



# Diagnostic Nodes of Patient Selection for Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Among Colorectal Cancer Patients: A Swiss National Multicenter Survey

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## Abstract

The management of patients with colorectal cancer (CRC) with peritoneal metastases is challenging, and the roles of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are unclear and debated among experts. Experts from 9 centers in Switzerland provided their decision algorithms for CRS/HIPEC for patients with or at high risk for peritoneal metastases from CRC; we used these algorithms to identify consensus and discrepancies. Multiple decision criteria relevant to all participating centers were identified. The consensus treatment algorithm included a total of 5 decision criteria. Because patient selection for CRS/HIPEC remains difficult, uniform criteria, such as those in the consensus algorithm, for the term, “high risk” for peritoneal metastases and systemic metastases are helpful.

**Background:** The management of patients with colorectal cancer (CRC) with peritoneal metastases is challenging, and the roles of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are unclear and debated among experts. **Materials and Methods:** The experts of the Swiss Peritoneal Cancer Group were contacted and agreed to participate in this analysis. Experts from 9 centers in Switzerland provided their decision algorithms for CRS/HIPEC for patients with or at high risk for peritoneal metastases from CRC. Their responses were converted into decision trees on the basis of objective consensus methodology. The decision trees were used as a basis to identify consensus and discrepancies. **Results:** The final treatment algorithms included a total of 5 decision criteria (age, Peritoneal Cancer Index [PCI], extraperitoneal metastases, Peritoneal Surface Disease Severity Score, and various risk factors [RF]) and 2 treatment options (HIPEC, yes or no). HIPEC was never recommended for patients without peritoneal metastases in the absence of RF for peritoneal metastases. For patients with a PCI  $\leq 15$  without organ metastases, all centers recommended CRS/HIPEC. There was also a consensus not to perform CRS/HIPEC in elderly patients (80 years and older), those with a PCI  $>20$ , and those with unresectable metastases. For patients with a PCI = 16 to 20, there was no consensus. **Conclusion:** Multiple decision criteria relevant to all participating centers were identified. Because patient selection for CRS/HIPEC remains difficult, uniform criteria for the term “high risk” for

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peritoneal metastases and systemic metastases are helpful. Future trials and guidelines should take these criteria into account.

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**Keywords:** Colorectal cancer, Cytoreductive surgery, HIPEC, Patient selection, Peritoneal malignancy

## Introduction

In patients with colorectal cancer (CRC), peritoneal recurrence is the second most common site of relapse accounting for up to 62% of all recurrences.<sup>1</sup> Improving oncologic outcomes for CRC patients at high risk for peritoneal recurrence has been a challenging goal for decades. Identifying these patients is important and might provide the basis for risk-adapted management and potentially improved survival in patients with CRC.<sup>2</sup>

Although 5% to 20% of patients have peritoneal seeding, only a limited number of these patients are ultimately treated with curative intent. Complete cytoreductive surgery (CRS) is performed only in approximately 25% of all eligible patients.<sup>3,4</sup> Several risk factors (RF) for the development of peritoneal metastases in patients with CRC have been identified.<sup>5</sup> Studies have revealed significantly improved survival rates in patients who are at high risk for locoregional recurrence if they are treated with perioperative chemotherapy.<sup>6-8</sup> Patients at high risk for minimal residual disease benefit most from modern therapeutic options including second-look surgery, CRS, and hyperthermic intraperitoneal chemotherapy (HIPEC).<sup>9-11</sup> Criteria for identifying patients at high risk for peritoneal recurrence or peritoneal metastases have been previously described (Table 1).<sup>5,12</sup>

Cytoreductive surgery and HIPEC can prevent death from the progression of peritoneal metastases in selected CRC patients,<sup>13,14</sup> and CRS/HIPEC have been implemented as clinical treatment recommendations in several countries worldwide. Despite a consensus statement published on the role of CRS/HIPEC in the management of CRC with peritoneal metastases,<sup>15</sup> there is ongoing controversy regarding the precise role of this multimodal approach in clinical routines.<sup>16</sup> Patient selection remains the major challenge. In clinical practice, decision criteria for CRS and HIPEC in patients with CRC might vary widely, and optimal patient selection is complex and difficult.<sup>17</sup> Despite multiple statements and recommendations, little is known about the applied decision criteria for patient selection for CRS and HIPEC in CRC in clinical routines and whether these decision criteria might provide a basis for consensus.

Clinical practice can vary considerably when evidence does not provide clear guidance. Even in the same setting, multiple experts might use different decision criteria and offer a variety of treatments.<sup>18-20</sup> Identifying what is being performed in the community can potentially provide additional information on issues of practicability and experience when evidence is not sufficient.<sup>19,21</sup> When expert clinical decision-making is expressed in decision trees and appropriately structured,<sup>22</sup> it might provide a basis for evaluating discrepancies and potentially for arriving at a consensus.<sup>23</sup>

Because of the controversies on appropriate selection of patients for CRS/HIPEC, we performed a survey among experts in the field of CRC surgery in Switzerland to investigate the variation of the use of

CRS/HIPEC for peritoneal metastases in CRC. The aim of this study was to assess the most relevant criteria in the complex process of patient selection and decision-making for CRS/HIPEC in CRC patients.

## Materials and Methods

Experts from the Swiss Peritoneal Cancer Group (SPCG) were contacted and agreed to participate in this analysis. The involved centers of the participating experts provide HIPEC in a several dozen cases per year; the exact number of cases was not provided. Overall, approximately 150 cases per year are treated in Switzerland spread over these centers. All experts are specially trained in the field by participating in dedicated courses on CRS and HIPEC. Each expert was asked the following question per e-mail: "Please describe under which circumstances you would recommend HIPEC for peritoneal carcinomatosis from colorectal cancer? Please describe any disease or patient characteristics relevant to your decision." Participants were asked to describe their individual clinical decision algorithm in the form of free text or diagrams. The individual decision trees were anonymized. No specific clinical scenarios, examples, or decision criteria were proposed to avoid influencing the experts' responses. All of the gathered information was converted into decision trees as described previously.<sup>22</sup>

Similar criteria were combined into new comprehensive categories to simplify their representation and enable cross-comparability (ie, the criteria for "RF": some centers included T4 tumors, ovarian metastases, or positive resection margins, whereas

**Table 1** Estimated Incidence of Local Recurrence and/or Peritoneal Metastases

Histological or Clinical Feature	Estimated Incidence in Colorectal Cancer, Observed During Follow-up, %
Positive Resection Margins	80
Peritoneal Nodules Detected During Primary Resection	70
Ovarian Metastases	60
Perforation Through the Primary Cancer	50
Positive Peritoneal Cytology Before or After Resection	40
Positive Imprint Cytology	40
T3 Mucinous or T4 Cancer	40
Adjacent Organ or Structure Invasion	20
Signet Ring Histology in Endoscopic Biopsy	20
Fistula Formation	20
Obstruction Due to Primary Cancer	20
Positive Lymph Nodes or Lymph Nodes Near the Resection Margin	20

**Table 2** Definition of “Risk Factors” According to Center (A-I)

	A	B	C	D	E	F	G	H	I
Tumor Extent (T4, Perforation)	×			×	×		×		
Ovarian Metastasis	×								
Incidental Finding of Peritoneal Carcinomatosis							×		
Positive Resection Margins	×			×					
Mucinous Histology				×					
No Risk Factors Defined		×	×			×		×	×

others described histology or ovarian metastases); these simplifications were documented and are presented in Table 2. Universally proposed prerequisites for HIPEC (ie, the criterion “operability” on the basis of performance status, comorbidities, or other contraindications for surgery, extensive bowel disease, infiltration of the root of the mesentery, or extensive aorto-caval lymph node disease) were not represented in the decision trees.

The resulting decision trees were presented to the participants for verification, and corrections were applied if necessary. The trees were finalized and confirmed by each center by July 2018. The decision trees were then analyzed to determine the majority recommendation for each possible combination of parameters on the basis of objective consensus methodology.<sup>22-24</sup>

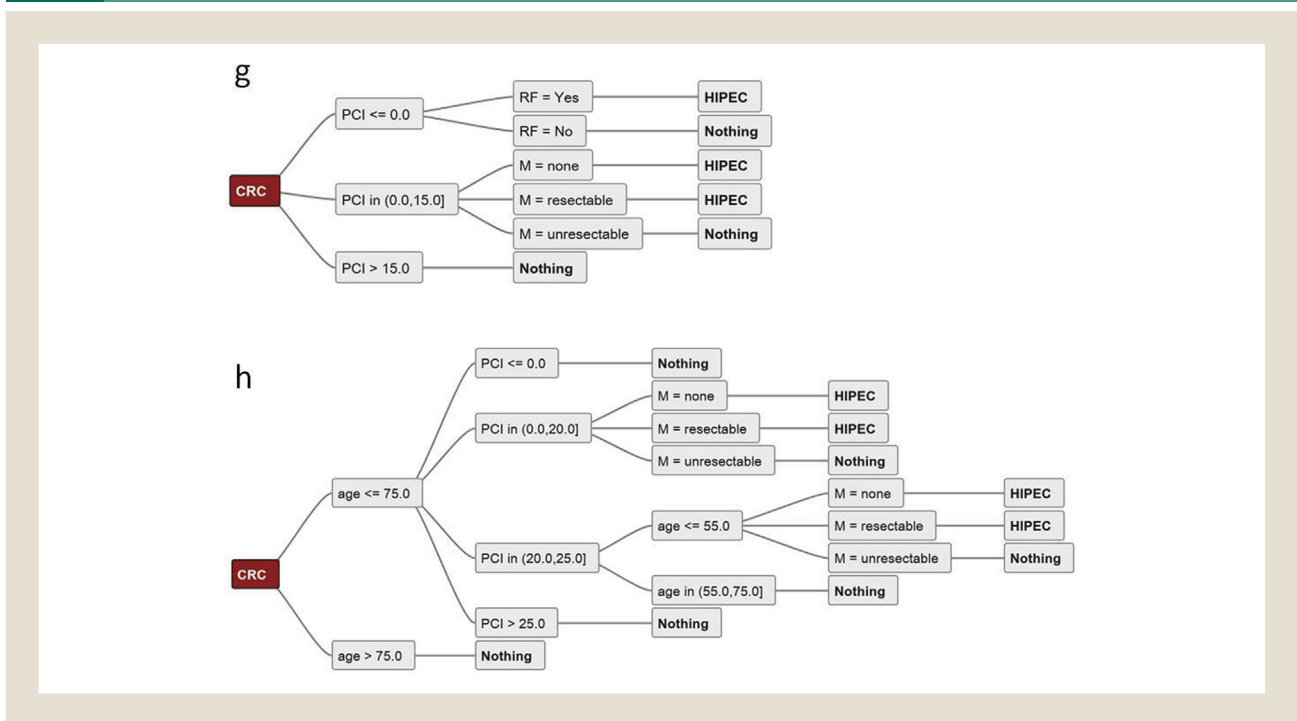
## Results

Experts from all 9 Swiss HIPEC centers (Kantonsspital St Gallen, Hirslanden Spital Zürich, Claraspital Basel, Kantonsspital Winterthur, and the university hospitals in Basel, Berne, Geneva,

Lausanne, and Zürich) participated and provided written or schematic information regarding their interdisciplinary local treatment strategy for peritoneal metastases in patients with CRC (Figure 1). The final treatment algorithms included a total of 5 decision criteria and 2 treatment options (HIPEC, yes or no). The parameters considered relevant for the decision of HIPEC were age, Peritoneal Cancer Index (PCI), extraperitoneal metastases (resectable or not), and no visible peritoneal metastases in the presence of RF (ie, PCI = 0; Table 3). One center also included the Peritoneal Surface Disease Severity Score as a relevant factor for performing HIPEC. The term “RF” was defined differently by the participating centers. In one center “extraperitoneal metastases” was an exclusion criterion for HIPEC. For some centers, only lung metastases were exclusion criteria. In patients with unresectable metastases, HIPEC was not performed. The definition of “resectable” had variable interpretations according to center (Table 4).

For all centers, the following factors were prerequisites for performing CRS/HIPEC: patients had to be fit, which was defined as

**Figure 1** Samples of 2 Decision Trees Illustrating Input From Centers G and H Included in the Analysis



Abbreviations: CRC = colorectal cancer; HIPEC = hyperthermic intraperitoneal chemotherapy; M = metastases; PCI = Peritoneal Cancer Index; RF = risk factors.

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**Table 3** Use of Decision Criteria According to Center

	A	B	C	D	E	F	G	H	I
Age	×						×		
PCI	×	×	×	×	×	×	×	×	×
PSDSS				×					
RF	×			×	×		×		
M	×	×	×	×	×	×	×	×	×

Abbreviations: M = metastases; PCI = Peritoneal Cancer Index; PSDSS = peritoneal surface disease severity score; RF = risk factors.

otherwise healthy and fit with a reasonable life expectancy, and without relevant comorbidities or contraindications for surgery. Other contraindications for CRS/HIPEC were extensive bowel disease, bowel obstruction, infiltration of the mesenteric root, extensive disease of the aortocaval lymph nodes, pregnancy, HIV (untreated or a high virus load), invasion of the omentum minus or ligamentum gastrocolicum, renal failure, and systemic or anti-angiogenetic therapy within 6 weeks of HIPEC. Multidisciplinary tumor board discussion was required to make the decision to perform CRS/HIPEC at each center. Complete cytoreduction (score = 0/1) before HIPEC was also mandatory.

No participating center recommended CRS/HIPEC for patients without peritoneal metastases in the absence of RF for peritoneal metastases. For patients with a PCI ≤15 without organ metastases, all centers recommend CRS/HIPEC, and for those with a PCI ≤16 without systemic metastases who were younger than 75 years of age, 8 of 9 centers recommend CRS/HIPEC. Eight of 9 centers perform CRS/HIPEC in patients younger than 75 years with a PCI ≤15 and resectable metastases (lung and/or liver). For elderly patients with resectable organ metastases and a PCI ≤15, CRS/HIPEC is still recommended in 7 of 9 centers. For 78% (7 of 9) of centers, CRS/HIPEC is an option for patients with a PCI = 17 to 18 in the absence of other metastases. Still, more than half of our experts (6 of 9) recommend CRS/HIPEC for patients with peritoneal metastases and a PCI = 17 to 18 with resectable organ metastases. There was consensus not to perform CRS/HIPEC in elderly patients (80 years and older), patients with a PCI >20, and those with unresectable metastases. In 1 center, age was a decision criterion, particularly for the management of peritoneal metastases in patients with a PCI between 20 and 25 (CRS/HIPEC was recommended only for patients younger than 55 years). However, in all of the other centers, a PCI >20 was an exclusion criterion for CRS/HIPEC. An overview of these results is shown in [Figures 2-5](#).

## Discussion

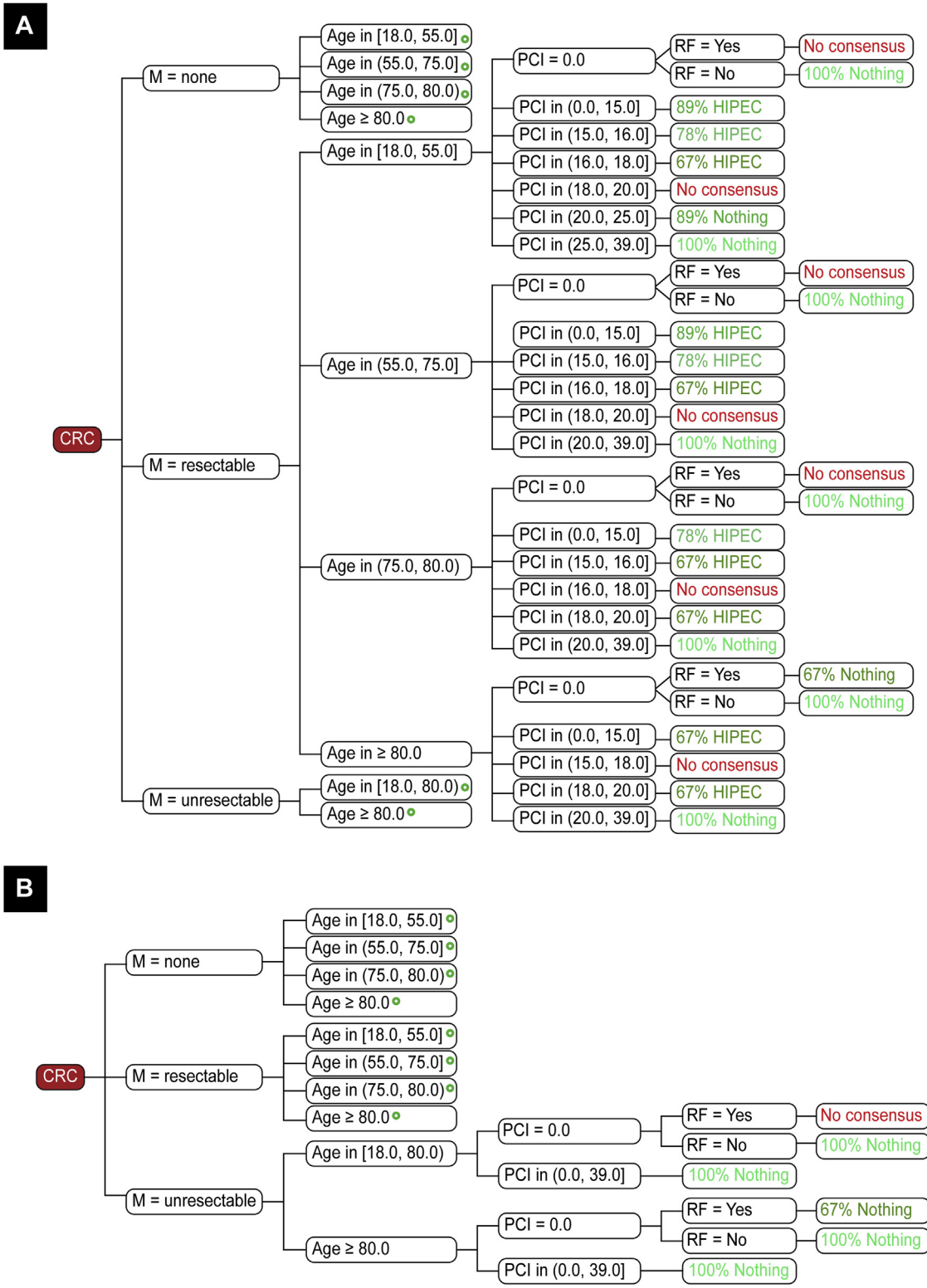
Promising results have been obtained during the past decade using CRS with HIPEC for selected patients with CRC.<sup>13-15</sup> Recently the results of the Partenariat de Recherche en Oncologie DIGEstive (PRODIGE) 7 trial were communicated and the authors concluded that the therapeutic curative management of CRC using CRS shows satisfactory survival results, but the additional use of HIPEC with oxaliplatin does not influence the overall survival.<sup>16</sup> The extent of these results are under discussion now and no universally valid recommendations are provided so far in the community. Other studies reported contradictory results with better overall survival (hazard ratio [HR], 0.25; 95% confidence interval [CI], 0.07-0.89; *P* = .039) and progression-free survival (HR, 0.31; 95% CI, 0.11-0.85; *P* = .028), but further phase III trials are needed.<sup>9</sup> After these studies with conflicting results, there is no clear consensus which patients with peritoneal metastases of CRC should be offered HIPEC. This is the first report, to our knowledge, to compare treatment algorithms for peritoneal metastases from CRC using objective consensus methodology. We performed a survey of all Swiss centers offering CRS/HIPEC and assessed the criteria for CRS/HIPEC for peritoneal metastases from CRC. The selection of participating centers and the number of centers included in this analysis was on the basis of the SPCG, which included 100% of the centers that perform HIPEC in Switzerland; we would not expect a different set of experts to provide a higher level of consensus.

Among the experts, we found varying decision criteria for CRS/HIPEC; in particular, the effect of the PCI varied among the participating centers. For PCI scores up to 15, there was consensus regarding patients without extraperitoneal metastases. All of the experts recommended HIPEC for patients with a PCI ≤15 who were younger than 75 years. For higher PCI scores, there was less consensus regarding performing CRS/HIPEC. This finding is reflected by the current literature, in which the extent of peritoneal metastases defined according to the PCI is probably the most

**Table 4** Definition of Resectable Metastases According to Center

	A	B	C	D	E	F	G	H	I
Up to 3 Liver Metastases	×				×	×	×		
No Major Resection	×		×	×	×	×	×	×	×
No Open Lung Resection			×						
One Lung Metastasis					×				
No Lung Metastases				×			×		
No Lung or Liver Metastases		×							

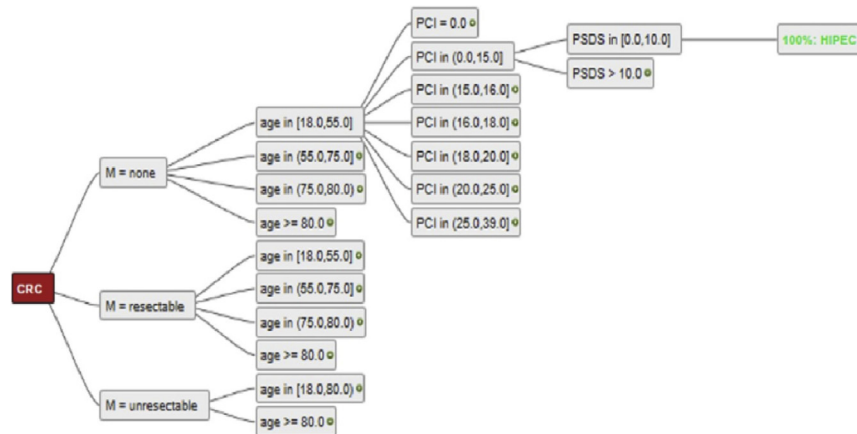
**Figure 2** Decision Trees Showing the Areas of Consensus (at Least 60%) for CRS/HIPEC in Patients Without or With Resectable (A) and Unresectable (B) Organ Metastases



Abbreviations: CRC = colorectal cancer; CRS = cytoreductive surgery; HIPEC = hyperthermic intraperitoneal chemotherapy; M = metastases; PCI = Peritoneal Cancer Index; RF = risk factors.

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**Figure 3** Consensus (9/9 Centers) for Performing HIPEC in Patients With CRC Without Other Organ Metastases



Abbreviations: CRC = colorectal cancer; HIPEC = hyperthermic intraperitoneal chemotherapy; M = metastases; PCI = Peritoneal Cancer Index; PSDS = peritoneal surface disease severity score.

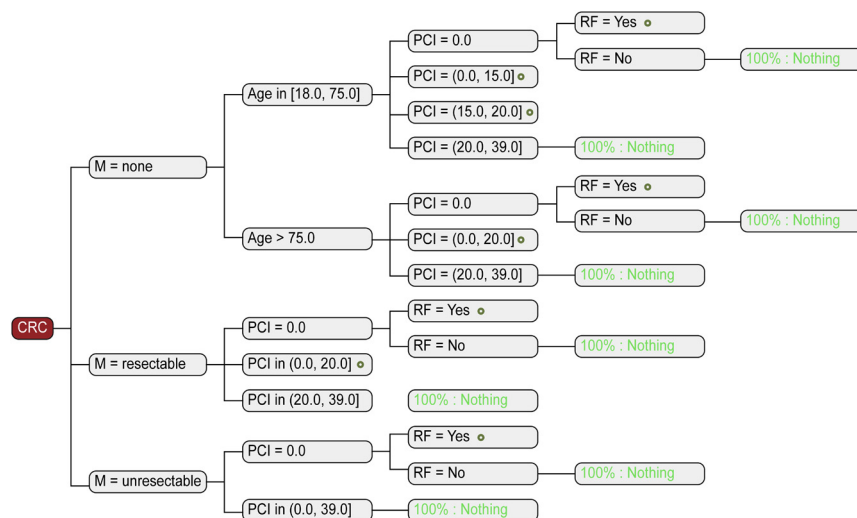
relevant selection factor. In CRC patients with a PCI greater than the range of 17 to 20, it is currently not recommended to perform CRS/HIPEC.<sup>12,17,25</sup> Interestingly, most of the centers perform CRS/HIPEC in patients younger than 75 years with a PCI of 16 to 20. Peritoneal malignancy and liver metastases are associated with a poor prognosis, with 5-year survival rates ranging from 18% to 28%.<sup>26</sup> The presence of liver metastases has often been considered an exclusion criterion for CRS/HIPEC, and some authors recommend a maximum of 3 wedge resections.<sup>27</sup>

Patient age as a factor for an impaired perioperative course has been studied extensively. It has been shown that this treatment can be performed safely in selected patients older than 70 years of age<sup>28</sup>

with perioperative morbidity and mortality comparable with those in younger patients.<sup>29</sup>

Limitations of this investigation are the complexity and heterogeneity of the patients in these situations; furthermore, patients' preferences were not addressed. We used a simplified and reduced number of decision criteria to better visualize and compare the decision trees, which does not necessarily always reflect clinical practice. In reality, other potential criteria might be considered. Lately, there is a certain uncertainty concerning the value of this treatment in CRC patients.<sup>16</sup> Quality of life was not addressed in this survey. However, consensus among the 9 centers was found concerning the PCI, patient age, and the presence of other organ metastases as relevant factors.

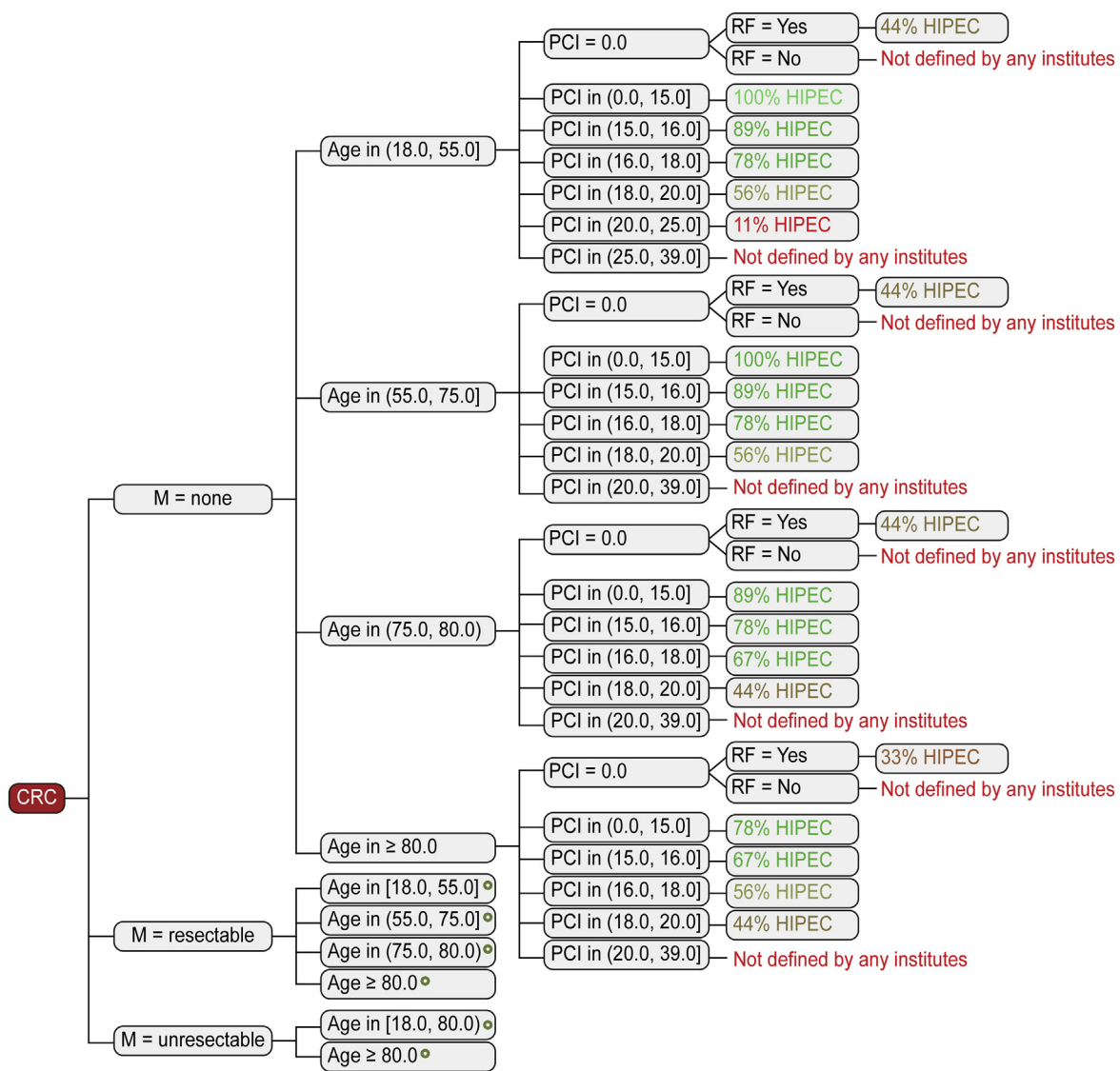
**Figure 4** Consensus (9/9 Centers) Not to Perform HIPEC in Patients With CRC



Abbreviations: CRC = colorectal cancer; HIPEC = hyperthermic intraperitoneal chemotherapy; M = metastases; PCI = Peritoneal Cancer Index; RF = risk factors.



**Figure 5** Areas of Consensus for Performing HIPEC in Patients With (PCI ≥1) or Without (PCI = 0) Peritoneal Metastases and No Evidence of Other Organ Metastases



Abbreviations: CRC = colorectal cancer; HIPEC = hyperthermic intraperitoneal chemotherapy; M = metastases; PCI = Peritoneal Cancer Index; RF = risk factors.

Several trials on the role of HIPEC for patients with peritoneal metastases from CRC are ongoing and the results, for example of the Dutch trial “Perioperative systemic therapy and cytoreductive surgery with HIPEC versus upfront cytoreductive surgery with HIPEC alone: a multicentre, open-label, parallel-group, phase II-III, randomised superiority study” (CAIRO 6 trial), are expected.<sup>30</sup> However, in the context of modern systemic chemotherapy, perhaps a shift away from surgical management toward modern systemic chemotherapy alone has been recently initiated.<sup>31</sup>

**Conclusion**

The aim of this study was to assess the most relevant criteria for the complex process of patient selection and decision-making for

CRS/HIPEC among CRC patients in Switzerland. This study was conducted because there is no conclusive evidence to aid patient selection. We found that there was consensus regarding performing CRS/HIPEC in patients with operable disease who were younger than 75 years, did not have other organ metastases, and had a PCI score of 15 or less. With an increasing PCI, there was decreased agreement regarding whether or not to perform CRS/HIPEC. The application of a decision tree analysis was able to identify decision criteria that were relevant for all participating centers. Because patient selection for CRS/HIPEC is difficult, uniform criteria for the term “high risk” for peritoneal metastases and systemic metastases are helpful. However, with the latest uncertainty in the context of the results of PRODIGE 7, not only decision-making but also the type of chemotherapy needs

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further research. Future trials and guidelines should take these criteria into account, and criteria for patient selection in other tumor entities (eg, gastric cancer) need to be elicited.

## Clinical Practice Points

- Because peritoneal metastasis in CRC is a relatively rare but complex disease, there is little financial support for academic clinical trials that require intensive teamwork combining diagnostics and therapeutic management.
- Thus, most of the unanswered questions regarding the optimal treatment strategies for patients with CRC and peritoneal metastases will remain unresolved in the coming years. Even the latest results from the PRODIGE 7 study cannot answer the open questions concerning, for example, patient selection for CRS/HIPEC.
- Considering this situation, we performed a survey among all Swiss experts in the field.
- In this article we present the basic consensus among the experts concerning patient selection for this treatment using decision nodes.
- The results of this survey indicated that it was possible to have consensus concerning the indication for CRS and HIPEC in patients with peritoneal carcinomatosis from CRC.
- Moreover, the criteria used today for patient selection seem to have been further developed than applied in the most recently published articles in the literature.

## Disclosure

The authors have stated that they have no conflicts of interest.

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