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EDITORIAL – PERITONEAL SURFACE MALIGNANCY

Repeat CRS/HIPEC: It Comes Down to Tumor Biology and Ability to Achieve a Complete CRS

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The concept of repeat cytoreductive surgery/hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) in appendiceal primaries was developed as a necessity directly related to the natural history of debilitating peritoneal recurrences after initial cytoreduction. This is accurately depicted in the 1957–1983 historic Mayo experience, where appendiceal and ovarian patients were treated with repeat debulking operations followed by intraperitoneal ^{32}P or ^{198}Au radiotherapy, or intraperitoneal 5-fluorouracil and cyclophosphamide, in an effort to address residual peritoneal disease. Despite the fact that, at that time, physical examination was the most common method detecting disease recurrence, 5- and 10-year survival was reported as 53% and 32%, respectively.[1]

The introduction of CRS/HIPEC along with modern imaging techniques dramatically improved survival outcomes, with expected 5-year survival routinely approaching 80% in low-grade appendiceal (LGA) primaries treated with CC0-R0/R1 complete macroscopic cytoreduction.[2–5] Despite the efficacy of CRS/HIPEC, up to 70% of patients, especially those presenting with voluminous disease (Peritoneal Cancer Index [PCI] >20), will eventually recur. Although a smaller subset of patients will exhibit recurrences with slow or no progression, the majority, if left untreated, will succumb to bowel obstruction. Given the lack of response to chemotherapy by the LGA primaries and the predominantly limited to the peritoneal cavity pattern of recurrence, up to 20% of patients will be offered repeat CRS/HIPEC.

One of the earliest series of repeat CRS/PIC (perioperative intraperitoneal chemotherapy) was published by Esquivel and Sugarbaker in 2001, introducing the concept of staged CRS/PIC procedures in patients with high-volume disease. A number of these repeat CRS/PIC cases were performed as scheduled second-look operations in patients presenting with neglected high-volume pseudomyxoma peritonei (PMP). These patients quite often present with depleted physiologic reserves and cannot sustain a single-stage surgical resection without a prohibitive risk of mortality. Of the initial 321 CRS/HIPEC patients, 79 (24.6%) underwent a second-look operation inclusive of CRS/PIC. Complete cytoreduction at the second index case achieved an 84% 5-year survival, compared with 68% for those patients who did not have repeat procedures.[6]

A few years later, the same group analyzed patients who developed a recurrence after prior CC-0/1 resection. They clearly demonstrated that the pattern of recurrence was also important, with diffuse peritoneal progression behaving much worse than isolated recurrence ($p = 0.006$), while complete CRS at the second operation was the only significant factor for extended survival. No patient was alive post 76 months without reoperation, demonstrating that the indolent behavior of these tumors will allow for long-term survival even after incomplete CRS, but not to the extent achieved by complete macroscopic CRS offered by a redo procedure.[7]

In this issue of *Annals of Surgical Oncology*, Lopez-Ramirez et al. elegantly demonstrate the natural course of the disease in cases where, for a number of reasons, a redo CRS/HIPEC was not attempted (control).[8] Fifty-five repeat

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HIPEC procedures (36 LGAs, 13 high-grade, and 6 signet ring) treated over a span of 22 years were compared with 55 propensity matched patients based on age at recurrence, PCI, completeness of CRS, lymph node status, grade of primary, and time to recurrence as an indirect indication of tumor biology. Morbidity and mortality were comparable with initial CRS/HIPEC. Repeat CRS/HIPEC was resetting the clock for the LGA group, with an achieved 5-year survival of 81.3% versus 46.3% ($p < 0.001$) for the control. In the high-grade primaries, the difference in the achieved 5-year survival was also in favor of repeat HIPEC (50 vs. 12%; $p = 0.02$), while there were no 5-year survivors for the signet ring cohort with or without reoperation.

The study is well aligned with prior work on the field and has similar limitations, including the underrepresentation of high-grade primaries as well as the inability of the current CC and R resection classification systems to define the exact volume of residual disease in cases of incomplete cytoreductions.[9,10]

It is not a coincidence that all published repeat CRS/HIPEC series from centers with more than 20 years of experience include a modest number of high-grade appendiceal (HGA) primaries and an even smaller number of signet ring cells, clearly depicting the vast differences in biologic behavior between HGA and LGA cancer. Achieving a CC0 resection during a repeat CRS for an HGA primary is an even rarer event than attempting it, due to the infiltrative and often sclerotic nature of these tumors, protracted courses of systemic chemotherapy, prior surgical resections, and, often, marginal functional status. Intense fibrosis is also present with redo LGA primaries or neglected first-time CRSs that have been left undiagnosed evolving over many years, possibly suggesting a proinflammatory or an overactivated cancer-associated fibroblast (CAF) pathway within the peritoneal/stroma microenvironment. Particularly in the LGA subgroup, patients succumb to mechanical obstruction with excessive fibrotic tissue and a relatively scarce number of cancer epithelial cells. Delineating the interaction framework between the epithelial and CAF component or the stroma for appendiceal primaries will likely facilitate identification of new therapeutic targets.

Another parameter that is well hidden within the resection scores, is the impact of residual macroscopic disease on outcomes for both first and repeat CRS/HIPEC operations. In other words, is a single-region CC1 pelvic resection (remaining disease <2.5 mm) for a high-grade primary, equal to CC1 resection involving all 13 peritoneal regions, in terms of time to progression, risk of HIPEC failure, and overall survival? We know from perfusion of 1 mm in size appendiceal cancer organoids, that approximately 20% of cells will stay alive after 2 h of heated chemoperfusion.[11] When the entire extent of the peritoneum is factored in with an average surface of 1.7–2 m^2, then the potential of HIPEC failure obtains a more robust dynamic. Is this the time to rethink of what we define as complete cytoreduction, not so much for LGA primaries or epithelioid mesothelioma but for primaries with more aggressive biologic behavior?

The interval between recurrence and initial CRS/HIPEC is used as an indicator of tumor biology. It is well-documented that the longer the interval, the better the survival outcomes, reflecting the selection of patients with favorable tumor biology.[12,13] How the extent of CC1 resection impacts the risk of dedifferentiation of a low-grade primary to high grade is unknown.[14]

We have a lot of work to do going forward but for now the take-home message is that complete repeat CRS/HIPEC is resetting the clock and prolongs survival in LGA and highly selected HGA primaries. Outcomes after repeat CRS predominantly depend on tumor biology and completion of CRS.

DISLCOSURE Konstantinos I. Votanopoulos declares no conflicts of interest.

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