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EDITORIAL

HIPEC FOR COLORECTAL PERITONEAL METASTASIS. SHOULD WE OPEN THE DOORS?

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Be patient toward all that is unsolved in your heart and try to love the questions themselves,
like locked rooms and like books that are now written in a very foreign tongue.
Do not now seek the answers, which cannot be given you because you would not be able to live them.
And the point is, to live everything. Live the questions now.
Perhaps you will then gradually, without noticing it, live along some distant day into the answer.

Rainer Maria Rilke (from Letters to a Young Poet)

Involvement of the peritoneum by metastatic colorectal cancer cells is commonly defined as peritoneal carcinomatosis. However, this term is now considered obsolete and should be replaced by the term peritoneal metastases (PMs), in analogy to the other main sites of metastasis (liver, lung and non-locoregional lymph nodes *in primis*). Approximately one quarter of patients with metastatic CRC have PM at onset (1), and even after radical surgery, CRC PM are estimated to develop in 15% of cases, an incidence that is probably underestimated (2).

Colorectal peritoneal metastases (CRC PMs) are an insidious site of metastasis because of their impact on bowel function (stenosis and dysmotility) and quality of life of affected patients and are often the cause of death in most of them (so-called peritoneal cancer syndrome). Patients with CRC PM have significantly worse survival in comparison with patients with CRC at other metastatic sites (3). Even after optimal treatment, survival in CRC PM can be prolonged up to 24 months with modern systemic chemotherapy regimens (4). The reasons why CRC PM is difficult to treat are somewhat intuitive but remain largely unknown and relatively understudied. Intrinsic adverse factors, such as the higher incidence of mucinous/signet ring cell histology and BRAF status in patients with CRC PM, are one of the possible explanations (5). Moreover, very few studies have investigated the role of epithelial-mesenchymal transition, angiogenesis and inflammation, and the microenvironment of the peritoneal nodules in terms of chemoresistance (6). On the other hand, peritoneal spread has a profound impact on bowel function, making the administration of chemotherapy quite problematic in several cases.

In the 1990s, before the introduction of modern treatments (oxaliplatin, irinotecan and biological agents) for CRC metastatic disease, the benefit of surgical treatment (called cytoreductive surgery, CRS) combined with intraperitoneal chemotherapy for CRC PM was first demonstrated. Paul Sugarbaker, widely regarded as the *deus ex machina* of this locoregional approach, described the surgical steps and the standardization of the CRS technique in a landmark article (7). Following this pioneering study, a randomized controlled trial (RCT) published by the Dutch group in 2002 showed that CRS with radical intent (no residual or millimetric residual disease) in combination with mitomycin-based hyperthermic intraperitoneal chemotherapy (HIPEC) could make a major contribution to modifying the natural history of the disease (8). Patients treated with radical CRS showed a significant survival benefit over those treated with chemotherapy alone, paving the way for this branch of surgical oncology to be widely used in more and more peritoneal cancer centres around the world, not only for CRC PM. Over the years, it has become clear that only selected patients can benefit from treatment. Peritoneal burden, expressed by the peritoneal cancer index (PCI), is directly related to prognosis after CRS-HIPEC. Only patients with a PCI of less than 15 may benefit from surgical treatment, and only if complete cytoreduction (no macroscopic residual disease) has been achieved (9).

Having established that CRS may be beneficial in selected patients with CRC PM, the role of HIPEC remains under investigation and several questions remain. In 2022, French groups published the results of a prospective RCT (PRODIGE 7) comparing CRC PM patients treated with CRS and oxaliplatin-based HIPEC with those treated with CRS alone after preoperative standard systemic chemotherapy (10). The results of the study were negative, showing no survival benefit with the addition of oxaliplatin-based HIPEC to CRS. The PRODIGE 7 trial confirmed an important finding that has been somewhat underestimated by the oncology community. Surgery works in CRC PM patients as the median survival of patients treated with CRS (with or without HIPEC) is around 42 months, similar if not better than the survival reported after radical surgery of other metastatic sites, liver *in primis*. The most valuable lesson from PRODIGE 7 is that surgery can be offered to patients with limited PMs if complete clearance of peritoneal nodules can be achieved through surgery in experienced healthcare centers.

For HIPEC after radical CRS, PRODIGE 7 did not support the use of oxaliplatin-based HIPEC, although a survival benefit was reported in a subgroup analysis of patients with PCI less than 15. This failure may be partly explained by the relative chemoresistance of peritoneal nodules. All the patients were heavily treated preoperatively with systemic oxaliplatin, and it is possible that oxaliplatin-based HIPEC is not the optimal regimen for the treated nodules. This hypothesis is also supported by clinical and experimental evidence showing that peritoneal cells after oxaliplatin-based chemotherapy are relatively resistant to exposure to oxaliplatin compared to other drugs commonly used for intraperitoneal chemotherapy (mitomycin). Patients who received oxaliplatin in the preoperative setting prior to CRS-HIPEC showed altered chemosensitivity to this drug (11). Recent studies on the gene expression profile based on the consensus molecular subtypes (CSM) in CRC PM showed that the majority of them were classified as CMS-4, with high expression of genes associated with epithelial mesenchymal transition, TGF-beta activation and angiogenesis (12, 13). The poorer survival outcomes associated with CSM-4 may partly explain the limited effect of oxaliplatin-based chemotherapy, and therefore oxaliplatin-based HIPEC, in CRC PM. The relative inefficacy of oxaliplatin-based HIPEC is also supported by the results of two RCTs on the use of HIPEC in CRC patients at high risk of developing PM in different settings, prophylactically at the time of primary treatment (COLOPEC) and in the II^ look setting (PRODIGE 15) (14, 15). Both trials were negative (no benefit of adding HIPEC at the time of primary treatment or after systemic chemotherapy). The results of PRODIGE 15, COLOPEC and especially PRODIGE 7 have been considered by some as the end of the road for HIPEC in CRC PM management. However, the debate is still open and evolving. Among HIPEC surgeons, CRS-HIPEC is still considered an indication for CRC PM and is still included in most national oncological guidelines (16). A step change is needed towards different HIPEC protocols with different drugs or drug combinations. A recent worldwide consensus of HIPEC surgeons considers mitomycin alone or in combination to be the best regimen for HIPEC in CRC PM (17). In this regard, the results of the Spanish HIPECT4 trial are encouraging, as proactive cytoreductive surgery combined with mitomycin-based HIPEC at the time of curative resection of primary cT4 colorectal cancer leads to a significant improvement in 3-year locoregional control rates

(97% in the HIPEC group *vs*. 87%) (18). This is the first RCT to support HIPEC. Another trial is underway with a similar design t0 PRODIGE 7 using mitomycin-based HIPEC after CRS (19).

There are still several areas of research open regarding CRC PM selected for CRS-HIPEC. We have to consider that most patients will relapse after treatment and only a few patients will have the chance of a definitive cure after treatment. Peritoneal recurrence is estimated to occur in almost 20-30% of patients during the first postoperative year. Therefore, there is an urgent need to improve patient selection, which today is mainly based on the PCI and the ability to achieve complete clearance of peritoneal nodules. Mutational analysis has been shown to better stratify the indication for CRS-HIPEC. A recent retrospective analysis has shown that wild-type patients (no RAS/RAF mutation) have significantly better survival compared to mutated patients (20, 21). In particular, BRAF-mutated patients had a very poor prognosis after surgery and the indication to proceed with CRS-HIPEC should be carefully weighed against other prognostic factors and probably represents a contraindication in most cases. On the other hand, microsatellite instability (detected in about 10% of CRC PM treated with CRS-HIPEC) seems to be associated with a very good prognosis. In unstable (microsatellite instability) patients with concomitant wild-type RAF/RAS status the median survival is around 95 months and even in RAS/RAF-mutated patients the presence of microsatellite seems to mitigate the adverse prognostic effect of mutation with a reported median survival of 44 months after CRS-HIPEC (21). In this perspective, the presence of mutation/microsatellite status should be systematically evaluated in the decision-making process before CRS-HIPEC and balanced with the other known prognostic factors, and a well-designed prospective analysis in this field is warranted.

Another critical issue is the role of systemic chemotherapy (SC) in patients selected for surgery. The indication and timing of systemic chemotherapy (SC) are still under debate (22). Treating patients with SC before surgery has the potential advantage of excluding patients with early disease progression and more aggressive biology who may not benefit from CRS-HIPEC. From an oncological point of view, postoperative SC is associated with a better prognosis, although importantly, selection bias may have influenced the results. The CAIRO 6 trial investigating the role of preoperative SC before CRS-HIPEC is ongoing and results are expected in the next few years (23). An interim analysis showed that SC didn't have an adverse effect on postoperative complications after CRS-HIPEC. Circulating tumor DNA (ctDNA) is an attractive test for patients at risk of developing systemic recurrence after CRS-HIPEC and is also a promising approach for selecting those patients who are likely to benefit from perioperative SC.

The level of evidence for HIPEC in CRC PM has increased in recent years, supported by the results of recently published RCTs (24). As in other metastatic sites (liver, lung), radical surgery for PM is an important resource in the context of multimodal treatment with SC. RAS/RAF mutation and MSI are important biomolecular markers for patient selection. For HIPEC after CRS, several questions remain open with certainties. Oxaliplatin-based HIPEC (after CRS or in the setting of II^ look/prophylactic strategies) should be abandoned and new HIPEC regimens are needed for testing. Recent evidence from clinical and *ex-vivo* studies confirms that mitomycin is an active drug for HIPEC and high-quality studies are underway to test its potential benefit. This will be the key to finally opening the doors to HIPEC in CRC PM.

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