


# Comparison of the Peritoneal Cancer Index and Dutch region count as tools to stage patients with peritoneal metastases of colorectal cancer

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**Background:** Extent of peritoneal metastases (PM) is among the most powerful prognostic factors for survival after cytoreductive surgery (CRS). This study aimed to compare the Peritoneal Cancer Index (PCI) and the Dutch region count as tools for staging PM of colorectal cancer. The Dutch region count is a simpler classification that distinguishes seven rather than 13 abdominal regions. Presence or absence of PM is recorded.

**Methods:** This was a retrospective cohort study in two tertiary referral centres in the Netherlands. Consecutive patients with colorectal PM who were intentionally treated with CRS and subsequent hyperthermic intraperitoneal chemotherapy in 2016 and 2017 were included. The PCI and Dutch region count were both recorded during laparotomy. Correlation between scoring tools was calculated using Spearman's rank correlation coefficient. Diagnostic values were calculated for different cut-off values of the PCI, alongside the Dutch region count. The correlation of both scores was determined for the exploration and validation cohorts separately.

**Results:** In the exploration and validation cohorts, 73 and 85 patients respectively were included. Spearman's correlation coefficients of 0.897 and 0.961 were observed for continuous scores of the Dutch region count and PCI in the exploration and validation group respectively. A cut-off value of 20 for the PCI score and 5 for the Dutch region count showed 91.9 and 94.5 per cent sensitivity, and 81.8 and 91.7 per cent specificity, respectively.

**Conclusion:** The Dutch region count correlated well with the PCI score, and may help to simplify reporting of the extent of peritoneal disease.

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## Introduction

Approximately 10 per cent of all patients with colorectal cancer eventually develop peritoneal metastases (PM)<sup>1,2</sup>. Cytoreductive surgery (CRS) with or without subsequent hyperthermic intraperitoneal chemotherapy (HIPEC) is a key treatment of multimodal management in selected patients<sup>3,4</sup>. Preliminary results of a French RCT<sup>5</sup> showed a median survival of 41 months in patients undergoing CRS–HIPEC, but surprisingly found the same survival time in patients who had CRS alone. Traditionally reported

prognostic factors of survival include nodal status of the primary tumour, extent of peritoneal disease and completeness of cytoreduction<sup>6–8</sup>. The latter two factors are clearly related<sup>9–12</sup>. Preoperative assessment of the abdominal cavity is therefore essential in selecting eligible patients for CRS or deciding on palliative treatment.

The Peritoneal Cancer Index (PCI) was introduced in the 1990s as an intraoperative assessment tool for surgical exploration of the abdomen to score the extent of peritoneal disease<sup>13,14</sup>. The PCI is a prognostic tool that combines the distribution of tumour in the abdomen

throughout 13 regions with a lesion size score. Nowadays, the PCI is commonly used to communicate between HIPEC centres and the appropriate method for reporting extent of disease, observed before surgery or during either diagnostic laparoscopy or CRS. At the Netherlands Cancer Institute (NCI), the Dutch region count was established and has commonly been used as a simplified approach to report the number of affected regions<sup>15</sup>. This count divides the abdomen into seven regions, and takes only the presence or absence of PM into account, irrespective of their size or the number of lesions within a region. This scoring tool may therefore be easier to use, particularly during imaging, laparoscopic evaluation or in non-HIPEC centres, as surgeons in these centres are likely to have less experience with this specific group of patients and clinical features during surgery. To have the ability to compare and report Dutch outcomes with internationally reported results, all centres have finally adopted the PCI. Assessing the PCI score, however, may be variable, especially in patients with multiple small nodules<sup>16–18</sup>.

In the Netherlands, cut-off values of 20 or less for PCI score and 5 or less for region count are used to consider patients eligible for CRS–HIPEC. Nowadays, patients with a higher score are considered ineligible for CRS–HIPEC, as this procedure would not prolong survival<sup>4,16,19</sup>. Some patients, however, would be eligible for CRS–HIPEC based on the PCI, whereas the region count would contraindicate CRS–HIPEC, and *vice versa*. The aim of this study was to compare and validate the region count with the PCI for selecting eligible patients for CRS–HIPEC.

## Methods

This was a retrospective cohort study performed in two high-volume tertiary referral centres for peritoneal surface malignancies in Amsterdam and Eindhoven, the Netherlands. The Amsterdam cohort was used as an exploration cohort and data were analysed first. Data collected in Eindhoven were used for validation. Consecutive patients with PM of colorectal origin who were intentionally treated with CRS–HIPEC in 2016 and 2017 were considered eligible for inclusion. Patients who were considered not amenable for subsequent CRS–HIPEC treatment during explorative laparotomy because of extensive PM, and who therefore had an open-and-close procedure, were also included. Data on patient characteristics included sex, age, ASA grade and co-morbidity. Tumour characteristics included tumour location, T category, N category, differentiation grade, histology, synchronous or metachronous setting, PCI and region count. Metachronous metastases were defined as

PM diagnosed at least 6 months after the initial diagnosis of colorectal cancer. Patients were excluded if the PCI score or region count was missing. Patients who had a second or third CRS–HIPEC procedure were excluded. Postoperative complications after CRS–HIPEC were scored according to the common terminology criteria for adverse events (v5.0)<sup>20</sup>. Patients who underwent a second CRS–HIPEC procedure for recurrent PM, as well as patients with PM of appendiceal origin, were also excluded. This study was performed in accordance with institutional medical ethical guidelines; board approval was waived owing to the retrospective nature of the study.

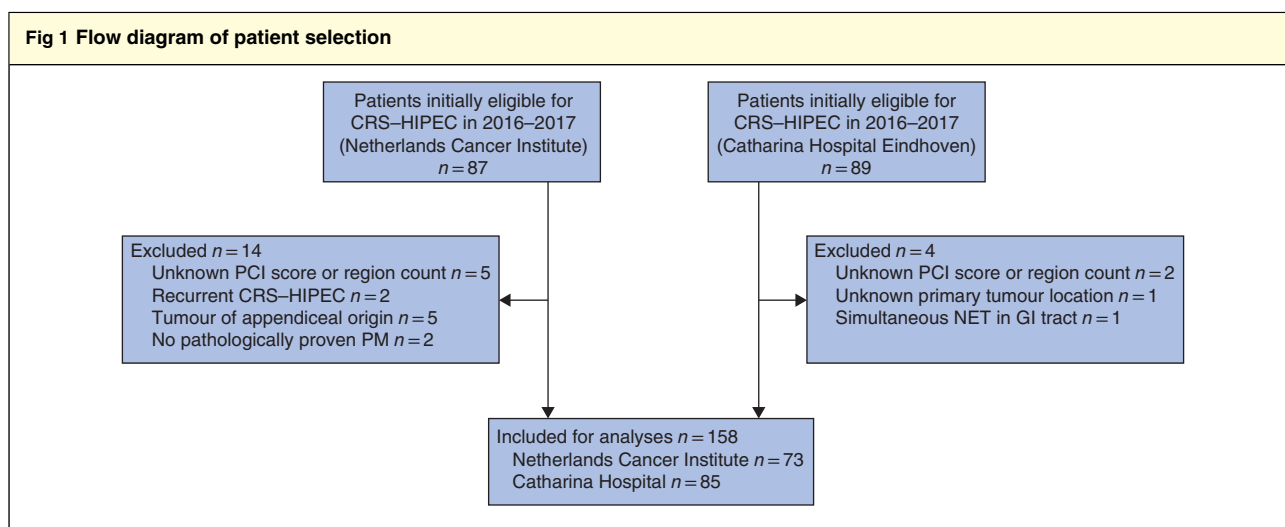
## Scoring tools

Diagnostic laparoscopy (DLS) was performed in a selected group of patients to gain insight into the extent of peritoneal disease. Selection of patients who have DLS first has varied over time, and the decision to perform DLS was made by the multidisciplinary team. Common indications to perform DLS were absence of histological confirmation that PM were present or doubt about the extent of disease. A 10-mm port was used to introduce the camera and at least one additional 5-mm port was used to allow for more accurate staging and biopsy of suspected lesions. In the exploration cohort, Dutch region count and PCI scores were also recorded in patients who underwent DLS.

In both cohorts, the procedure in patients considered eligible for surgical exploration and subsequent CRS–HIPEC started with an exploratory laparotomy to record the extent of peritoneal disease by using the PCI and Dutch region count.

Using the PCI, the abdomen is subdivided into 13 regions. The presence and size of lesions are recorded<sup>13</sup>. Lesion size (LS) of 0, 1, 2 or 3 in each region corresponds to no tumour, tumour up to 0.5 cm, tumour between 0.5 and 5.0 cm, and tumour larger than 5.0 cm or confluent PM, respectively. Therefore, the PCI score ranges from 0 to 39. In the Netherlands, all centres use a PCI cut-off value of 20 or less to decide whether or not to proceed with CRS–HIPEC. In this study, PCI was classified into three subgroups: PCI score of 10 or less, limited peritoneal disease; PCI score of 11–20, moderate peritoneal disease; and PCI score of 21 or more, extensive peritoneal disease.

The NCI introduced the Dutch region count to score the extent of peritoneal disease<sup>15</sup>. The region count divides the abdomen into the following seven regions: pelvis; right lower abdomen; omentum and transverse colon; small bowel and mesentery; subhepatic space; right diaphragm; and left diaphragm. A score of 0 of 7 means no affected regions and a score of 7 of 7 indicates that all regions are



CRS-HIPEC, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy; PCI, Peritoneal Cancer Index; NET, neuroendocrine tumour; GI, gastrointestinal; PM, peritoneal metastases.

affected. A cut-off value of 5 of 7 affected regions is used to decide whether or not to continue with CRS-HIPEC<sup>16</sup>. The region count was classified as: limited peritoneal disease, two or fewer affected regions; moderate peritoneal disease, three to five affected regions; and extensive peritoneal disease, six or more affected regions.

Until 2014, only the Dutch region count was used in the NCI. In 2015, the NCI started using the PCI as well, mainly to facilitate international communication and comparison. Catharina Hospital had switched to PCI earlier, but still recorded the Dutch region score for research purposes and internal communication. Validation of the results found in the NCI was performed in the concurrent data set of consecutive patients treated at Catharina Hospital.

## Treatment

In patients considered eligible for CRS-HIPEC, the surgical treatment aimed for complete cytoreduction, after exploration of the abdominal cavity. The completeness of cytoreduction (CC) was recorded in all patients after CRS-HIPEC. CC-0 resection implied no visible macroscopic disease, in CC-1 resections tumour nodules smaller than 2.5 mm were left behind, and in CC-2 resections residual tumour nodules 2.5 mm or larger were left behind in the abdomen. Subsequently, HIPEC was performed using either mitomycin C or oxaliplatin as intraperitoneal drug. The choice of the HIPEC regimen was based on surgeon/hospital experience; most patients at the NCI were treated using oxaliplatin (460 mg/m<sup>2</sup> for 30 min), and most patients at Catharina Hospital were treated

with mitomycin C (35 mg/m<sup>2</sup> for 90 min)<sup>21,22</sup>. Systemic chemotherapy was administered in selected patients only, as this has not been the standard of care in the Netherlands since 2016. The current ongoing CAIRO6 study<sup>23</sup> is a prospective comparison of oncological outcomes in patients treated with perioperative systemic therapy and CRS-HIPEC *versus* CRS-HIPEC alone. Hospital stay, ICU stay and in-hospital mortality were recorded.

## Statistical analysis

Categorical variables are presented as numbers of patients with percentages. Continuous and some of the ordinal variables are presented as median (i.q.r.) values. Baseline characteristics were compared using  $\chi^2$  test or Fisher's exact test for categorical variables. Continuous variables were compared using unpaired t test or Mann-Whitney *U* test, depending on distribution. Scatter plots were generated to show the relationship between the PCI and region count. Spearman's rank correlation was used to evaluate the association between the two continuous scoring tools. Additionally, the correlation coefficient was calculated for the extent of peritoneal disease at DLS and CRS-HIPEC, when available. Values of Spearman's correlation coefficient were interpreted as very weak (0.00–0.19); weak (0.20–0.39); moderate (0.40–0.59); strong (0.60–0.79); or very strong (0.80–1.00)<sup>24</sup>. Diagnostic values (sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and accuracy) of the region count with categories 0–5 and 6–7 were calculated with the PCI as standard and for different PCI cut-off values.

Table 1 Baseline characteristics of the study population			
	Netherlands Cancer Institute (n = 73)	Catharina Hospital (n = 85)	P‡
<b>Age (years)*</b>	61.8 (38.2–84.2)	66.0 (47.1–81.6)	0.010§
<b>Sex ratio (M : F)</b>	30 : 43	33 : 52	0.771
<b>ASA grade</b>			< 0.001
I	27 (37)	7 (8)	
II	42 (58)	60 (71)	
III	4 (5)	18 (21)	
<b>Co-morbidity</b>			0.947
Cardiovascular	10 (14)	20 (24)	
Hypertension	21 (29)	36 (42)	
Diabetes	7 (10)	13 (15)	
<b>Type of intraperitoneal chemotherapy used for HIPEC</b>			< 0.001
Oxaliplatin	60 (82)	3 (4)	
Mitomycin C	6 (8)	70 (82)	
Open-and-close	7 (10)	12 (14)	
<b>Completeness of cytoreduction</b>			0.391
CC-0	65 (89)	73 (86)	
CC-1	1 (1)	0 (0)	
Open-and-close	7 (10)	12 (14)	
<b>Region count†</b>	3 (2–5)	3 (2–5)	0.968§
0–2	25 (34)	30 (35)	
3–5	34 (47)	40 (47)	
6–7	14 (19)	15 (18)	
<b>PCI score†</b>	10 (4–15)	10 (5–16)	0.972§
0–10	38 (52)	43 (51)	
11–20	27 (37)	33 (39)	
21–39	8 (11)	9 (11)	
<b>Grade of SAE</b>			0.112
No SAE	51 (70)	46 (54)	
1	0 (0)	4 (5)	
2	11 (15)	16 (19)	
3	7 (10)	15 (18)	
4	4 (5)	3 (4)	
Unknown	0 (0)	1 (1)	
<b>Reoperation</b>			0.398
Yes	10 (14)	8 (9)	
No	63 (86)	77 (91)	
<b>In-hospital mortality</b>	0 (0)	0 (0)	
<b>Systemic chemotherapy</b>			0.528
None	50 (68)	60 (71)	
Adjuvant	9 (12)	6 (7)	
Neoadjuvant	9 (12)	15 (18)	
Perioperative	5 (7)	4 (5)	
<b>pT category</b>			0.368
pT2	1 (1)	3 (4)	
pT3	26 (36)	37 (44)	
pT4	43 (59)	42 (49)	
Unknown	3 (4)	3 (4)	
<b>pN category</b>			0.284
pN0	13 (18)	24 (28)	
pN1	24 (33)	23 (27)	

Table 1 Continued			
	Netherlands Cancer Institute (n = 73)	Catharina Hospital (n = 85)	P‡
pN2	33 (45)	34 (40)	
Unknown	3 (4)	4 (5)	
<b>Liver metastasis</b>			0.765
Yes	7 (10)	7 (8)	
No	66 (90)	78 (92)	
<b>Location of primary tumour</b>			0.562
Right colon	27 (37)	38 (45)	
Left colon	36 (49)	35 (41)	
Rectum	10 (14)	12 (14)	
<b>Differentiation grade</b>			0.421
Good	6 (8)	2 (2)	
Moderate	54 (74)	52 (61)	
Poor	12 (16)	11 (13)	
Missing	1 (1)	20 (24)	
<b>Primary tumour type</b>			0.881
Adenocarcinoma	59 (81)	66 (78)	
Mucinous adenocarcinoma	12 (16)	16 (19)	
Signet ring cell carcinoma	2 (3)	3 (4)	
<b>Peritoneal metastases</b>			0.649
Synchronous	36 (49)	45 (53)	
Metachronous	37 (51)	40 (47)	
<b>ICU stay (days)*</b>	1 (0–16)	2 (0–16)	0.718§
<b>Hospital stay (days)*</b>	12 (4–80)	10 (2–62)	<0.001§

Values in parentheses are percentages unless indicate otherwise; values are \*median (range) and †median (i.q.r.). HIPEC, hyperthermic intraperitoneal chemotherapy; PCI, Peritoneal Cancer Index; SAE, serious adverse event. § $\chi^2$  or Fisher's exact test, except §Mann-Whitney *U* test.

All analyses were performed using SPSS® version 25.0 for Windows® (IBM, Armonk, New York, USA) and GraphPad Prism® version 7.03 for Windows® (GraphPad Software, San Diego, California, USA).

## Results

### Exploration cohort

Of 87 patients operated on during the study interval at the Netherlands Cancer Institute, 73 were included in the analysis (Fig. 1); 66 patients underwent CRS–HIPEC and seven had an open-and-close procedure because PM were too extensive. Baseline characteristics of all patients are presented in Table 1. The median PCI was 10 (i.q.r. 4–15) and the median region count was 3 (2–5).

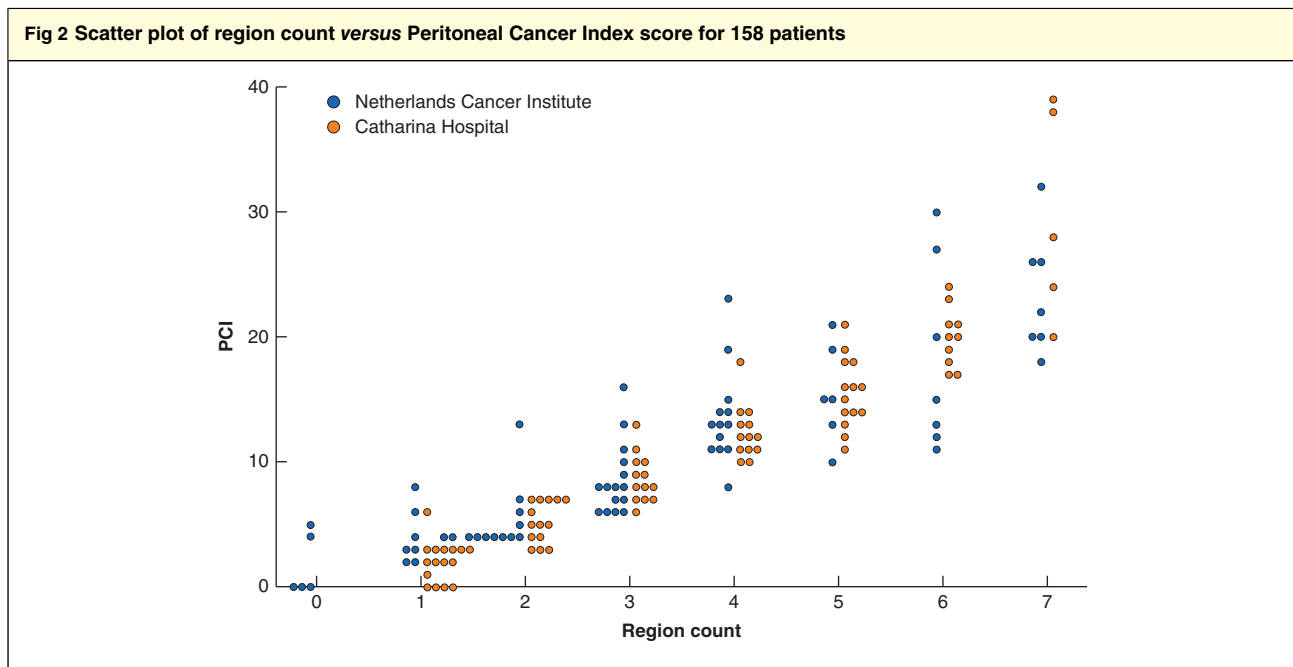
The relationship between PCI score and region count is presented in Fig. 2 and Table 2. For continuous region count (0–7) and PCI score (0–39) at the time of CRS–HIPEC a Spearman correlation coefficient of 0.897 ( $P < 0.010$ ) was observed. This correlation value is classified as a 'very strong correlation'<sup>24</sup>. The accuracy for all different cut-off values was good. For a PCI cut-off

value of 20, the best diagnostic values based on the region count were observed to decide whether patients were eligible for CRS–HIPEC.

Eighteen (25 per cent) of the 73 patients had DLS before CRS–HIPEC, all were performed at the NCI. CRS–HIPEC was eventually performed on 15 (83 per cent) of these 18 patients, and three (17 per cent) had an open-and-close procedure. The median time from DLS to CRS–HIPEC was 20 (i.q.r. 12–43) days. A Spearman correlation coefficient of 0.903 ( $P < 0.010$ ) was observed when comparing the region count observed at DLS with the count found during CRS–HIPEC. A Spearman correlation coefficient of 0.739 was observed when comparing the PCI score between DLS and CRS–HIPEC.

### Validation cohort

At the Catharina Hospital, 85 of 89 patients met inclusion criteria (Fig. 1). Compared with patients in the exploration cohort, those in the validation cohort were older, had a higher ASA grade and were discharged earlier from hospital (Table 1).



PCI, Peritoneal Cancer Index.

**Table 2 Diagnostic value of different Peritoneal Cancer Index cut-off values for the Netherlands Cancer Institute and Catharina Hospital**

PCI score cut-off	Region count cut-off 0–5, 6–7				
	Sensitivity (%)	Specificity (%)	PPV	NPV	Accuracy (%)
<b>Netherlands Cancer Institute</b>					
0–20, 21–39	87.7 (77.2, 94.5)	75.0 (34.9, 96.8)	96.6 (89.5, 99.0)	42.9 (25.9, 61.7)	86.3 (76.3, 93.2)
0–15, 16–39	93.1 (83.3, 98.1)	66.7 (38.4, 88.2)	91.5 (84.0, 95.7)	71.4 (47.6, 87.3)	87.7 (77.9, 94.2)
0–17, 18–39	91.7 (81.6, 97.2)	69.2 (38.6, 90.9)	93.2 (85.8, 96.9)	64.3 (41.9, 81.8)	87.7 (77.9, 94.2)
0–19, 20–39	91.9 (82.2, 97.3)	81.8 (48.2, 97.7)	96.6 (89.0, 99.0)	64.3 (42.6, 81.4)	90.4 (81.2, 96.1)
<b>Catharina Hospital</b>					
0–20, 21–39	90.8 (82.0, 96.2)	88.9 (51.8, 99.7)	98.6 (91.6, 99.8)	53.3 (35.2, 70.6)	90.6 (82.3, 95.9)
0–15, 16–39	100 (94.2, 100)	65.2 (42.7, 83.6)	88.6 (81.6, 93.1)	100.0	90.6 (82.3, 95.9)
0–17, 18–39	97.0 (89.6, 99.7)	72.2 (46.5, 90.3)	92.9 (86.0, 96.5)	86.7 (61.7, 96.3)	91.8 (83.8, 96.6)
0–19, 20–39	94.5 (86.6, 98.5)	91.7 (61.5, 99.8)	98.6 (91.4, 99.8)	73.3 (51.1, 87.9)	94.1 (86.8, 98.1)

Values in parentheses are 95 per cent confidence intervals. Sensitivity ( $a/a + b$ ), specificity ( $d/c + d$ ), positive predictive value (PPV) ( $a/a + c$ ), negative predictive value (NPV) ( $d/b + d$ ) and accuracy ( $a + d/a + b + c + d$ ), where  $a$  = true positives,  $b$  = false positives,  $c$  = false negatives and  $d$  = true negatives.

The relationship between PCI score and region count is presented in Fig. 2 and Table 2. A Spearman correlation of 0.961 ( $P < 0.010$ ) was observed for continuous region count (0–7) and PCI score (0–39) at the time of CRS–HIPEC, classified as a ‘very strong correlation’<sup>24</sup>.

A PCI cut-off value of 20 showed the best diagnostic values based on region count to determine patient eligibility for CRS–HIPEC.

Three patients had a PCI score above 20 and a region count of 5 or below. Fifteen patients had a PCI score of 20 or less and a region count of more than 5.

## Discussion

The PCI and Dutch region count can both be used to determine whether patients are eligible for CRS with or without HIPEC, based on a very strong correlation between the classifications. The best diagnostic values were observed with a PCI cut-off value of 20 in combination with a region count cut-off value of 5; these cut-off values correspond to the values applied in the institutes<sup>25</sup>. CRS–HIPEC is performed in only a few specialized hospitals. Surgeons in regional hospitals are likely to be less



experienced in estimating the extent of peritoneal disease, because of limited exposure to patients with PM compared with surgeons in HIPEC centres<sup>26,27</sup>. Reporting of PCI remains the preferred scoring system for assessment before CRS, as this score provides more information and may allow for better international comparison of results after CRS with or without HIPEC. The present authors, however, recommend including the Dutch region count, particularly for surgeons in referring centres, for preoperative imaging and during laparoscopy, as it is easier to apply, especially for those not performing CRS, and it correlates well with PCI.

PCI is widely accepted as scoring tool of choice to determine the extent of PM<sup>13</sup>, but international consensus on a cut-off value is lacking. Several studies<sup>13,25,28,29</sup> indicate a cut-off value of 20. A cut-off value of 15 has been applied by others<sup>16,30</sup>, and the BIG-RENAPE Working Group<sup>31</sup> used a cut-off value of 19. Another report<sup>19</sup> attempted to find a PCI threshold to select patients for CRS-HIPEC, and considered 17 to be the optimal cut-off value. The Dutch region count was introduced in the NCI in the late 1990s and has been used ever since. Five or fewer affected regions has been associated with a relatively good prognosis<sup>15</sup>, and therefore this cut-off value has been used in daily practice. In another study<sup>16</sup>, authors reconstructed the PCI score retrospectively and compared it with other scoring tools. They concluded that the PCI is tedious to implement, and there is a possibility of underestimating or overestimating tumour load and distribution.

The literature has described several obstacles for using PCI<sup>16,19,25</sup>, particularly during laparoscopy, because of incomplete visualization of the abdominal cavity or because dissection planes could not be reopened<sup>19,25</sup>. This is less problematic for region count, as the number of regions is lower and tumour burden within one region does not influence the score. Difficulties have been also reported in assessing the PCI in preoperative imaging studies<sup>19</sup>, as it appeared to underestimate tumour burden in at least one-third of the patients. Thus, scoring the extent of peritoneal disease according to the Dutch region count seemed more adapted to laparoscopy and, although this method is less refined, it has a major advantage of identifying patients with unresectable disease earlier in the process<sup>19</sup>.

Scoring of lesion size by the PCI might overestimate the extent of disease. CRS aims to remove all macroscopic tumour. Instead of merely focusing on peritoneal distribution, the PCI places great value on the lesion size. Historical reports showed improved survival for patients with a smaller volume of peritoneal carcinomatosis<sup>32</sup>, yet there is no clear evidence of differences in oncological outcome between lesion size 1 and 3 in particular. In

theory, one region with a big lesion size (LS 3) resembles the same extent of disease as three regions with small lesions (LS 1). Unilocular big masses and confluent multiple small deposits are both defined as high-volume disease, whereas these two categories have different tumour biology and prognostic impact<sup>16</sup>. The region count does not take lesion size into account, and thus might prevent overestimation. In the patient selection process for CRS-HIPEC, imaging and laparoscopy play an important role. Promising results<sup>33-35</sup> have also been reported using diffusion-weighted (DW) MRI (DW-MRI) to predict a PCI below 21. This accuracy was significantly better than the diagnostic value reported for CT, and may lead to the omission of laparoscopy in patients with a low (less than 10) or high (more than 24) PCI score<sup>35</sup>. However, DW-MRI is time-consuming, and patients are usually staged using CT, also to check for extraperitoneal disease.

This study has several limitations. Selection bias is inherently present owing to the retrospective design and inclusion of patients selected for surgical exploration alone. Patients who were considered ineligible for CRS during the preoperative process were not included. Moreover, although a good and significant correlation coefficient was seen in patients who had DLS, the number of patients who had this investigation was too small to draw valid conclusions. Although generalizability was pursued by external validation in this study, the patient populations differed.

The authors consider the region count very helpful, but acknowledge that evidence is lacking to support its additional value for non-CRS-HIPEC centres and abdominal radiologists. Future research on these scoring tools should focus on implementation of the region count into preoperative imaging and DLS to improve and simplify patient selection for CRS-HIPEC.

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F.S.V. and C.B. contributed equally to this publication.

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