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REVIEW

Effective Strategies to Predict Survival of Colorectal Peritoneal Metastases Patients Eligible for Cytoreductive Surgery and HIPEC

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Abstract: Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), often combined with systemic therapy, can be offered to selected colorectal peritoneal metastases (PM) patients. However, clinical heterogeneity and the lack of high-level evidence challenges determination of the correct treatment strategy. This review aims to provide an overview of current strategies to predict survival of colorectal PM patients treated with CRS and HIPEC, guiding clinicians to select a suitable treatment-strategy and to inform patients about their prognosis. First, the prognostic relevance of several clinicopathological prognostic factors, such as extent of PM, location of primary tumor, histology type, and the presence of lymph node or liver metastases will be discussed. Subsequently, special attention will be given to recent developments in several aspects of tumor biology such as RAF/RAS mutations, circulating tumor DNA, immunoprofiling, and consensus molecular subtypes. Finally, currently available prognostic models to predict survival will be evaluated, concluding these models perform moderate to good, but most of them partly rely on intra-operative data. New insights in tumor biology, as well as the reliable assessment of extent of peritoneal disease by diffusion weighted MRI pose promising opportunities to establish an adequate and clinically meaningful preoperative prognostic model in the near future.

Keywords: colorectal neoplasms, peritoneal metastases, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, prognosis, survival

Introduction

Peritoneal metastases (PM) occur in approximately 10% of the patients with colorectal cancer.[1,2] Not that long ago, the majority of these patients were treated with best supportive care only. During the last two decades, new chemotherapeutic agents led to an increase in the use of systemic treatment. This was for instance demonstrated in a nationwide cancer registry, showing an increase in the proportion of patients with colorectal PM receiving systemic treatment from 23% to 56%.[3,4] Furthermore, a selection of patients with limited and mostly isolated colorectal PM is currently treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). This multimodality treatment strategy led to an increase in survival in numerous large series of selected patients with colorectal PM and to a significant increase in median overall survival of these patients on a population-wide level from 6.0 months between 1995 and 2000 to 12.5 months between 2010 and 2014.[4]

The clinical heterogeneity of colorectal PM patients makes the correct treatment strategy a real challenge. The lack of high-level evidence and subsequent lack of

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reliable pre-treatment survival prediction tools increases the difficulty of this task. Nonetheless, physicians treating these patients need to base their treatment-strategy and patient-communication upon the best available evidence. New insights in prognostic factors develop so rapidly, it is quite demanding to constantly provide an up-to-date evidence-based treatment.

This review aims to describe current strategies to predict survival in peritoneally metastasized colorectal cancer patients, with a special focus on recent developments in tumor biology as well as eligibility for CRS and HIPEC. This study focuses solely on colorectal cancer, and does not cover the subject of appendiceal neoplasms. First, some general and historical aspects of colorectal PM will be discussed, followed by several clinical factors associated with survival, before more recent insights in tumor biology and genetic aspects of colorectal PM will be addressed. This overview may provide clinicians an aid to guide their treatment-strategy and to inform patients about their prognosis.

Colorectal Peritoneal Metastases

Colorectal cancer is the fourth most prevalent type of cancer and ranks second in the number of cancer deaths in the United States.[5] Metastatic disease is the main cause of death in colorectal cancer patients. Nearly 25% of all these patients present with synchronous stage IV disease.[6] Another 20–30% develop systemic metastases during follow-up.[7] Besides the liver, the peritoneal cavity is the second most prevalent site of metastatic disease in colorectal cancer patients.[8] Approximately 5% of the patients present with synchronous peritoneal metastases and another 5% develop these metastases during the follow-up period.[2,9] Known risk factors for the development of colorectal PM are primary tumor characteristics such as an advanced T stage, lymph node metastases, right-sided tumors and a poor differentiation grade.[2,10] Besides, adenocarcinomas with mucinous differentiation or signet ring cell appearance are known to spread to the peritoneal cavity more frequently.[8]

Historical Survival of Colorectal PM

The disease-course of patients with colorectal PM is typically characterized by rapid progression of intra-abdominal tumor deposits, frequently leading to loss of physical performance, cachexia, malignant ascites, and ultimately gastro-intestinal obstruction or perforation. Due to this aggressive disease-course with limited palliative options, the prognosis of these patients is traditionally poor. Large series of patients diagnosed in the 1990s reported median survival rates of just 6 months after treatment with best supportive care, palliative surgery, palliative chemotherapy, or a combination of these modalities.[11–13] Population-based data of 1995–2000 from the Netherlands showed comparable survival rates for both synchronous and metachronous peritoneally metastasized colorectal cancer patients.[1–4]

Survival PM Compared to Other Metastatic Sites

Systemic therapy is the backbone of the treatment of stage IV colorectal cancer patients.[14] Both population-based data as well as large comparative studies of patients treated with systemic chemotherapy report on lower overall survival rates in colorectal PM patients as compared to patients with other systemic metastases.[2,3,15,16] The most frequently mentioned reason for this phenomenon is the lower sensitivity of peritoneal metastases for systemic therapy, probably because the peritoneum is poorly vascularized and peritoneal metastases spread through the locoregional route, rather than the hematological route. Indeed, a pooled subgroup analysis of multiple Phase 3 randomized trials in stage IV colorectal cancer patients treated with systemic therapy showed better survival in patients with isolated non-peritoneal metastases than in isolated peritoneal metastases (Hazard ratio (HR) 0.75 (95% confidence interval (CI) 0.63–0.91, p=0.003)).[15] The diminished sensitivity of colorectal PM for systemic therapy is further supported by a pathology study that showed lower major and complete pathologic response rates of peritoneal metastases following neoadjuvant chemotherapy as compared to colorectal liver metastases.[17–19] In addition, a contributing factor to the relatively poor reported survival rates of colorectal PM patients might be their high level of systemic disease-burden, representing advanced metastatic disease.[15]

Type of Treatment as Prognosticator

The survival of colorectal PM patients is strongly dependent on the type of treatment (eg, palliative care versus systemic therapy versus CRS and HIPEC).[20,21] Randomized controlled trials comparing different treatments in these patients are limited. The randomized controlled trial by Verwaal et al showed a survival benefit of cytoreduction and HIPEC over palliative systemic

treatment.[22] Very recently the Prodige-7 trial was published, investigating the addition of HIPEC with oxaliplatin to CRS in colorectal PM patients.[23] This study showed no survival benefit of HIPEC, which might be explained since 80% of the included patients underwent extensive neo-adjuvant systemic treatment (73% oxaliplatin-based regimens). With this strategy, mainly patients without progression during systemic treatment and thus with biologically less aggressive tumors were considered for surgery, which is reflected by a very high median survival rate of 41 months in both arms. Additionally, systemic treatment with oxaliplatin might have led to oxaliplatin-resistance of peritoneal cancer cells, reducing the effect of intraperitoneal oxaliplatin as was also shown in a recent in vitro study.[24] Thus, the results of the Prodige-7 trial are not generalizable to settings where other HIPEC regimens are used or patients receive less systemic treatment and should therefore be interpreted with caution.

In addition, the response to neoadjuvant chemotherapy can be used as prognosticator for CRS and HIPEC.[25] Patients with disease progression upon neoadjuvant treatment might not benefit from CRS and HIPEC because of aggressive tumor biology. The use of this response to neoadjuvant treatment as selection mechanism might explain the very promising survival rates of retrospective series of patients treated with upfront chemotherapy followed by cytoreduction and HIPEC compared to CRS and HIPEC alone (hazard ratio 0.23).[26] The currently recruiting randomized CAIRO6 trial (perioperative systemic therapy + CRS and HIPEC vs CRS and HIPEC alone) will answer this question.[27]

Since most clinical evidence consists of cohort studies, selection bias inevitably plays an important role in described survival benefits of patients treated with systemic therapy or CRS and HIPEC. Important selection criteria, such as performance status, age and extent of peritoneal disease, are factors often associated with poor performance and prognosis in general. For example, a diminished performance score, indicated by a high Eastern Cooperative Oncology Group (ECOG) performance score, is associated with higher treatment-related morbidity and an impaired survival after surgery.[28] Although age often is not recognized as a prognostic factor and CRS and HIPEC can be performed safely in elderly, it is one of the major decision criteria for offering curative surgery.[29–31] Furthermore, the extent of peritoneal disease is strongly associated with macroscopic complete cytoreduction as well as with overall survival.[25,32,33] Because of this significant influence of selection bias, it remains challenging to assess the expected survival of colorectal PM in relation to treatment and to assess the true effect on survival of a specific type of treatment.

Extent of Peritoneal Disease

In colorectal PM patients, the extent of peritoneal disease is closely related to overall survival.[32,34,35] The extent of peritoneal disease is generally measured by the PCI score, ranging from 0 to 39 according to the extent of disease in 13 abdominal regions.[36] It is not possible to define an absolute cut-off value above which CRS and HIPEC should not be performed, since long-term survival in selected cases with high PCI values is sometimes possible.[37] Nevertheless, global experts agree that surgical treatment should only be performed if complete macroscopic cytoreduction is achievable.[38] This general opinion is based upon the strongly diminished survival of patients with incomplete macroscopic cytoreduction.[34,39] Because of the vast prognostic importance of extent of peritoneal disease and the closely related macroscopic complete cytoreduction rate, it would be very valuable to adequately assess the preoperative extent of peritoneal disease.

Currently, standard preoperative work-up of colorectal PM patients consists of a thoraco-abdominal CT-scan,[38] but an adequate assessment of the extent of peritoneal disease on CT is difficult and often underestimated.[40,41] This underestimation leads to relatively high rates (up to 23%) of unexpected irresectable peritoneal disease at explorative laparotomy in colorectal PM patients planned for CRS and HIPEC.[42] Therefore, diagnostic laparoscopy is currently often used in patients with alleged borderline-resectable peritoneal metastases. Indeed, adding diagnostic laparoscopy to the preoperative work-up led to a slight, but not-significant, decrease of open and close procedures.[43] Nevertheless, a significant number of patients cannot be staged adequately preoperatively. Therefore, one of the major challenges nowadays is to improve preoperative accuracy of detection of peritoneal implants. When an adequate estimation of the preoperative PCI score is possible, the most important prognostic factor can be taken into account to predict outcome prior to surgery, something that is currently lacking.

In a recent Dutch study, the predictive value of diffusion weighted (DW) MRI in detecting peritoneal metastases appeared to be promising and superior to CT.[44] MRI-PCI was closely correlated to the surgical PCI, with

intraclass values of 0.83 and 0.88. Additionally, the area under the curve to predict resectability by scoring a PCI score of 20 or lower was 97%. In a recent meta-analysis, the pooled sensitivity and specificity of 92% and 85% for detecting PM by DW-MRI confirm these promising results.[41] In this meta-analysis, positron emission tomography (PET)-CT showed a comparable overall diagnostic performance compared to DW-MRI, but is less available in daily practice. Therefore, MRI seems to be the imaging method of choice for colorectal PM.[41] With the above-mentioned results in mind, the predictive value of MRI concerning overall and disease-free survival has also been investigated.[45] It appears that MRI-PCI is strongly correlated to overall as well as disease-free survival in both colorectal PM patients treated with CRS and HIPEC and patients treated with palliative intent. Since the extent of peritoneal disease is one of the most important prognostic factors, this preoperative prognostic marker poses promising possibilities in predicting survival in colorectal PM patients eligible for CRS and HIPEC as well as in the palliative setting.

Other Clinicopathological Factors

Numerous clinical studies have aimed to predict survival of colorectal PM patients by identifying prognostic factors associated with overall survival. Several recent systematic reviews and meta-analyses give a comprehensive overview of the most important factors that impact survival after cytoreduction and HIPEC. In this section, the most important factors besides the extent of peritoneal disease will be discussed.

Recently, two study groups assessed the prognostic value of the change of the PCI score in time. In the first study with metachronous colorectal PM patients, the time between primary resection and cytoreduction and HIPEC was combined with the PCI score to create the volume-time index (VTI).[46] A high VTI (relatively short time between primary resection and CRS and HIPEC and/or high PCI) was negatively associated with overall survival after surgery. Another study developed the delta PCI, describing the change in PCI score between diagnostic laparoscopy and explorative laparotomy during cytoreductive surgery and HIPEC.[47] Comparably, a larger delta PCI was independently associated with impaired overall survival. Both studies suggest that the increase in PCI score during a certain period may be used as a marker for the aggressiveness of tumor biology.

In colorectal PM literature, colon and rectal tumors are often considered the same entity with regard to their surgical treatment. Nevertheless, rectal tumors differ from colon tumors in primary tumor treatment, local recurrence rate, and prevalence of PM.[48] Because of small numbers of rectal cancer patients treated with CRS and HIPEC, studies that compare colon and rectal PM report conflicting results. However, meta-analyses combining these studies show a slightly worse prognosis in rectal PM patients compared to colon cancer patients.[28,30,49] Therefore, especially in rectal PM patients, the surgical treatment should be patient-tailored and centralized. To prevent ambiguity, these two distinct patient groups ideally should be published separately.

Colorectal PM can be divided in three different histological subtypes, namely adenocarcinomas (70–85%), mucinous adenocarcinomas (15–22%), and signet ring cell carcinomas (SRCC, 1–7%).[8,21] Both prognosis and treatment type are dependent on histological subtype, and especially patients with SRCC are known to have a poor prognosis of just 12 months after CRS and HIPEC.[21,50] These poor results are confirmed by several studies looking at prognostic factors for overall survival.[28,32,51] Therefore, SRCC is nowadays considered a relative contraindication for CRS and HIPEC and this treatment should be reserved for very fit patients with a low PCI.

Generally, locoregional lymph node metastases are a negative prognostic factor in patients with colorectal cancer. In the prognostically unfavorable group of patients with peritoneal metastases, the prognostic relevance might be less clear. However, most of the recent meta-analyses identified locoregional lymph node metastases as a negative prognostic factor (HR 1.88 (1.48–2.39) and HR 1.33 (1.04–1.72)).[28,35] The presence of lymph node metastases might result in more extra-peritoneal metastases impairing survival of colorectal PM patients treated with cytoreduction and HIPEC. As a result, prognostic scores such as the Peritoneal Surface Disease Severity Score (PSDSS) and the Colorectal Peritoneal Metastases Prognostic Surgical Score (COMPASS) incorporate locoregional lymph node status in their models.[32,51]

Limited synchronous liver metastases as exclusion criterion for CRS and HIPEC has been a topic of discussion in many studies. Several large comparative studies and some of the most recent meta-analyses report a worse outcome of patients who underwent treatment with curative intent of combined liver and peritoneal metastases.[28,52,53] Other studies, including the most recent

meta-analysis, describe a trend towards worse outcome but did not find a statistically significant impact of liver metastases on survival.[35,54] These results underline that the combined treatment of colorectal liver and peritoneal metastases should be limited to highly selected patients with minimal hepatic disease and proven favorable tumor biology. The tumor load-based nomogram developed by Elias aims to predict the prognosis of colorectal cancer patients with combined liver and peritoneal metastases.[55]

RAF/RAS Mutations

KRAS and BRAF proteins are downstream messengers of the epidermal growth factor receptor pathway (EGFR), that controls cell proliferation and survival. The prevalence of gene mutations in KRAS and BRAF in metastatic colorectal cancer patients is approximately 36% and 7%, and these mutations are associated with an impaired overall and progression-free survival in stage IV colorectal cancer.[56] This might be partly due to the less effective treatment with EGFR-inhibitors such as cetuximab and panitumumab in KRAS and BRAF mutated patients compared to wild-type patients.[57,58] Nevertheless, it is argued by some that KRAS/BRAF mutations are a negative prognostic marker of its own, so far for undetermined reasons.[59] Additionally, BRAF mutated tumors are associated with poor prognostic features, such as poor differentiation and mucinous histology in both the localized and the metastasized setting, and tend to metastasize to the peritoneum and distant lymph nodes more frequently.[60] In patients undergoing resection for colorectal liver metastases, RAS mutations are a negative prognostic factor on both survival as well as recurrence, regardless of anti-EGFR treatment.[61]

The prognostic relevance of RAS/RAF mutations in patients undergoing cytoreductive surgery for colorectal PM specifically is yet unclear. Several studies report on KRAS mutational status to be a negative prognostic factor.[62–64] In contrast, other studies cannot report on such significant prognostic differences between KRAS mutant and wild-type tumors.[65–68] With regard to BRAF mutations, comparable findings are reported, with several studies suggesting an impaired prognosis in colorectal PM patients with a BRAF mutation.[64,65,69] Two small studies did not find significant prognostic value of BRAF mutations, probably because of the low number of BRAF mutated tumors.[63,67] To assess the specific implications of RAS/RAF mutations in colorectal PM, the exact etiology of the possible prognostic impact of RAS/RAF mutations in colorectal cancer needs to be better understood.

Circulating Tumor DNA

Circulating tumor (ct)DNA is the fraction of cell-free (cf) DNA detected in de plasma of a cancer-patient.[70] ctDNA is released in the circulation by tumor cells undergoing necrosis or apoptosis. It can be easily obtained by taking blood samples preoperatively or during follow-up, so is less invasive than taking tumor biopsies. With next-generation sequencing, ctDNA has shown promising accuracy for detecting colorectal cancer and tumor-specific mutations. Indeed, with concordance of >90%, ctDNA analyses closely mirrored the prevalence of RAS/RAF mutations present in the primary colorectal tumor of patients with metastatic colorectal cancer.[71] In colorectal PM patients, ctDNA also gives a reliable depiction of a tumor's DNA and mutations.[72] Besides high concordance between ctDNA and primary tumor DNA, the clinical applicability of ctDNA is determined by the percentage of patients with detectable ctDNA. In a recent study among patients with stage I–III colorectal cancer, ctDNA was detectable with PCR-based, next-generation sequencing in 88.5% of the patients.[73] Nevertheless, in studies among metastatic colorectal cancer patients, the detection of RAS mutations in ctDNA was far lower in patients with PM compared to patients with liver metastases.[74–76] Some recent data among colorectal PM patients gives some more insight into ctDNA among this subgroup of patients. In a recent Dutch feasibility study, only 33% of the colorectal PM patients planned for CRS and HIPEC had detectable ctDNA. Postoperatively, mainly patients with early systemic recurrence had detectable ctDNA.[72] These results suggest a limited release of ctDNA by peritoneal metastases, probably, because PM spread by a locoregional route rather than through the hematological route. Therefore, ctDNA does not seem to be a very sensitive marker for detection or follow-up of peritoneal metastases.

Nevertheless, ctDNA might be of clinical use in several different ways. The above-mentioned findings suggest that high preoperative ctDNA might indicate the presence of undetected systemic micro-metastases, to which CRS and HIPEC will be ineffective. In the recent Dutch study, the presence of preoperative ctDNA was indeed associated with a shorter disease-free survival after cytoreduction and HIPEC (HR 3.5), mainly because of early systemic

recurrence.[72] In these patients, the presence of ctDNA might aid in the decision to treat patients with perioperative systemic chemotherapy or even withhold them from CRS and HIPEC because of (micro)systemic disease. Secondly, ctDNA might be of value in detecting recurrence during follow-up after treatment, by improving early detection and thus early treatment in selected patients. More research is warranted to determine the exact clinical value of ctDNA.

Immunoprofiling

Several studies among colorectal cancer patients describe the use of immune profiling as a promising prognostic factor.[77,78] The presence and location inside a tumor of tumor-infiltrating lymphocytes indicate a patient's immune response to the tumor. The presence of T-cell markers (CD3, CD4, CD8, and FoxP3) is associated with better disease-free survival in patients with stage 1–3 colon cancer.[79] A recent internationally validated model including CD3+ and CD8+ T-cells (consensus Immunoscore) was even superior to the TNM classification in predicting recurrence after surgery in stage I-III colon cancer.[80] Until recently, evidence in stage IV colorectal cancer was limited. However, a recent study among colorectal PM patients with a low PCI score showed an increased survival in patients with a low CD3+/CD4+ ratio.[81] In this study, the Immunoscore was not of prognostic significance, possibly because the role of the immune system within the peritoneal cavity is less significant. Nevertheless, immune profiling in colorectal PM warrants further investigation to assess the prognostic value in both systemic and surgical therapy.

Consensus Molecular Subtypes

Colorectal cancer is a very heterogeneous disease, with varying presentations, responses to therapies, and outcomes in survival. In 2015, the Colorectal Cancer Subtyping Consortium developed a classification system based upon gene-expression, resulting in four consensus molecular subtypes (CMS).[82] A detailed description of the different subtypes is beyond the scope of this review, but each subgroup has distinct biological characteristics and its own prognostic significance. CMS-4 accounts for approximately 25% of all colorectal tumors and is characterized by high expression of genes reflecting epithelial-to-mesenchymal transition, transforming growth factor (TGF) β activation, and angiogenesis, and has been associated with a worse overall and relapse-free survival compared to the other subtypes.[82,83] This might be partly due to the limited effect of systemic therapies such as anti-EGFR therapy and oxaliplatin-based chemotherapy in these patients.[83,84] In a recent Dutch study among colorectal PM patients treated with CRS and HIPEC, as much as 60% of the primary tumors and 75% of the peritoneal metastases was classified as CMS-4, with significant heterogeneity in CMS-status between primary tumor and peritoneal lesions.[85] The high percentage of CMS-4 in colorectal PM in combination with the possible ineffectiveness of Oxaliplatin in CMS-4 tumors, stresses the need for more insight in the effect of systemic and intraperitoneal chemotherapy in colorectal PM patients.

Prognostic Models

In this review, various clinical, pathological, and biological factors associated with survival in colorectal PM patients eligible for CRS and HIPEC have been discussed. The prognostic value of these individual factors is often quite apparent, but given the complex interplay between other known and unknown prognostic factors makes combining them the real challenge. Nevertheless, such multifactorial models are essential in predicting survival of colorectal PM patients treated with CRS and HIPEC. Several research groups have tried to develop such prognostic models to aid clinicians in adequately selecting patients for CRS and HIPEC, as well as to provide information about prognosis after treatment.

The most frequently evaluated prognostic score for colorectal PM patients is the PSDSS, which includes abdominal symptoms, CT-PCI score, and primary tumor histology (lymph node status and differentiation grade).[86] Although the statistical evidence behind this score is not entirely clear, several external validation cohorts found some predictive value in the PSDSS.[51,87] Nevertheless, the PSDSS does not seem to have a superior prognostic value over the PCI score alone.[88] Furthermore, in the validation cohort of the PSDSS, the CT-PCI or the intraoperative PCI was used depending on availability prior to surgery. However, it should be realized that both versions of the PCI score are suboptimal, as the intraoperative PCI is generally underestimated by the CT-PCI.[40]

The oldest available prognostic model is the prognostic score (PS), including location of the primary tumor, tumor differentiation, SRCC appearance and number of affected regions.[39] This score was developed in 102 patients and predicted survival to a certain level, but the exact prognostic accuracy was not mentioned in the development study. In

2012, the preoperative COlo-REctal-Pc (COREP) score was developed, and mainly focused on serum tumor markers such as Carcinoembryonic Antigen (CEA), cancer cell-surface antigen (CA) 125, CA 15–3, and CA 19–9.[89] In a comparative study, the accuracy to predict survival <12 months was 84% for the COREP score versus 54% and 55% for the PSDSS and the PS, respectively.[90]

The more recently developed COMPASS prognostic model included age, PCI score, lymph node status, and signet ring cell histology.[32] This statistically sound model was internally validated and had a Harrel's C statistic of 0.72, which means moderate-good discrimination. Additionally, COMPASS was externally validated and performed similar to the development cohort.[91] In this model, the more reliable and better reproducible intraoperative PCI score was used. As a result, COMPASS cannot be used preoperatively without diagnostic laparoscopy/laparotomy, which makes this model less suitable for preoperative survival prediction.

In 2018, the modified COREP (mCOREP) was developed, including CEA, CA 19–9, CA-125, C-reactive protein, albumin, platelet count and signet-cell histology.[92] In this study, the mCOREP was compared to the PSDSS, COMPASS, and CEA/PCI ratio. Both the COMPASS and the mCOREP were able to significantly predict the risk of short survival <12 months, and only COMPASS was able to significantly predict overall survival. Although the CEA/PCI ratio had prognostic value in the development cohort, these results could not be reproduced in this validation study.[92,93]

In the light of growing evidence and knowledge of tumor biology, two new models that included RAS/RAF mutational status were developed. The first study by Schneider et al included RAS/RAF mutational status besides more traditional factors such as intraoperative PCI score, lymph node status, and differentiation grade in the BIOSCOPE score.[64] In the development cohort, this model performed similar to the COMPASS model with an area under the curve of 0.72. In the other study, RAS mutation status was added to the PSDSS, leading to the RAS-PSDSS.[62] According to the authors, this RAS-PSDSS outperformed the traditional PSDSS, but the lack of traditional statistical outcomes makes comparison with other prognostic models difficult.

As discussed before, the prognosis of colorectal PM patients is ideally assessed prior to surgical treatment in demanding procedures such as CRS and HIPEC. Current prognostic models mostly lack this preoperative approach, because the majority of the included factors are determined during surgical exploration or even after surgery, such as primary tumor histology, lymph node status, and the PCI score. In the near future, less invasive techniques to determine tumor biology such as ctDNA, in combination with reliable preoperative assessment of the PCI-score on DW-MRI might provide a solution for this challenge. Although these techniques are already available, large groups of patients with sufficient follow-up time are needed to develop and validate prognostic models including these parameters. This requires intensive collaboration and exchange of relevant data between expert centers around the world.

Conclusion

The prognostic impact of several individual clinical and pathological factors has been well established, with the PCI score and the necessity of macroscopic complete cytoreduction as most evident aspects. Although currently available prognostic models perform moderate to good, most models rely on data that are gathered during or after surgery. A prognostic model to predict survival for colorectal PM patients treated with CRS and HIPEC based on parameters known prior to surgery with high accuracy would be very valuable but is currently not available yet. Recent insights in tumor biology, such as the influence of RAS/RAF status, immunoprofiling, and ctDNA as well as the reliable assessment of PCI by DW-MRI pose promising opportunities to establish an adequate and clinically meaningful preoperative prognostic model in the near future.

Disclosure

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