer. However, its accuracy of identifying peritoneal metastases from gastrointestinal and gynecological malignancies by CT scan is low [11,12]. We present the findings of a multi-institutional prospective observational registry study of patients with peritoneal carcinomatosis from colorectal cancer wherein PCI based on CT and intraoperative exploration was compared.

PATIENTS AND METHODS

Patient Recruitment

Based on a previously published consensus statement of CRCPC [13], a prospective multi-institutional registry study was initiated. This study comprised patients from various International Peritoneal Surface Malignancy Centres that were evaluated between 1990 and 2007. Of the first 157 patients with intraoperative diagnosis of carcinomatosis, the mean PCI was 13 (SD = 5). Lesion sizes and the PCI were assessed both by preoperative CT scan and intraoperatively during exploratory laparotomy in 52 patients, who form the cohort for this subset analysis from the main registry study. Patients without CT assessment of PCI were excluded.

Computed Tomography Scan Peritoneal Cancer Index

Multi-slice CT scan was performed at each institution utilizing 5-mm contiguous reconstruction algorithms and an adequate volume (based on site-specific protocols) of oral and intravenous contrast agents administered to accentuate bowel, vasculature, and visceral metastases. In each institution, the CT scan was reviewed by an experienced radiologist and surgical oncologist with special interest in peritoneal surface malignancies. During the review of scans, the lesion size (LS) was graded: LS 0: no macroscopic tumor; LS 1: tumor < 0.5 cm; LS 2: tumor 0.5–5 cm; and LS3: tumor > 5 cm according to the tumor distribution in the 13 total abdominopelvic regions and small bowel segments. The CT-PCI was quantified as the total LS score using a standardized form [7].

Intraoperative Peritoneal Cancer Index

PCI was assessed intraoperatively by the surgical oncologist at the time of exploratory laparotomy. Upon entering the peritoneal cavity, ascites was drained and division of adhesions was performed. When the entire length of the small bowel was freed, surgical exploration and palpation were commenced. This involved careful inspection and palpation to carefully and completely identify size and distribution of tumor deposits in the aforementioned anatomical

regions [7]. The same standardized PCI scoring form was used to record the LS in each abdominopelvic regions and along the small bowel segments. The summation of the lesion size score in each of the 13 regions defined on the PCI, ranging from a minimum of 0 to a maximum score of 39, was quantified as the intraoperative PCI for each patient.

Peritoneal Surface Disease Severity for Colorectal Cancer

A sub-category on the Peritoneal Surface Disease Severity for CRCPC assessed the extent of carcinomatosis. On this staging system, the extent of carcinomatosis was graded as low, moderate, and severe. Low extent of carcinomatosis was a PCI < 10, moderate was a PCI 10–20, and severe was a PCI > 20. To determine the accuracy and clinical relevance, patients were specifically grouped within these three categories.

Statistics

Both data on CT and intraoperative LS at exploration in all 13 regions were recorded on the standardized form and submitted to the principal investigator (J.E.). Summary statistics were obtained using established methods. Continuous data were presented as means with standard deviations (\pm SD) in the text and tables. Associations between categorical factors were studied with Fisher's exact test or chi-squared test, as appropriate. Accuracy which is judged by the concordance between CT assessment of LS and intraoperative assessment of LS was analyzed using the Kappa statistic on SPSS (version 13.0, SPSS, Inc., Chicago, IL) and StatExact (StatExact for unbalanced tables). A *P*-value of < 0.05 was considered significant.

RESULTS

Accuracy of Lesion Size Assessment on CT scan and Intraoperatively

Fifty-two patients (mean age 52.6 ± 12.4 years) from 16 institutions with peritoneal surface malignancy of colonic origin were enrolled in this prospective multi-institutional registry study. Proportion of patients with tumor present on exploration per abdominopelvic regions and the small bowel segments are shown in Table I. The most common regions involved by tumor were the pelvis (75%), right (71%) and left (67%) lower quadrants, distal ileum (69%), and central abdomen (65%).

The accuracy of determining LS in each region using CT scans compared to intraoperative assessment via an exploratory laparotomy conducted by an experienced surgical oncologist is presented in Table I. The CT-PCI false-negative rate by anatomic region varied from 10% (left upper quadrant) to 25% (pelvis) to 35% (distal ileum). There were significant inaccuracies in CT-based assessment of lesion sizes in all 13 anatomical regions studied (Table I). The CT-PCI false-positive rate by anatomic region varied from 2% to 6%. The accuracy of CT scan to detect the presence of lesions (of any size) compared to the true finding on exploratory laparotomy is demonstrated in Table II. The regions where assessment on CT scan correlated well with intraoperative assessment were in the epigastrium (83%), left upper quadrant (81%), and central abdomen (75%) (Fig. 1).

Accuracy and Clinical Relevance of CT-PCI

When the CT-PCI was compared to the intraoperative PCI at exploratory laparotomy, there was a significant underestimation of the intraoperative (true) PCI by the CT scan (mean CT-PCI, 8.7 ± 5.5 ;

TABLE I. Accuracy of CT-PCI and Intraoperative PCI at Exploratory Laparotomy (ExLap) With Demonstration of Number of Accurate, Over-Estimate, and Under-Estimate Cases

Region #	Region	Presence of disease at ExLap (n, %), n = 52	Accuracy of assessing lesion sizes using CT scans and intraoperative ExLap			Kappa	P-value	Sensitivity (%)	Specificity (%)
			CT = ExLap (n, %)	CT > ExLap (n, %)	CT < ExLap (n, %)				
0	Central	34 (65%)	39 (75%)	2 (4%)	11 (21%)	0.65	<0.0005	76	90
1	RUQ	30 (58%)	37 (71%)	1 (2%)	14 (27%)	0.55	<0.0005	73	96
2	Epigastrium	25 (48%)	43 (83%)	8 (15%)	1 (2%)	0.70	<0.0005	98	77
3	LUQ	22 (42%)	42 (81%)	3 (6%)	7 (13%)	0.67	<0.0005	86	91
4	L Flank	28 (54%)	36 (69%)	3 (6%)	13 (25%)	0.51	<0.0005	73	89
5	LLQ	35 (67%)	32 (62%)	1 (2%)	19 (37%)	0.46	<0.0005	63	47
6	Pelvis	39 (75%)	35 (67%)	4 (8%)	13 (25%)	0.55	<0.0005	73	76
7	RLQ	37 (71%)	30 (58%)	4 (8%)	18 (35%)	0.42	<0.0005	63	79
8	R Flank	29 (56%)	34 (65%)	3 (6%)	15 (29%)	0.44	<0.0005	69	88
9	Proximal jejunum	22 (42%)	35 (67%)	4 (8%)	13 (25%)	0.34	0.0025	73	88
10	Distal jejunum	28 (54%)	30 (58%)	5 (10%)	17 (33%)	0.30	0.001	64	83
11	Proximal ileum	27 (52%)	34 (65%)	4 (8%)	14 (27%)	0.41	<0.0005	71	86
12	Distal ileum	36 (69%)	29 (56%)	3 (6%)	20 (38%)	0.37	<0.0005	59	84

intraoperative PCI 12.9 ± 7.4 ; $P = 0.003$). The categorization of CT-PCI and intraoperative PCI according categories of low, moderate, and severe is shown in Table III. Categorical comparison using chi-squared test demonstrated significant discordance between CT and intraoperative categorization ($P < 0.001$). Analysis of individual cases revealed that of 52 cases, 34 cases (65%) were accurately classified into the categories by the CT-PCI when compared to intraoperative PCI. One case (2%) was an overestimation and 17 cases (33%) were underestimations by CT-PCI.

To determine the clinical relevance, the 17 cases where CT-PCI was an underestimation of the true intraoperative PCI were individually studied. Eleven cases (21%) were upstaged from low-to-moderate PCI, four cases (8%) were upstaged from low-to-high PCI, and two cases (4%) were upstaged from moderate-to-high PCI. Given that the current consensus of selecting patients for treatment is based on a PCI < 20 (low or moderate), only six cases (four cases from low to high and two cases from moderate to high) (12%) would become ineligible for CRS. This represents a true rate of inaccuracy of the CT-PCI to be 12% when this threshold (PCI < 20) is utilized for the purpose of patient selection for CRS on the basis of extent of carcinomatosis.

TABLE II. Accuracy of Predicting the Presence of Lesions (Any Sizes) Based on CT Scans and Intraoperatively via an Exploratory Laparotomy (ExLap)

Region #	Region	CT(+) ExLap (-) (n, %)	CT (-) ExLap (+) (n, %)
0	Central	1 (2%)	9 (17%)
1	RUQ	1 (2%)	12 (23%)
2	Epigastrium	1 (2%)	7 (13%)
3	LUQ	3 (6%)	5 (10%)
4	L Flank	2 (4%)	12 (23%)
5	LLQ	1 (2%)	14 (27%)
6	Pelvis	3 (6%)	13 (25%)
7	RLQ	3 (6%)	9 (17%)
8	R Flank	3 (6%)	14 (27%)
9	Proximal jejunum	2 (4%)	12 (23%)
10	Distal jejunum	3 (6%)	15 (29%)
11	Proximal ileum	2 (4%)	13 (25%)
12	Distal ileum	1 (2%)	18 (35%)

A positive CT but negative ExLap would indicate a false-positive finding and a negative CT but a positive ExLap would indicate a false-negative finding.

Diagnostic Accuracy of CT-PCI Extent of Carcinomatosis

As intraoperative assessment represents the most accurate way of calculating the PCI, when compared against the CT-PCI used as a preoperative evaluation tool, 46 cases were accurately classified with clinical concordance and 6 cases were false negative indicating that classification was inaccurate leading to clinical discordance. There were no true-negative or false-positive cases. Hence, the sensitivity [true positive/(true positive + false negative)] is estimated to be 88%.

DISCUSSION

This multi-institutional study compared the assessment of PCI lesion score using CT and direct intraoperative observation during exploratory laparotomy in patients with CRCPC. In addition, the impact of CT-directed assessment of peritoneal surface tumor burden was evaluated with surgical practice-altering CT underestimation in only 12% of patients, in whom more extensive carcinomatosis was found at exploration which precluded a complete cytoreduction. Although the findings are not able to select out patients for and against an exploratory laparotomy, which remains the gold-standard of evaluating the PCI, we conclude that CT-PCI interpreted by dedicated radiologists and surgical oncologists may represent an accurate depiction of the clinically relevant extent of carcinomatosis and may be able to support surgical decision making in terms of guiding patient selection for CRS and HIPEC with a clinical accuracy rate of 88%.

Our findings are similar to those recently published by Koh et al. [12]. In their study, Koh et al. evaluated the utility of preoperative CT scan in estimating PCI during the surgical patient selection process by comparing radiological and intraoperative LS and PCI scores. These authors report a 60% accuracy, 33% underestimation, and 7% overestimation of CT-PCI in a small cohort of 19 patients, demonstrating a statistically significant difference in radiological PCI versus intraoperative PCI in nearly all abdominopelvic regions [12]. Correction for multiple comparisons was not performed in that study. Furthermore, it was not reported how the discordance between CT-based estimation of PCI actually altered the selection of patients for CRS. The clinical impact of CT-PCI discordance is the subject of our investigation.

We found significant discordance between assessment of LS in the various abdominopelvic regions and small bowel segments, most

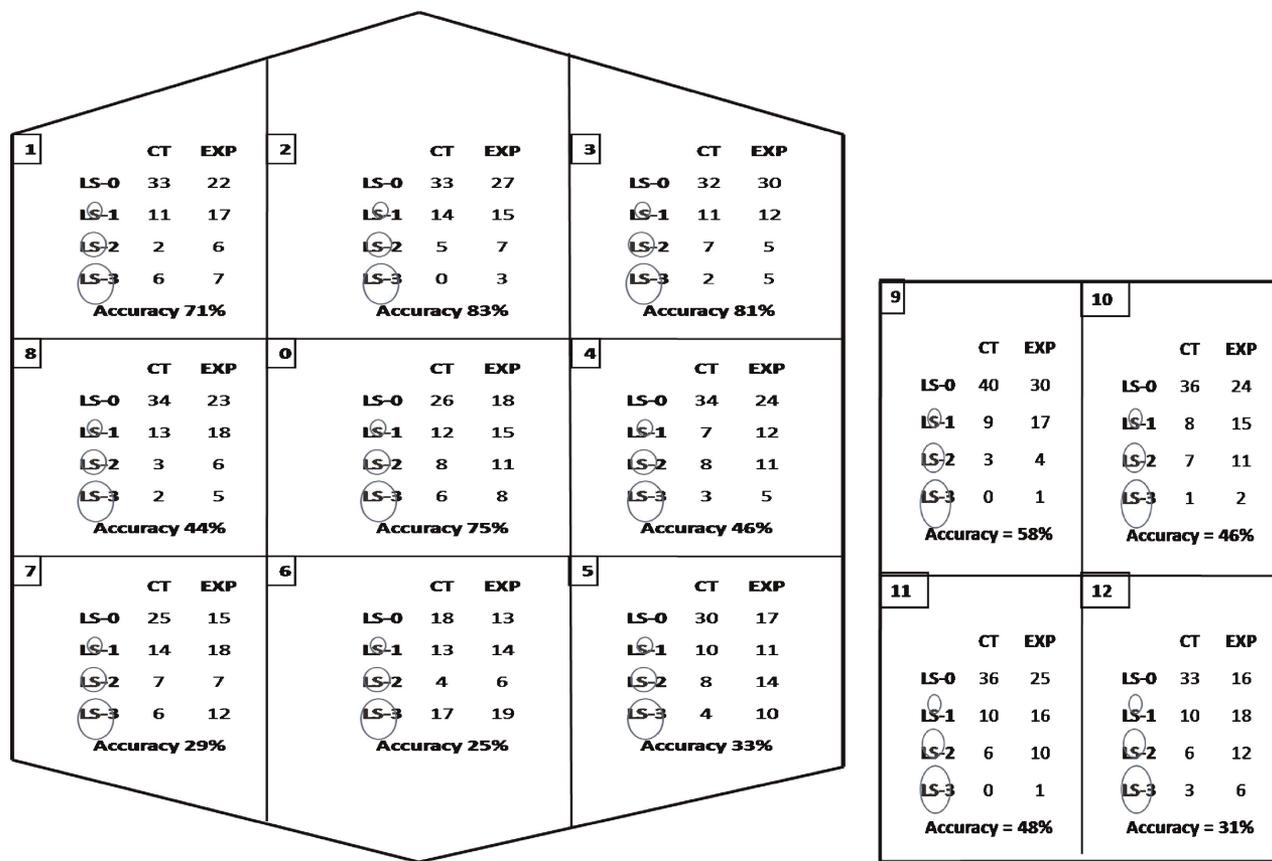


Fig. 1. Accuracy of CT assessment of lesion size compared to intraoperative assessment during exploratory laparotomy (adapted with permission from Koh et al. [12]).

commonly in the right upper quadrant, bilateral lower quadrants, distal jejunum, and distal ileum. The discrepancy between CT and exploratory laparotomy was most significant in the small bowel where a negative CT scan finding but a true exploratory laparotomy finding of peritoneal lesions occurred in 23–35% of cases in the different segments of the small bowel. The total summation of LS scores in each of the 13 abdominopelvic regions defined as the aggregate PCI score was found to be discordant between CT-PCI and intraoperative PCI at exploratory laparotomy. When PCI was classified based on the extent of carcinomatosis using the low, moderate, and severe sub-category of the PSDS, discordance between CT-based and intraoperative assessments of PCI remained. Our findings pointing to the inaccuracies of CT determined PCI and the underestimation of extent of peritoneal surface disease by CT alone is consistent with the published findings of others [11,12,14–17]. To further improve the role of CT-based estimation of PCI, thin cut slices of CT with reconstructions of 1–2 mm may improve the accuracy rate of CT-PCI detection of sub-centimeter peritoneal nodules.

TABLE III. Extent of Carcinomatosis Based on CT and Intraoperative Exploratory Laparotomy Assessment ($P < 0.001$)

Extent of carcinomatosis	CT-PCI (n, %)	Intraoperative ExLap PCI (n, %)
Low (PCI < 10)	32 (61%)	18 (35%)
Moderate (PCI 10-20)	18 (35%)	26 (50%)
Severe (PCI > 20)	2 (4%)	8 (15%)

To determine the clinical relevance of the variance between CT and operative PCI, we classified cases according to low, moderate, and severe peritoneal surface disease burden that was the classification of peritoneal disease measurement according to the peritoneal disease severity score for colorectal cancer. An analysis was subsequently performed to identify underestimation of the PCI that occurred on CT based that led to the change in classification. We regarded a classification change as an inaccuracy. In total, there were 17 cases that were mis-classified. The inaccuracies were determined to be clinically relevant if the underestimation of the CT resulted in an intraoperative PCI > 20 that would render the case inappropriate for CRS. Of 17 cases, 11 cases (21%) which were upstaged from low-to-moderate PCI and were regarded as not clinically relevant. There were four cases (8%) which were upstaged from low-to-high PCI and two cases (4%) which were upstaged from moderate to high PCI. As aforementioned, if cases were upstaged to severe, it would be regarded as clinically relevant as the current consensus agreement is that patients with a PCI > 20 are not suitable candidates for CRS. Out of 17 cases, there were 6 cases (12%) judged to be clinically relevant as a result of the inaccuracies of the CT-based interpretation of the PCI. Taken together, of 52 patients with CRCPC, 46 patients were classified appropriately with preoperative CT such that despite the events of upstaging occurring during the intraoperative exploration, the surgical procedure would not be abandoned. Hence, a clinically relevant CT determined PCI accuracy of 88% was achieved. However, the negative predictive value of 25% is poor and this underscores the risk of potential false-negative findings in CT-based interpretation of the PCI.

Among the patients who had a severe extent of carcinomatosis when classified according to the PSDS for colorectal cancer, for the four patients where CT-PCI had estimated a low extent of carcinomatosis had a CT-PCI of 6, 3, 1, and 9 that was subsequently determined to be 36, 21, 25, and 32 at exploratory laparotomy, respectively. For the two patients who had a moderate extent of carcinomatosis based on CT-PCI, their CT-PCI were 14 and 13, and at exploratory laparotomy, their PCI were 25 and 22, respectively. Therefore, only 12% of patients with a truly severe extent of carcinomatosis based on the PSDS were underestimated by the CT-PCI.

Radiological manifestations of peritoneal carcinomatosis of colorectal origin are diverse and include ascites, peritoneal thickening and enhancement, mesenteric effacement, luminal narrowing, and peritoneal nodules or bulky mass lesions. Interpretation of these often subtle imaging findings is challenging, requires diligence, and should be done by experienced radiologist or surgical oncologists dedicated to the care of patients with peritoneal surface malignancy. The limitations of this study include the lack of an interobserver reliability testing and the response rate of CT-based PCI from the registry data acquisition of only 52 out of 157 (33%). The lack of interobserver agreement is an important element in the assessment of a diagnostic test. However, based on the nature of data acquisition and study design, we simply are unable to perform this analysis. Further, the 33% response received on CT-based assessment of PCI may lead us to conclude this is not routinely performed among cytoreductive surgical units. As the selection criteria for CRS in colorectal cancer is now limited to patients with a PCI of less than 20, only a small proportion of patients (15%) in the study cohort had a PCI above 20. Although this may have affected the true pick-up rate that could reflect the inaccuracies of CT scan, the authors believe that the impact of this is not significant as the intention of this article is to demonstrate the surrogate ability of CT scan in being able to provide a crude classification of patients according to the extent of carcinomatosis. Nevertheless, the clinical implications reported in this study supports the assertion that if a standardized classification schema for determining peritoneal surface disease burden is utilized, a purposeful clinical outcome can be achieved to appropriately select patients for CRS.

Nevertheless, an alternative imaging modality with a higher accuracy in identifying peritoneal LS and overall extent of carcinomatosis would be invaluable. Thus far, PET scans have appeared to be promising. However, PET is insensitive for the detection of sub-centimeter hyper-metabolic lesions, for neoplasms with prolonged doubling times, and for neoplasms with substantial non-viable content (i.e., mucin, keratin, collagen). Therefore, PET fails to smaller lesions (LS-1) that would characteristically form on the bowel and mesenteric surfaces, which are of paramount importance in determining the operability of patients. A recent study by Pfannenberget al. [18] that compared CT, PET, and a combination of PET/CT to intraoperative PCI found that PET/CT was the most accurate among these three imaging modalities in estimating the extent of carcinomatosis. This method involves image co-registration of both CT and PET scans to produce a single image that depicts the spatial distribution and also demonstrate anatomic accuracy in localizing the site of metabolic activity, hence providing more precise anatomic localization to functional imaging which is lacking in pure PET scans. Alternatively, a minimally invasive approach of diagnostic laparoscopy may be performed to provide direct visualization of the peritoneal cavity [19–21]. This technique is useful in assessing patients in whom there is inadequate information or uncertainty in the extent of carcinomatosis.

In conclusion, the estimation of the PCI if based purely on quantified parameters (summation of lesion size, PCI score) is likely to be prone to high rates of intrarater and interrater variability and statistically significant discordance between CT interpretation and that of intraoperative exploration and estimation of peritoneal surface

disease burden. This manuscript provides meaningful analysis on a collection of rare patients where PCI is scored at both times of preoperative CT imaging scan and intraoperatively during exploratory laparotomy. In doing so, our analyses have shown that although the decision to undertake CRS is dependent on the PCI at exploration, classifying the CT-PCI into the categories based on clinically relevant extent of carcinomatosis may provide a useful preoperative guiding tool. CT-PCI will remain as a mandatory imaging tool and may be supplemented with other tools such as a positron emission tomography scan or diagnostic laparoscopy, in the patient selection for CRS and HIPEC.

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