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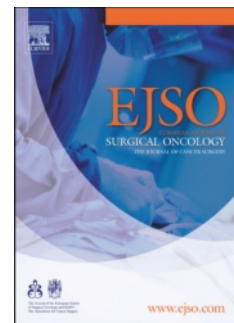
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Quantitative intra-operative assessment of peritoneal carcinomatosis
- A comparison of three prognostic tools

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ABSTRACT

Aims: Selecting patients for cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy (HIPEC) remains challenging. We compared the predictive power of three intra-operative assessment tools of peritoneal involvement of colorectal cancer.

Methods: 92 procedures (1999-2005) were prospectively scored using the Simplified Peritoneal Cancer Index (SPCI) and 7 Region Count. The Peritoneal Cancer Index (PCI) was retrospectively scored using the SPCI tool, operative notes and pathological reports. Endpoints were completeness of cytoreduction and overall survival. Logistic regression and Receiver Operating Characteristic (ROC) curves were applied to compare the predictive value of the 3 scoring systems on completeness of cytoreduction.

Results: After a median follow-up of 31 months, the median overall survival was 25.6 months. It decreased to 7.3 months, when cytoreduction was incomplete ($p=0.001$). An increased PCI, SPCI or number of regions were all associated with a decrease in probability of complete cytoreduction ($p<0.05$). With complete cytoreduction as outcome, the ROC area for the PCI, SPCI and 7 Region Count were 0.92, 0.94 and 0.90 respectively ($p=0.14$). Using a cut-off value of 16 in the PCI system ($p=0.03$), 13 in the SPCI system ($p=0.04$) and 6 regions in the 7 Region Count ($p=0.0002$) the probability of complete cytoreduction decreased significantly.

Conclusion: The PCI, SPCI and 7 Region Count are useful and equally effective prognostic tools predicting completeness of cytoreduction and associated improved survival. The 7 Region Count may be preferred due to its practical simplicity.

Keywords: Colorectal cancer, HIPEC, peritoneal carcinomatosis, peritoneal cancer index, simplified peritoneal cancer index.

INTRODUCTION

Peritoneal carcinomatosis (PC) is a manifestation of colorectal cancer being present in roughly 10% of patients at time of initial diagnosis and in approximately 25% of patients with recurrent disease¹⁻³. The natural history of PC is associated with a median survival of approximately 6 months^{4,5}. A prospective randomised phase III study⁶ and a multi-institutional study⁷ have both demonstrated that cytoreductive surgery followed by Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) improves survival in patients with peritoneal carcinomatosis of colorectal origin. These results have encouraged many surgical teams worldwide to embark on this relatively new treatment modality. Several studies show that HIPEC only works in patients who have undergone complete cytoreduction^{6,8}. Long-term survival only seems to be reserved for this subset of patients, as reported in the long-term results of the abovementioned randomized controlled trial. After a median follow up of almost 8 years we found a 5-years survival of 45% in this subset of patients.⁹

Patient selection is crucial to restrict this complex and potentially toxic treatment to patients in whom complete cytoreduction is feasible. Cytoreductive surgery combined with HIPEC is associated with high costs, a treatment related morbidity of 27-35 % and a mortality of 1.5-5%¹⁰⁻¹². Furthermore, early disease progression has been observed in up to 30% of patients.¹⁰

Consensus has been reached regarding pre-operative selection criteria. Patients with signs of extra-abdominal disease, with inoperable intra-abdominal disease, or with poor performance status are generally excluded from this extensive treatment. However, the low sensitivity of CT^{13,14} or MR imaging of PC, especially when tumour deposits are smaller than 1cm, makes pre-operative selection difficult and inaccurate. Exploratory laparotomy is often the only way to reliably assess and select patients.

At present, five quantitative intra-operative abdominal assessment tools have been described for this treatment modality: Gilly Staging¹⁵, Japanese Gastric Cancer P score¹⁶, Peritoneal Cancer Index (PCI)¹⁷, Simplified Peritoneal Cancer Index (SPCI)⁸ and the 7 Region Count⁸. Comparison between these prognostic tools with regards to their power to predict complete cytoreduction and long-term survival has yet not been attempted.

In this study, we compare 3 tools namely: the PCI, as introduced by Sugarbaker at the Washington Cancer Institute, the SPCI and the 7 Region Count, as used at Netherlands Cancer Institute, in a series of 92 patients with peritoneal carcinomatosis of colorectal origin treated at the Netherlands Cancer Institute between 1999 and 2005.

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PATIENTS AND METHODS

Scoring tools

The Peritoneal Cancer Index (PCI) was established at the Washington Cancer Institute by Sugarbaker¹⁷ and combines cancer implant size with cancer distribution, throughout 13 abdominopelvic regions, producing a quantitative score with a maximum of 39. Two transverse and two sagittal straight lines, together with a division of the small bowel, artificially divide the abdomen into 13 regions. Each region is defined by the anatomic structures situated in that region. Figure 1 describes how lesion size and distribution are scored.

The Simplified Peritoneal Cancer Index⁸ (SPCI) was established in the Netherlands Cancer Institute. The SPCI, like the PCI, calculates the tumour load, incorporating the tumour thickness with extent of peritoneal dissemination. However, the abdomen is, for practical convenience, divided into 7 anatomical regions. Each region incorporates certain anatomical structures and scoring is based on the visualized maximum thickness of tumour nodules in each region. The SPCI adds up to a maximum score of 21 (figure 1).

The more user friendly 7 Region Count⁸ (figure 1) was introduced by the Netherlands Cancer Institute following the SPCI and solely describes the number of affected regions out of 7 in the SPCI system, regardless of the tumour volume. Since 2002, 6 or 7 affected regions has served as a contra-indication for the combined modality treatment in the Netherlands Cancer Institute.

Data collection

Ninety-two patients with peritoneal carcinomatosis of colorectal origin were treated by cytoreductive surgery and intra-operative HIPEC, between 1999 and 2005, at the Netherlands Cancer Institute. Procedures were performed as described by our group previously¹². Patients with pseudomyxoma peritonei or other malignancies were not included.

During laparotomy, involvement of 7 peritoneal regions, as well as tumour nodule size per region were prospectively recorded using the SPCI registration form¹⁸. With the help of operative notes and pathological reports, procedures were subsequently retrospectively scored using the PCI scoring system. In cases where information on regions and/or tumour load was incomplete, missing data was translated from the SPCI scoring sheet to the PCI scoring sheet. The PCI lesion size (LS) groups differ

in magnitude from the SPCI groups (table 1). LS-0, -2 and -3 are convertible from SPCI to PCI. However, when directly converting the LS-1 score from the SPCI score (<2cm) to the PCI score (<0.5cm) lesions measuring 0.5-2cm in the PCI tool would be underscored (1 instead of 2). We corrected for this underscored PCI group 0.5-2cm by allocating 1.5 instead of 1 point to the PCI group LS-1. When tumour location in the small bowel was inconclusive it was scored as follows: the distal ileum was scored when only isolated lesions were recorded which did not require partial bowel resection. The proximal and distal ileum were scored when the small bowel mesentery was involved or when partial resection was recorded. The distal jejunum was added to the combination when multiple small bowel resections were recorded and all four regions were scored when extensive small bowel infiltration was recorded to have created a surgical dilemma.

Completeness of cytoreduction was recorded as follows; R1: no macroscopic residual tumour, R2a: residual tumour ≤ 2.5 mm and R2b: residual tumour > 2.5 mm. Complete cytoreduction was defined as a R1 or R2a result in this study.

Statistical analysis

Logistic regression and Receiver Operating Characteristic (ROC) curves were applied to compare the predictive value of the 3 scoring systems on completeness of cytoreduction, e.g. R1 or R2a and R2b. Statistical level of significance in predicting complete cytoreduction was set at $p=0.050$. Overall survival was calculated from date of HIPEC procedure until date of death or date of last follow-up. Progression free survival was calculated from date of HIPEC procedure until date of progression or recurrence, date of death or date of last follow-up. Overall and progression free survival were investigated by a Cox regression. An uni- and multivariate analysis was performed for the following factors: gender, affected region, number of affected regions, result of cytoreduction, SPCI score and PCI score.

RESULTS:

Quantitative assessment analysis

Ninety-two procedures were performed and analyzed in 49 women and 43 men. The median follow-up was 31 months (range 0-67). The median PCI score was 8.8 (range 0-26) and the median SPCI score was 6 (range 0-18). The mean number of affected regions was 3.8 of the 7 regions while in 20 patients more than 5 of the 7 regions were affected. The mean number of affected regions in the PCI system was 5 of the 13. In 58 patients a recurrence or progression developed. Forty-five patients died of which 42 due to disease and 3 due to complications.

Results of the PCI system showed that the pelvis was the most affected region (80 of the 92 patients), followed by the central abdomen affected in 72 patients and the lower ileum affected in 65 patients. Volume of tumour was also found to be the greatest in the pelvis region followed by the central abdomen with a lesion size of >5cm in 24 and 14 patients, respectively. In the 7 regions used in the SPCI and the 7 Region Count similar results were noted in the pelvis and omentum/ transverse colon regions. The least affected regions in the PCI system were the lower jejunum (7 patients) followed by the upper jejunum together with the left flank, both affected in 8 patients. In the SPCI/ 7 Region Count the left subphrenic space was least affected (16 patients).

After cytoreductive surgery, no residual tumour (R-1) was left in 58 patients while in 26 patients residual tumour deposits measured less than 2.5mm (R-2a). In 8 patients the cytoreduction was grossly incomplete (R-2b). In the latter group the PCI score ranged between 13-21 with a median of 18 while the SPCI score ranged between 10-18 with a median of 12. The median number of affected regions in this group was 6.5 of the 7 regions.

Logistic regression on result of cytoreduction

In the univariate analysis, both an increased PCI and SPCI, as well as an increased number of affected regions, were significantly associated ($p<0.05$) with a decrease in probability of complete cytoreduction (figure 2). Using, in the literature described, cut-off values of <16 in the PCI system ($p=0.0002$), <13 in the SPCI system ($p=0.0011$) and <6 regions in the 7 Region Count ($p=0.0018$) the probability of complete cytoreduction decreased significantly when the cut-off was exceeded, as shown in table 2.

Figure 3 shows the ROC curves for the three prognostic tools. The ROC areas for the PCI, SPCI and 7 Region Count tools were 0.92 (95% CI 0.84-0.98), 0.94 (95% CI 0.89-0.99) and 0.90 (95% CI 0.83-0.97), respectively. By nearing the maximum value of 1, these estimates of the ROC areas indicate that all three prognostic tools are highly accurate in predicting a complete cytoreduction result. The difference between the three was not significant ($p=0.14$), suggesting that the three systems are similar.

Survival analysis

The median overall survival was 25.6 months (95%CI 20.9 - 29.4), with a median progression free survival of 13.6 months (95%CI 11.2-16.4). The overall survival decreased from 26.2 to 7.3 months when cytoreduction was incomplete ($p=0.001$, hazard ratio 3.9, 95%CI 1.7-8.8). In all three tools the quantitative scores were significant prognostic factors for overall survival, whereby a higher score/number of affected regions correlated with a decreased survival. Using the cut-off values of <16 in the PCI system ($p=0.03$), <13 in the SPCI system ($p=0.04$) and <6 regions in the 7 Region Count ($p=0.0002$) the overall survival decreased significantly when the cut-off was exceeded, as shown in table 2.

In univariate analysis, 3 of the 13 PCI regions [right upper (Hazard-Ratio 2.7), epigastrium (HR 3.9) and lower ileum (HR 2.3)] and 4 of the 7 SPCI regions [small bowel and mesentery (HR 2.5), right lower abdomen (HR 2), subhepatic space (HR 4.1) and left subphrenic area (HR 2.7)] were, when affected, significantly associated with decreased overall survival and progression free survival (except small bowel and mesentery).

In the multivariate analysis of affected regions and result of cytoreduction, the epigastric region (HR 3.3) in the PCI system and the subhepatic space (HR 2) in the SPCI system were independent significant prognostic factors for overall survival.

DISCUSSION

Prime objective is complete cytoreduction

The results of this study are in line with previous studies with regard to poor overall survival in patients in whom cytoreduction is incomplete. Prime objective in the selection of patients for this therapy must therefore be the probability to achieve complete cytoreduction. Our results show that the PCI, SPCI and the 7 Region Count scoring systems are equally effective in this respect. The 7 Region Count is however the easiest to implement, and may therefore has some advantage over the other systems.

Cut-off values for the PCI

The Washington Cancer Institute, pioneering the treatment modality, established the Peritoneal Cancer Index¹⁷ and implemented it in the assessment of peritoneal involvement of sarcoma¹⁹, mesothelioma²⁰, ovarian²¹ and colorectal cancer²². Sugarbaker²² reported that the 5 year survival of approximately 100 colon cancer patients was 50% with a PCI less than 10, 20% with a score of between 11-20 and 0% in those with a score of more than 20. They suggest a cut-off PCI of 20 above which the treatment should be abandoned and be replaced by palliative surgery. Elias and colleagues²³ described that a PCI of less than 16 resulted in a significantly more favourable prognosis. In a series of 64 patients with peritoneal involvement of colorectal cancer they reported a 3 year survival of 60% versus 33 % using this cut-off value. Our study confirmed these results whereby a PCI score < 16 was associated with a median survival of 25.6 months while it was 11.3 months for a score of 16 or more (p=0.03). Remarkably, there was no survival advantage of a PCI cut-off of >20 versus >16, as no patients in our study survived 30 months with a PCI of >16 or >20. The following critical comments regarding the PCI should, however, be addressed. Firstly, the numerous amount of 13 regions makes the tool tedious to implement. Secondly, the negative effect of small bowel involvement on prognosis is together with other crucial anatomical sites a well known and important fact. However, the desired advantage by encompassing this fact (dividing the small bowel into 4 regions) is neutralized by the increased chance of an inaccurate overestimation of this region. The subjective and vague transitional point of the proximal and distal small bowel creates a possibility to under or overestimate tumour load and distribution. Resectable tumour nodules situated on transitions or if one small lesion is resectable on

each of the four small bowel regions should leave the patient with sufficient functional small bowel but would receive a highly overestimated PCI.

Cut-off values for the SPCI and 7 Region Count

Our group⁸ previously described important factors predicting poor outcome including poor differentiation, signet cell histological type and primary location of tumour in the rectum. Furthermore, no long-term survival has been achieved in patients where complete cytoreduction failed, acknowledging that complete cytoreduction is a basic necessity for a positive outcome¹⁸. We introduced a simplified version of the PCI scoring system to maximize simplicity and practicality and proved that it was useful in patients with colorectal cancer. Using the simple seven anatomic regions we observed that patients where more than 5 of the 7 regions are affected or with a SPCI greater than 12, the possibility of treatment benefit significantly diminished and was related to an increased rate of post-operative complications resulting in a higher morbidity and mortality rate¹². We then went on to suggest that a SPCI of greater than 12 or 6-7 regions affected should serve as an intra-operative exclusion criterion. The results of this study confirm these previous reports. A SPCI score of lower than 13 was associated with a significantly increased overall survival (overall 25.6 versus 20.9 months, $p=0.04$) compared to patients with a higher SPCI. Furthermore, patients in whom up to 5 regions were affected had an overall survival of 27.7 months. This decreased drastically to 12.6 months when 6-7 regions were affected. A shortcoming of these two versions of the SPCI tool is the inadequacy to encompass the additional negative prognostic value of anatomical crucial sites.

Other scoring systems

The assumption underlying the PCI and SPCI is that tumour size, additional to tumour distribution predicts outcome. This is in line with the TNM system widely used in oncology and validated for many types of cancer, which shows that more cancer predicts poorer prognosis. So why does it seem to be different in peritoneal carcinomatosis of colorectal origin? A clue may be that many of the high volume regions recorded in our patients were ovarian metastases, omental metastases and primaries or recurrences around the cecum. These tumour deposits usually are technically easy to resect. In this series, high volume disease in these areas did not adversely affect completeness of cytoreduction or survival. On the other hand, even small tumour deposits in the porta hepatis and around the pancreas

are difficult to resect completely. This may explain why tumour deposits in these areas related significantly to poorer survival. It must also be emphasized that both PCI and SPCI are including both unilocular big masses and confluent multiple small deposits as high volume disease. It seems clear that these two categories of high volume disease represent a different tumour biology, and probably a different prognostic impact. In this respect Gilly probably has a point when he emphasizes the prognostic significance of the distinction between localized and diffuse presentation of PC. He introduced the Gilly Peritoneal Carcinomatosis Staging¹⁵ which incorporates implant size (<5mm, 5-20mm, >20mm) and distribution (localized or diffuse). Its efficacy was demonstrated in the EVOCAPE⁵ study investigating the natural history of peritoneal involvement in patients with amongst others gastric, pancreatic, liver and colorectal cancer (n=118). The tool was also implemented in a study of 56 patients receiving the combined modality treatment²⁴. The prognostic efficacy of the tool in the 26 colorectal cancer patients included in this study was however not reported. Unfortunately, a shortcoming of this simple prognostic tool is that the distribution is unspecific and incomplete in stages 3 and 4. The tool is inadequately capable of discriminating stages 2, 3 and 4. Stage 3 and 4 incorporate only the size of a lesion, without describing distribution. With the likelihood of cytoreduction being a chief prognostic indicator, a technically resectable solitary large tumour mass of 4cm on the descending colon (stage 4) is related to a better prognosis than small nodules diffusely spread over the abdomen (grade 2). Finally, the Japanese¹⁶ established and validated a relatively simple tool to assess peritoneal involvement of gastric malignancy. Patients are divided into 4 groups after exploration and cytological tests. To our knowledge, no reports have been made on the implementation of this tool in colorectal cancer patients. Because we studied patients with PC of colorectal origin in this series, we chose to exclude the latter two scoring systems in our study.

Study Limitations

Due to its design, this study has its limitations. Although the SPCI and the 7 Region Count were prospectively recorded and are probably accurate, the PCI was retrospectively assessed. This may have led to some underscoring, especially regarding tumour distribution and tumour size on the small bowel. Another weak point is the fact that from 2002 onwards, patients with 6 or 7 affected regions were excluded from the treatment causing a selection bias in our study population. It is however

difficult to foresee any new studies that will neglect the important lessons for selection that have been learnt the hard way during the past decade, both by our group and others. A prospectively designed study would more accurately be able to compare the scoring systems. A large disadvantage, however, is that it would take numerous years before survival analysis can be done and conclusions made.

Conclusion

Notwithstanding this, the message from this study is clear: Intra-operative selection for cytoreduction and HIPEC in patients with peritoneal involvement of colorectal cancer should be based on early assessment of the extent of the peritoneal deposits. A PCI ≥ 16 , a SPCI ≥ 13 and a 7 Region Count >5 are indications to abort the attempt to complete cytoreduction and scale back to palliative approaches. These three staging tools are equal in their accuracy.

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Conflict of interest

The authors state that they have no conflict of interest.

Legends:

Table 1: Scoring of the lesion size

* to correct for an underscored PCI group 0.5-2cm, score=1 in the SPCI was scored as 1.5 in the PCI group. For example, a tumour nodule sized 1,3cm was scored 1 point in the SPCI system and 1,5 in the PCI system. It would have received 1 without this correction and 2 if it was prospectively scored using the PCI system.

Table 2: Prognostic tools with associated probability of complete cytoreduction and overall survival

Figure 1: The 3 prognostic tools: Peritoneal Cancer Index (PCI)*, Simplified Peritoneal Cancer Index (SPCI) and 7 Region Count

* with permission from P. Sugarbaker.

Figure 2: Estimated probability of complete cytoreduction using the PCI, SPCI and the 7 Region count

Figure 3: Receiver Operating Characteristic Curve

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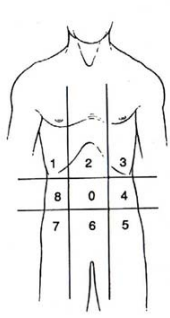
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Lesion Size (LS)		
Lesion Size Score	PCI	SPCI
0	None	None
1*	< 0.5cm	<2cm
2	0.5-5cm	2-5cm
3	>5cm	>5cm
Total Maximum Score (regions \times LS)	39 (13 \times 3)	21 (7 \times 3)

	PCI		SPCI		7 region count	
	<16	≥16	<13	≥13	0-5 regions	6-7 regions
Number of patients	82	10	83	9	72	20
Probability complete cytoreduction (95%CI)	96 (89-99)	50 (23-78)	95 (88-98)	56 (25-82)	97 (90-99)	70 (47-86)
Median overall survival (95%CI)	25.6 (21-33)	11.3 (7-28)	25.6 (21-61)	20.9 (10-28)	27.7 (23-61)	12.6 (10-23)

A


Regions

- 0 Central
- 1 Right Upper
- 2 Epigastrium
- 3 Left Upper
- 4 Left Flank
- 5 Left Lower
- 6 Pelvis
- 7 Right Lower
- 8 Right Flank
- 9 Upper Jejunum
- 10 Lower Jejunum
- 11 Upper Ileum
- 12 Lower Ileum

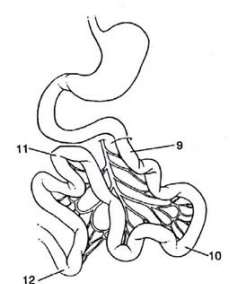
Lesion Size

Lesion Size Score

- LS 0 No tumor seen
- LS 1 Tumor up to 0.5 cm
- LS 2 Tumor up to 5.0 cm
- LS 3 Tumor > 5.0 cm or confluence

PCI

☐


B

<u>Tumour Size</u>	None	<2cm	2-5cm	>5cm
Score	0	1	2	3
Pelvis				
Right Lower Abdomen				
Omentum/Transverse Colon				
Small Bowel/ Mesentery				
Subhepatic Space/ Stomach				
Right Subphrenic Space				
Left Subphrenic Space				

C

Regions	Affected: yes/no
Pelvis	
Right Lower Abdomen	
Omentum/Transverse Colon	
Small Bowel/ Mesentery	
Subhepatic Space/ Stomach	
Right Subphrenic Space	
Left Subphrenic Space	

