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Adding diagnostic laparoscopy to computed tomography for the evaluation of peritoneal metastases in patients with colorectal cancer: a retrospective cohort study

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Running head: Peritoneal metastases at CT and laparoscopy

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Abstract

Background: Despite its widespread use, computed tomography (CT) is not perfect for evaluating peritoneal metastases of colorectal origin before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS+HIPEC). We therefore evaluated the value of adding diagnostic laparoscopy to CT when assessing patient eligibility for CRS+HIPEC.

Methods: This was a retrospective study of a consecutive series of 112 patients evaluated systematically by diagnostic laparoscopy and CT between January 2012 and January 2018. Patient eligibility for CRS+HIPEC was assessed by the peritoneal cancer index (PCI) both at the time of initial diagnostic laparoscopy and during the retrospective review of CT images. Two experienced radiologists who were blinded to the PCI result at laparoscopy then independently estimated the PCI based on CT imaging. The primary outcome was the number of patients eligible for CRS+HIPEC by each method.

Results: We identified 112 patients, of whom 95 (85%) were eligible for CRS+HIPEC based on diagnostic laparoscopy and 84 underwent CRS+HIPEC. Overall, 14 patients (17%) experienced an "open-and-close" procedure. In contrast to diagnostic laparoscopy, 100 patients (89%) were identified as being eligible for CRS+HIPEC by CT ($p = 0.13$), which would have resulted in an additional five open-and-close procedures.

Conclusions: Adding diagnostic laparoscopy to CT produced a clinically relevant, but statistically non-significant, reduction in the number of patients eligible for CRS+HIPEC. We conclude that diagnostic laparoscopy may be of use in preoperative assessments when systematic analysis by CT scores the PCI as greater than ten. Future research should focus on the cost-effectiveness of this approach.

Keywords: Induced Hyperthermia; Colorectal Neoplasms; Peritoneal Neoplasms

1. INTRODUCTION

Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CRS+HIPEC), which was first implemented in the early 1990s, is a curative treatment for patients with low-volume peritoneal metastases without other distant metastases [1]. Before its introduction, there was no viable cure for patients with peritoneal metastases of colorectal origin. The five-year survival after treatment with CRS+HIPEC now varies between 41% and 45% [2, 3].

Computed tomography (CT) is typically considered the diagnostic standard for determining whether patients with peritoneal metastases of colorectal origin are eligible for CRS+HIPEC [4]. Peritoneal metastases can be quantified on CT by the peritoneal cancer index (PCI), which scores the tumor load in the abdomen and has been shown to predict survival reliably [5-7]. However, CT has a wide sensitivity range of 24.5%–79% for detecting peritoneal metastases, potentially underestimating the PCI by 24%–33% [4, 8-12]. Although patients with very low PCIs are ideal candidates for CRS+HIPEC, small peritoneal lesions are difficult to detect by CT [13-15]. Furthermore, if tumor loads are found to be excessive at operation, underestimation can lead to unnecessary “open-and-close” procedures and avoidably prolonged recovery times and complications. Accurate patient identification can therefore ensure optimal use of surgical and financial resources. To correct for this, it has been proposed that PCI estimation before CRS+HIPEC be performed by CT and diagnostic laparoscopy. Indeed, the latter has proven feasibility and safety, with the potential to prevent 28%–55% of unnecessary laparotomies [16-20]. To date, however, no study has compared CT- and laparoscopy-based PCI, leaving uncertainty as to whether the addition of diagnostic laparoscopy to CT could prevent more open-and-close procedures than CT alone.

In this study, our aim was to evaluate whether diagnostic laparoscopy should be added

to CT when selecting patients for CRS+HIPEC. We hypothesized that fewer patients would be declared eligible for CRS+HIPEC when using diagnostic laparoscopy than when using CT.

2. MATERIALS AND METHODS

2.1. Study design

This was a single-center retrospective study performed at the University Medical Center Groningen, which is a tertiary referral center for a region with 3.5 million inhabitants. The hospital accepts referrals for patients with peritoneal metastases who could be suitable for treatment by CRS+HIPEC. Since 2012, we have used diagnostic laparoscopy as a standard procedure to select patients for CRS+HIPEC. The number of peritoneal metastases was quantified systematically by estimating the PCI at diagnostic laparoscopy (Figure 1) [21]. A PCI exceeding 20 was again taken as a cut-off point, above which CRS+HIPEC was not performed. In general, patients are considered ineligible for CRS+HIPEC when the PCI exceeds 20, they show extra-abdominal metastases other than resectable liver metastases or if they are not fit enough for surgery. CT scan was used to detect extra-abdominal metastases rather than peritoneal metastases. Therefore there was no systematic scoring of the PCI following the PCI score form during our daily clinical practice. During the study period, diagnostic laparoscopy was not performed in patients that clearly showed irresectable disease during the initial CT-evaluation, which did not include the PCI score form. These patients could therefore not be included in this study.

In this research, we included all consecutive patients with peritoneal metastases due to colorectal cancer who were seen between January 2012 and January 2018, excluding patients with other synchronous malignancies of non-colorectal origin. The study was approved by the Central Ethical Committee of the University Medical Center Groningen.

2.2. Data collection

The PCI scores determined during diagnostic laparoscopy were extracted from the patients' files. We also collected data on the following characteristics: age, gender, body mass index, comorbidities, tumor location, previous surgery, conversion of laparoscopy to laparotomy, and complications within 30 days of laparoscopy. Next, the PCIs from CT scans were obtained based on retrospective reviews by two radiologists with eight- and five-years' experience in reading abdominal CT scans. All images were independently analyzed in coronal and transverse views, without knowledge of the laparoscopic PCI result, using a picture archiving and communication system (Carestream Health, Rochester, NY). In case of discrepancies in the PCI, consensus was reached through discussion between the radiologists.

2.3. Endpoints

The primary endpoint was the number of patients deemed eligible for CRS+ HIPEC according to either diagnostic laparoscopy or CT. The secondary endpoint was the difference in PCI estimation overall and in different intra-abdominal regions of the PCI (upper, central, and lower abdomen, plus the small intestines; Figure 1). Other outcomes of interest were as follows: agreement between the diagnostic laparoscopy and the CT results, the number of conversions to laparotomy, the complications of diagnostic laparoscopy by 30 days post-surgery according to Clavien–Dindo classification [22], and the interrater reliability between the two radiologists. The latter was used as a measure of quality.

2.4. Statistical analysis

Patient characteristics are reported using descriptive statistics. The McNemar test was used to compare the number of patients that would have been found eligible for CRS+HIPEC by CT and diagnostic laparoscopy. To evaluate whether the differences in the overall PCI between CT and diagnostic laparoscopy were comparable, the nonparametric Wilcoxon signed-rank test was used. A Bland–Altman plot was used to visualize differences between

the overall PCI estimated by CT and that reported by diagnostic laparoscopy. The interrater reliability between the two radiologists was determined by the intraclass correlation coefficient (ICC). Interpretation of the ICC was as follows: <0.0 = poor; 0.0–0.2 = slight; 0.21–0.4 = fair; 0.41–0.6 = moderate; 0.61–0.8 = substantial; and 0.81–1 = almost perfect) [23]. We used IBM SPSS, Version 23.0 (IBM Corp., Armonk, NY, USA), to conduct all analyses.

3. RESULTS

3.1. Patient characteristics

In total, 112 consecutive patients were included in the study. Excluded were 2 patients with other synchronous malignancies, as they would not have been suitable for CRS+HIPEC due to that malignancy. The baseline characteristics of the included patients are shown in Table 1. Most had a primary tumor in the colon (90%) and had undergone previous abdominal surgery (80%), such as hemicolectomy, sigmoid resection, or appendectomy. In our center patients receive upfront CRS+HIPEC. However, eight patients of this cohort received neoadjuvant chemotherapy, seven as part of another study [24] and one to downstage synchronous liver metastases. Although 95 patients (88%) were eligible for CRS+HIPEC based on diagnostic laparoscopy, only 84 underwent a laparotomy because 11 withdrew their consent for CRS+HIPEC after the diagnostic laparoscopy. After laparoscopy patients were better informed about how extensive CRS will be and their prognosis afterwards. Some patients therefore decided to not undergo CRS+HIPEC. Of these 84 patients, 14 (17%) underwent an open-and-close procedure. Reasons for open-and close procedures are listed in table 3. Median time between diagnostic laparoscopy and laparotomy was 41 days (4-323) in all patients. For patients that experienced an open- and-close procedure median time between diagnostic laparoscopy and laparotomy was also 41 days (4-

176). A flow-chart of the eligibility of patients for CRS+HIPEC can be found in figure 2.

3.2. PCI scores

A PCI estimate from diagnostic laparoscopy was available for 108 patients (96%). Estimation was impossible in three cases due to the presence of extensive adhesions and in one case due to a tumor limiting visualization. During diagnostic laparoscopy, 13 patients (12%) had a PCI score above 20 and were therefore ineligible for HIPEC. Although a PCI estimate was possible by CT scan for all patients, two CT scans were difficult to interpret due to motion artifacts and one CT scan had a limited view (only a part of the diaphragm was shown). The ICC between the two radiologists for the overall PCI score was substantial at 0.74 (95% confidence interval 0.63–0.81). Of note, there was no statistically significant difference between the overall estimated PCI by diagnostic laparoscopy (median PCI, 5) and that by CT (median PCI, 6) ($p = 0.88$; Table 2). The differences in PCI estimates between diagnostic laparoscopy and CT were independent of the average PCI (Figure 3).

3.3. Differences in eligibility for CRS+HIPEC

There was no statistically significant difference between the numbers of patients found to be eligible for CRS+HIPEC by diagnostic laparoscopy (95/112; 84.8%) and by CT (100/112; 89.3%) ($p = 0.125$). All, but one, patient who were found ineligible for CRS+HIPEC by CT scan were also found ineligible by diagnostic laparoscopy. From the 112 included patients 95 were found eligible for CRS+HIPEC, this means that 7 diagnostic laparoscopies were necessary to prevent one open-and-close procedure. Without the addition of diagnostic laparoscopy, 5 additional patients (4.6%) who were unsuitable for CRS+HIPEC might have undergone an open-and-close procedure. All 5 of these patients had a PCI score between 12 and 15 on their CT scan.

4. DISCUSSION

We showed that adding diagnostic laparoscopy to CT produced a statistically non-significant reduction in the number of patients eligible for CRS+HIPEC, but that this approach was associated with fewer open-and-close procedures. However, failure to show a statistically significant difference in the PCI estimation by CT or diagnostic laparoscopy conflicts with our hypothesis that diagnostic laparoscopy would have a higher sensitivity than that of CT for detecting peritoneal metastases.

To date, we could find no studies comparing diagnostic laparoscopy with CT in patient selection for CRS+HIPEC based on the estimated PCI. Although some studies have been performed comparing the accuracies of CT and laparotomy [4, 10-12], these showed that the median PCI score estimated by CT (7–26) was significantly lower than that estimated by laparotomy (13–39) (p-value, <0.001 to 0.003) [4, 10-12]. One study illustrated that, despite CT scans underestimating the PCI, only 12% of patients would require an open-and-close procedure [4]. The unexpected high accuracy of CT scans in our study might reflect improvements in the quality of CT scans since those data were published. Other explanations are that the radiologists were very experienced in this subject matter and that they used a systematic method to estimate the PCI.

Our results showed that significantly more peritoneal lesions in the small abdomen were detected by diagnostic laparoscopy than by CT scan. These results seem to be consistent with other research showing that CT has a low sensitivity for detecting peritoneal metastases of the small intestines, with rates ranging from 8% to 25% [10, 11]. This is an important finding because small intestine involvement is a factor that limits tumor resectability. If extensive removal of the small intestines is required, patients can be left with functional problems, such as the short-bowel syndrome, after surgery. If CT is used in isolation for diagnosis before CRS+HIPEC, the potential for open-and-close procedures may be increased for patients with nonresectable involvement of the small intestine.

Our results showed that there was a non-significant reduction in the rate of open-and-close procedures based on adding diagnostic laparoscopy to the preoperative workup. However, 17% of patients were still ineligible for CRS+HIPEC at the time of laparotomy. This is comparable to data in the literature, where the incidence of open-and-close procedures after diagnostic laparoscopy is reportedly 13%–38% [17-20, 25, 26]. This high residual incidence might be explained by the inability to evaluate all regions of the peritoneal cavity evenly in the presence of adhesions or tumor processes. This makes it questionable if diagnostic laparoscopy is the ideal diagnostic measurement. However, at this moment, this is the best diagnostic tool available, that does not include high risks for the patient. Furthermore, tumor progression might occur during the waiting time before CRS+HIPEC. Although waiting time between DLS and laparotomy in patients that experienced an open-and-close procedure was comparable to that of patients that underwent CRS+HIPEC, tumor progression may be faster in some patients than in others. In addition, diagnostic laparoscopy might introduce the risk of port-site metastases, but this has not been observed in any of our patients.

We could identify no other research comparing diagnostic laparoscopy with CT as a tool to facilitate patient selection for CRS+HIPEC in cases of colorectal cancer. The experience of our radiologists preclude extrapolating the study results to other medical centers, where there should be awareness of the need for an adequate learning curve. A limitation of this study is its retrospective design, meaning that the radiologists already knew that patients had peritoneal metastases and were participating in a study. Although this may have increased the detection rate of peritoneal metastases, we are convinced that it is consistent with the ability of experienced radiologists to determine the PCI using a systematic methodology. For example, radiologists in our tertiary referral center often re-evaluate CT scans from other hospitals, knowing that the patients are being evaluated for their suitability

for CRS+HIPEC. Consequently, the research approach strongly resembled clinical practice. The substantial intraclass correlation in this study also confirms that the estimation of the PCI by CT is reliable when done by an experienced radiologist and that it can serve as a quality measure for inter-observer reliability. Another limitation is the small number of included patients, which might be the reason that the differences described in this study did not reach statistical significance.

Although we found no significant difference in the number of patients eligible for CRS+ HIPEC between the two diagnostic methods, the inclusion of diagnostic laparoscopy in the preoperative workup did most likely prevent five patients from undergoing avoidable open-and-close procedures assuming they would have all consented to CRS+HIPEC. To avoid one open-and-close procedure it is necessary to perform seven diagnostic laparoscopies, which seem justified as a diagnostic laparoscopy is known to be associated with both a short recovery time and a low risk of complications [17-19]. By contrast, open-and-close procedures place significant burdens on the patient and on hospital resources, which is important where health care rationing is a reality. By adding diagnostic laparoscopy to CT, these patients avoided unnecessary risks during their final phase of life. In case a HIPEC procedure is deemed impossible, patients can only be treated with palliative chemotherapy. After a laparotomy, however, time is required for recovery and, therefore possibly delaying the start of palliative chemotherapy. Had the procedures been performed, they would also have led to the loss of five full days in surgery and would have required 35 days of extra inpatient care. Although diagnostic laparoscopy also requires resources, the procedure normally takes one hour to perform and patients will normally stay in hospital for one to three days. We must also consider that, in this study, 20 cases required conversion to laparotomy, requiring a total time of two to three hours in surgery. The main reason for these conversions were adhesions making it impossible to determine the PCI. This also illustrates

the drawback of a diagnostic laparoscopy. However, we are still convinced that even a conversion to a diagnostic laparotomy is less invasive as an open-and-close procedure as this often results in only an upper or lower midline incision in contrast to an incision from xiphoid to pubic symphysis. Finally, given that a CT scan is part of the standard workup of a patient with peritoneal metastases (to rule out distant metastases), this approach requires no additional resources.

In the present research, all patients who would have experienced an open-and-close procedure without diagnostic laparoscopy had a PCI that exceeded ten. Therefore, when considering the optimal use of hospital resources and the costs and benefits for patients, it might be reasonable to use CT scans as the first-line tool for PCI estimation. Only in cases where the CT-based PCI exceeds ten do we recommend adding diagnostic laparoscopy to the preoperative workup. Furthermore, when the origin of the peritoneal metastases is unclear, a biopsy taken during laparoscopy provides an opportunity to add histological information.

When CT is applied in a structured way to estimate the number of peritoneal metastases, it achieves comparable sensitivity to that of diagnostic laparoscopy. To further improve sensitivity, (diffusion weighted) magnetic resonance imaging (MRI) might prove useful for PCI estimation. Initial results with this approach have shown promise, with several studies describing higher accuracies for PCI estimation by MRI (82.1%–88%) than by CT (63%) [27-30]. However, MRI is not widely used in preoperative staging for several reasons. First, it is more time consuming than CT, making it unsuitable for many institutions. That said, MRI evaluation would take approximately one hour, effectively requiring less time than a diagnostic laparoscopy. Second, its long scanning time and large field of view can lead to artifacts. Third, some patient groups are unable to undergo MRI, such as those with non-compatible pacemakers or severe claustrophobia. In the future, a prospective study should be conducted to evaluate the accuracy of MRI versus diagnostic laparoscopy. This should follow

a pre-determined protocol in which estimates for each method are made by independent evaluators. Cost-effectiveness analyses should also be central to any such study given that MRI is an expensive imaging modality.

5. CONCLUSION

We conclude that adding diagnostic laparoscopy to CT during preoperative staging leads to a clinically relevant, but a statistically non-significant, reduction in the rate of open-and-close procedures among patients with peritoneal carcinomatosis. Diagnostic laparoscopy can be added to preoperative staging when the PCI of a systematically reviewed CT scan exceeds ten.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure and Table legends

Figure 1. Sugarbaker's peritoneal cancer index

Tumor load is identified by nine abdominal regions and four small intestinal regions. The largest tumor lesion in each region is measured and rated as 0 (no tumor load) to 3 (lesion size >5 cm) points. Note: upper abdomen = regions 1, 2, and 3; central abdomen = regions 0, 4, and 8; lower abdomen = regions 5, 6, and 7; and small intestines = regions 9, 10, 11, and 12. Abbreviations: LS = lesion size score.

Previously published as *Jacquet P & Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treatment and Research 1996 [21]*. Permission for usage was granted.

Figure 2. Flowchart of patients eligibility

Figure 3. Bland–Altman Plot of the differences in the overall PCI by CT and diagnostic laparoscopy

Abbreviations: CT = computed tomography; PCI = peritoneal cancer index.

Table 1. Characteristics of patients diagnosed with peritoneal metastases

Data are presented as medians (range), unless specified otherwise.

Abbreviations: HIPEC = hyperthermic intraperitoneal chemotherapy

Table 2. Outcomes of computed tomography and diagnostic laparoscopy

Data are presented as medians (25^{th} percentile; 75^{th} percentile) and were analyzed using the Wilcoxon signed-rank test, unless otherwise specified. * McNemar test was used. ** Despite the comparable medians, the significant difference between the PCI estimated by each method is seen in the different data distributions (note the 75^{th} percentile). Abbreviations: HIPEC = hyperthermic intraperitoneal chemotherapy; PCI = peritoneal cancer index.

Table 3. Reasons for open-and-close procedures