

# Patient selection for cytoreductive surgery and HIPEC for the treatment of peritoneal metastases from colorectal cancer

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**Abstract:** Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a viable option for selected patients with peritoneal metastases (PM) from colorectal origin, resulting in long-term survival and even cure in some cases. However, adequate patient selection for this treatment is currently one of the major challenges. The aim of this review is to provide a comprehensive overview of clinically relevant factors associated with overall survival. This may help to guide clinicians through the complex interplay of patient, tumor, and treatment characteristics to adequately select patients who benefit the most from this extensive surgical treatment. First, basic principles of colorectal PM and the CRS and HIPEC treatment will be discussed. According to available literature, especially extent of peritoneal disease, completeness of cytoreduction, and signet ring cell histology have great influence on the outcome after CRS and HIPEC. Other factors that seem to have a negative prognostic value are the presence of liver metastases and the absence of treatment with neo-adjuvant systemic therapy. Prognostic models combining the above-mentioned factors, such as the Colorectal Peritoneal Metastases Prognostic Surgical Score nomogram, may provide clinically relevant tools to use in everyday practice.

**Keywords:** cytoreductive, hyperthermic intraperitoneal chemotherapy, colorectal neoplasms, peritoneal metastases, prognostic factors

## Introduction

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is an extensive surgical treatment for patients with colorectal peritoneal metastases (PM). One of the major challenges is adequate patient selection for this procedure. This review aims to give a comprehensive overview of this disease and its treatment, with special emphasis on patient selection. Therefore, the most important prognostic factors will be discussed according to available literature. This review will help to guide clinicians through a complex interplay of patient, tumor, and treatment characteristics to adequately select patients who benefit the most from this extensive surgical treatment.

## Colorectal cancer

In Western countries, ~15% of all cancer diagnoses have a colorectal origin. Colorectal cancer is the fourth most prevalent type of cancer and ranks second in the absolute number of estimated cancer deaths in the United States.<sup>1</sup> Metastatic disease is the most important cause of death in colorectal cancer patients. Up to one-quarter of the patients present with synchronous stage IV disease, and another 20%–30% develop recurrent or systemic disease during the follow-up period after curative treatment of the primary tumor.<sup>2–5</sup> The liver is the most common metastatic site of colorectal cancer.<sup>6</sup>

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The second most common manifestations are metastases to the peritoneal cavity, which have major consequences for treatment and prognosis.<sup>7</sup>

## PM

PM, commonly referred to as peritoneal carcinomatosis, are metastatic deposits on the peritoneal surface throughout the abdominal cavity. These deposits may invade abdominal organs and structures, thereby frequently causing bowel obstruction, ureteral obstruction, and malignant ascites. PM may arise from virtually every primary tumor, with the most common origins being ovarian cancer in females and colorectal cancer in males.<sup>8</sup> Other frequent origins include the stomach and pancreas, whereas the primary origin remains unknown in a substantial number of patients.<sup>9-11</sup> Pseudomyxoma peritonei is another rare disease entity that frequently presents with peritoneal depositions. This condition is characterized by mucinous ascites and mucinous peritoneal implants, which most often originate from a ruptured low-grade mucocele of the appendix.<sup>12</sup>

In summary, PM may originate from various underlying diseases with a large variation in epidemiology, treatment strategy, and prognosis. This review will solely discuss the treatment of patients with PM from colorectal origin.

## Epidemiology of colorectal PM

The incidence of synchronous PM in patients with colorectal cancer is ~5%, comprising 25% of all patients with synchronous stage IV disease.<sup>13,14</sup> PM developing in the follow-up period after curative treatment of the primary colorectal tumor is called metachronous PM. Eventually, ~5% of the patients develop clinically relevant metachronous PM during the disease course.<sup>14-16</sup> Given the PM rate of up to 40% in autopsy studies, the previously mentioned percentages are thought to be an underestimation of reality.<sup>17</sup> This may be caused by a large group of patients without specific symptoms in whom PM were not discovered during life, probably due to the low accuracy of conventional imaging.<sup>18</sup>

## Risk factors for colorectal PM

Lemmens et al have identified an advanced T stage, lymph node metastases, and a poor differentiation grade as independent risk factors for synchronous PM.<sup>13</sup> Since the possibilities for preventing metachronous PM are more promising than for synchronous PM, the evidence regarding risk factors for metachronous metastases is more extensive. According to several studies, independent risk factors for metachronous PM are advanced T and N stage, emergency surgery, a colon

versus rectal primary, and free intraperitoneal cancer cells before and/or after primary tumor resection.<sup>14-16,19</sup> Besides these factors, mucinous adenocarcinomas and signet ring cell carcinomas tend to metastasize more frequently to the peritoneum than other histological subtypes.<sup>7</sup>

## Preventing metachronous colorectal PM in high-risk patients

One of the most promising subjects of future research is the prevention of metachronous colorectal PM. Although results were biased, a recent systematic review pointed toward promising results of adjuvant intraperitoneal chemotherapy in colorectal cancer patients at high risk of PM.<sup>20</sup> Following these results, the randomized controlled COLOPEC trial is currently including patients in the Netherlands.<sup>21</sup> In the experimental arm of this trial, patients with pT4 or perforated colon cancer who underwent curative resection receive adjuvant treatment with HIPEC, which is thought to reduce the risk of peritoneal recurrence.

## Systemic treatment of colorectal PM

For many decades, there has been little interest in investigating the treatment of colorectal PM, mainly due to the rapid progression of the disease and the lack of curative options. Curative intent surgery played a minor role in the treatment, which mainly focused on symptom relief. The efficacy of palliative systemic chemotherapy for colorectal PM remains less evident than its efficacy for other colorectal cancer metastases.<sup>22</sup> Population-based studies reported median survival rates of up to 12 months in patients with colorectal PM who were treated with palliative systemic therapy.<sup>23</sup> The highest currently achievable median survival in selected patients treated with systemic chemotherapy is 24 months.<sup>24</sup> Other studies demonstrated that the addition of targeted agents to systemic chemotherapy might further improve survival.<sup>25,26</sup> However, as the peritoneum and abdominal cavity have an impaired blood supply the efficacy of systemic therapy remains limited.

## CRS and HIPEC

Based on the hypothesis that colorectal PM are a locoregional disease, a new surgical technique was first described in 1980 and further introduced by Paul Sugarbaker in the early 1990s.<sup>27,28</sup> This multimodality treatment generally consists of two steps. First, all macroscopically visible tumor tissue is removed from the peritoneal surface by performing both peritoneal and visceral resections. This part is called CRS.

CRS is followed by HIPEC, which is thought to eliminate the remaining microscopic tumor cells.

The effect of CRS and HIPEC in patients with colorectal PM has been investigated in two randomized controlled trials.<sup>29,30</sup> The first study by Verwaal et al showed a significant survival benefit in patients who underwent CRS and HIPEC followed by adjuvant systemic 5-fluorouracil with leucovorin compared to patients who received systemic 5-fluorouracil with leucovorin. However, due to this study's outdated systemic chemotherapy regimen and the lack of a CRS only control group, several questions regarding the true benefit of CRS and HIPEC remain unanswered. The randomized controlled trial by Cashin et al was terminated prematurely due to recruitment difficulties. Nevertheless, with 24 patients in each arm a significant survival benefit was found in patients treated with CRS and HIPEC compared to patients treated with oxaliplatin-based chemotherapy. Because of difficulties in conducting more randomized controlled trials, the current practice is mainly based on large retrospective cohort studies. These multicenter analyses reported median overall survival rates of up to 63 months in highly selected patients successfully treated with CRS and HIPEC.<sup>24,31–34</sup> In a small percentage of patients, this treatment even achieved cure.<sup>35</sup> Based on these randomized trials and cohort studies, CRS and HIPEC is currently incorporated in many guidelines worldwide.<sup>36</sup>

## Patient selection for CRS and HIPEC

Although CRS and HIPEC is the standard of care in selected patients with colorectal PM in several countries, various clinical issues urgently need to be optimized to improve the outcome for these patients. While the reported median survival is ~36 months, the 1-year mortality rate and the 1-year recurrence rate after CRS and HIPEC are 13% and 35%, respectively.<sup>37,38</sup> Currently, the major challenge is to select patients for CRS and HIPEC who benefit the most from this treatment along with acceptable treatment-related morbidity and mortality. In this review, several aspects of patient selection for CRS and HIPEC as treatment for colorectal PM are discussed.

## Extent of peritoneal disease

Probably, the most important and evident prognostic factor is the extent of peritoneal disease. Although several scoring systems exist, the peritoneal cancer index (PCI) score is the most commonly used and best validated.<sup>39</sup> Numerous large cohort studies have identified the PCI score as a major prognostic

factor.<sup>31,33,40–42</sup> Goéré et al even stated that CRS and HIPEC does not seem to offer any survival benefit in patients with a PCI score of  $\geq 17$ .<sup>43</sup> Based on results from the aforementioned studies, surgeons should withhold performing CRS and HIPEC in patients with a PCI score  $>20$ . Furthermore, a closely related factor is the extent of small bowel involvement.<sup>44</sup> CRS and HIPEC should not be performed if such a large portion of the small bowel is affected by disease that resection would result in a short bowel syndrome.

Computed tomography (CT) has a low sensitivity and specificity for detection of PM, and the radiological extent of peritoneal disease does not adequately correlate with the intraoperative PCI score.<sup>18</sup> Improved performance may be expected from magnetic resonance imaging or from the combination of positron emission tomography and CT.<sup>45,46</sup> Unfortunately, these imaging modalities also underestimate small peritoneal lesions, and more sensitive imaging techniques are therefore required. So far, diagnostic laparoscopy with histological confirmation remains the gold standard for diagnosing and quantifying colorectal PM, despite its more invasive character.<sup>47</sup>

## Completeness of cytoreduction

The completeness of cytoreduction score measures the amount of macroscopically visible tumor that is seen after CRS. Completeness of cytoreduction is so essential that experts agree that CRS and HIPEC should only be performed if complete or nearly complete macroscopic cytoreduction is feasible.<sup>36</sup> In a study by Verwaal et al, patients with gross residual disease of  $>2.5$  cm (R2b) had a median survival of just 5 months, compared to 17 months in patients with residual disease between 2.5 mm and 2.5 cm (R2a) and 39 months in patients with macroscopic complete cytoreduction (R1).<sup>48</sup> Similar results were found by other large studies with a focus on prognostic factors.<sup>31,33,42,49,50</sup> In more recent studies, the completeness of cytoreduction is less often identified as a prognostic factor, mainly because of a low number of incomplete cytoreductions.<sup>41</sup>

Since the likelihood of a complete macroscopic cytoreduction is related to a surgeon's experience, CRS and HIPEC should only be performed in specialized high-volume centers.<sup>51</sup> When implementing this procedure in a new center, extensive training from experienced colleagues is essential.

The development of intraoperative fluorescence imaging techniques for detecting PM provides interesting possibilities for more effective cytoreduction. The general concept of these techniques is to combine a tumor-specific antibody with a fluorescence probe, thus enabling intraoperative visualization

of tumor spots with near-infrared light. Several preclinical studies showed that these techniques have great potential for detecting PM.<sup>52,53</sup> Clinical research is needed to confirm these promising results in the near future.

## Liver metastases

For a long time, patients with combined peritoneal and liver metastases were not treated with curative intent, which at least partly attributed to the poor population-based median survival of 5 months.<sup>54</sup> However, a curative approach may be considered in highly selected PM patients with limited and resectable hepatic disease.<sup>55,56</sup> Consequently, over the last decade, a substantial number of studies have reported on patients who were treated with CRS and HIPEC combined with local treatment of liver metastases.

In these patients, a recently updated review of clinically heterogeneous studies revealed a median overall survival that ranged from 6 to 49 months, which was lower than in patients with isolated PM in most of the included studies.<sup>55</sup> Additionally, a recent meta-analysis reported a significantly higher risk of death (hazard ratio 1.30) for patients with both liver metastases and PM treated with curative intent compared to patients with isolated PM.<sup>56</sup> In addition, several retrospective cohort studies reported similar or slightly impaired survival outcomes in patients with CRS and HIPEC for PM combined with liver surgery for hepatic metastases, along with similar treatment-related morbidity.<sup>57–59</sup>

In conclusion, a patient tailored approach in patients with both peritoneal and liver metastases may result in long-term survival with acceptable morbidity. Nevertheless, survival seems to be slightly diminished compared to patients with isolated PM. Elias et al developed a tumor load-based nomogram to predict survival prior to optimal surgery in these patients, which might be of value in the complex process of decision making for this intensive treatment.<sup>60</sup>

## Signet ring cell carcinomas

Generally, colorectal carcinomas are divided into three different histological subtypes; adenocarcinomas (85%–90%), mucinous adenocarcinomas (10%–15%), and signet ring cell carcinomas (1%).<sup>7</sup> Regardless of treatment, the prognosis of patients with colorectal PM is strongly influenced by these histological types.<sup>26</sup> Signet ring cell histology is particularly associated with a poor prognosis, with a median survival of <3 months when treated with palliative care.<sup>61</sup>

The negative prognostic impact of this histological subtype has also been described in patients who were treated with CRS and HIPEC.<sup>62–65</sup> In several retrospective cohort series,

median survival rates do not exceed 13 months after CRS and HIPEC, and 5-year survivors have not been reported. Additionally, several studies that focused on prognostic factors identified signet ring cell histology as an important negative factor with hazard ratios ranging from 2.0 to 3.7.<sup>41,48,56,66</sup>

Nevertheless, with respect to palliative care, a similar relative survival gain can be achieved by CRS and HIPEC in patients with signet ring cell histology compared with patients with adenocarcinomas and mucinous adenocarcinomas.<sup>61</sup> The authors from this population-based study conclude that patients with signet ring cell carcinomas benefit from CRS and HIPEC. Since patients with these carcinomas are often young, an aggressive surgical approach may be a realistic option in a highly selected subgroup.

## Rectal origin of PM

In non-metastasized patients, colon and rectal cancer are considered as separate entities with a different treatment and prognosis.<sup>67,68</sup> In peritoneally metastasized patients who are treated with CRS and HIPEC, these differences are less evident. Colorectal PM are often considered as one disease, regardless of their colon or rectal origin. As a result, the large group of colon cancer patients often camouflages the results of the small portion of rectal cancer patients.

The available evidence that reported on survival rates of patients with rectal PM treated with CRS and HIPEC is contradictory and consists of retrospective cohort studies. The most recent and largest study included 29 rectal cancer patients and reported similar recurrence and survival rates compared with colon cancer patients, with 5-year survival rates of ~30% in both groups.<sup>69</sup> Similar results were found in two smaller retrospective studies.<sup>70,71</sup> These results are in contrast with two studies with rectal cancer patients who were treated with CRS and HIPEC (n=5 and 11), in which survival was diminished compared to colon PM patients.<sup>48,72</sup> In large studies that investigated prognostic factors for survival after CRS and HIPEC, a rectal origin did not seem to influence survival.<sup>33,40,56,73</sup> Even in selected cases of locally advanced rectal cancer with synchronous PM, long-term survival and acceptable morbidity were achieved with a combination of CRS and HIPEC and intraoperative radiotherapy.<sup>74</sup> In conclusion, CRS and HIPEC is a feasible option in selected patients with PM from rectal cancer, with similar outcomes as patients with PM of colon cancer.

## Neo-adjuvant systemic treatment

The value of neo-adjuvant systemic therapy remains controversial due to an absence of randomized studies. Several

retrospective observational studies analyzed survival outcomes of patients who were stratified for neo-adjuvant versus no neo-adjuvant systemic therapy.<sup>31,33,35,75–78</sup> However, results of studies on this topic are hardly interpretable due to clinical heterogeneity, selected populations, and the absence of details on systemic regimens.<sup>86</sup> Therefore, available evidence does not allow for definitive conclusions and recommendations.

Hypothetically, neo-adjuvant systemic therapy may increase the chance of achieving a complete cytoreduction by preoperative tumor downsizing. However, a pooled subgroup analysis of randomized studies in advanced colorectal cancer endorses the dogma that colorectal PM are relatively resistant to systemic therapy compared to other isolated sites of metastases.<sup>22</sup> By using Blazer's classification, Passot et al reported a complete and major pathological response rate of 10% and 20%, which was lower than the reported pathological response rates of colorectal liver metastases.<sup>79–81</sup> To date, no studies have prospectively investigated the pathological tumor response of colorectal PM to neo-adjuvant systemic therapy. Three single arm Phase II studies are currently investigating the safety, feasibility, and efficacy of neo-adjuvant FOLFOX with bevacizumab (BEV-IP trial, NCT02399410), FOLFOX-IRI with bevacizumab (CARCINOSIS trial, NCT02591667), and FOLFOX/FOLFIRI with cetuximab (COMBATAC trial, NCT01540344) prior to CRS and HIPEC for potentially resectable colorectal PM. Results of these studies will provide more insight in the sensitivity of colorectal PM to modern neo-adjuvant chemotherapy with targeted agents.

Besides preoperative tumor downsizing, improved patient selection is another potential and more commonly accepted advantage of neo-adjuvant systemic therapy. It may be postulated that patients with disease progression upon neo-adjuvant systemic therapy do not benefit from CRS and HIPEC due to aggressive tumor biology. A French study reported an impressive median overall survival of 63 months in selected patients who received CRS and HIPEC after they revealed a favorable tumor response upon neo-adjuvant systemic therapy.<sup>24</sup> To compare, median survival was 39 months in another cohort that received upfront CRS and HIPEC intentionally followed by adjuvant systemic therapy.<sup>77</sup> However, nothing is known about the number of patients that do not qualify for CRS and HIPEC due to disease progression or severe toxicity upon neo-adjuvant systemic therapy, thereby impeding an intention-to-treat comparison between these treatment strategies. For example, an intention-to-treat analysis in resectable colorectal liver metastases revealed no overall survival difference of perioperative systemic therapy and surgery compared to upfront surgery.<sup>82</sup> Given

the absence of such studies in colorectal PM, the CAIRO6 trial (NCT02758951) will soon start to randomize patients with potentially resectable colorectal PM between upfront CRS and HIPEC and CRS and HIPEC with perioperative systemic therapy consisting of neo-adjuvant FOLFOX with bevacizumab.

Taken together, neo-adjuvant systemic therapy may improve survival after CRS and HIPEC by improving patient selection, but its benefit on an intention-to-treat basis needs to be confirmed by results of ongoing and future studies.

## Prognostic models to predict survival

This review discussed several important factors for overall survival after CRS and HIPEC. Ideally, these factors are combined in a prognostic model to predict survival of colorectal PM patients treated with curative intent. Indeed, several prognostic scores have been published. Verwaal et al were the first to combine location of the primary tumor, histological subtype, and extent of peritoneal disease into a prognostic model.<sup>48</sup> However, to the knowledge of the authors, this statistically sound model has never been externally validated or extensively used in clinical practice.

To date, the Peritoneal Surface Disease Severity Score (PSDSS) is the most frequently evaluated model for colorectal PM patients.<sup>66</sup> It was developed by Pelz et al and includes the preoperative CT scan-based PCI score, histological subtype, lymph node status, and clinical symptoms. The development study only included 40 patients and did not seem to use regression coefficients to determine the weighed scores. Several multi-institutional studies evaluated the prognostic value of PSDSS and agreed that it has some predictive value.<sup>32,83,84</sup> Nevertheless, none of these studies assessed the predictive value of PSDSS according to validated model performance measures such as the Harrel's C index or Nagelkerke  $R^2$  statistic. Additionally, PCI appeared to be superior to PSDSS in predicting overall and disease-free survival in colorectal PM patients treated with CRS and HIPEC.<sup>85</sup>

A recent study externally validated the PSDSS, and its performance was suboptimal with a Harrel's C index of 0.62 and a Nagelkerke  $R^2$  statistic of 0.08.<sup>41</sup> Subsequently, the authors developed a new prognostic score named Colorectal Peritoneal Metastases Prognostic Surgical Score (COMPASS). This Cox regression-based nomogram included four factors: age, PCI score, lymph node status, and signet ring cell histology. With a Harrel's C index of 0.72 and a Nagelkerke  $R^2$  statistic of 0.19, it performed considerably better than the PSDSS. Future research focusing on external validation of

the new COMPASS model is warranted and will give more insight into the possibilities of this score for colorectal PM patients treated with CRS and HIPEC.

## Conclusion

CRS and HIPEC is a viable option for selected patients with PM from colorectal origin, resulting in long-term survival and even cure in some patients. However, adequate patient selection for this treatment is currently one of the major challenges. This review focused on several important issues in this complex interplay of patient, tumor, and treatment characteristics. According to available literature, especially extent of peritoneal disease, completeness of cytoreduction, and signet ring cell histology have great influence on the outcome after CRS and HIPEC. The presence of liver metastases seems to have a negative prognostic impact. In contrast, treatment with neo-adjuvant systemic therapy seems to prolong survival after CRS and HIPEC. Additionally, rectal cancer should not be regarded as a strong negative prognostic factor. In general, only patients with limited peritoneal disease, eligible for complete macroscopic cytoreduction and without signet ring cell histology, are able to achieve long-term survival after CRS and HIPEC. Prognostic models combining the above-mentioned factors, such as the COMPASS nomogram, may provide clinically relevant tools to use in everyday practice.

## Disclosure

The authors report no conflicts of interest in this work.

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