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HEPATOBILIARY TUMORS

Progression of Colorectal Cancer Liver Metastasis After Chemotherapy: A New Test of Time?

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With the increasing use of chemotherapy prior to resection for colorectal liver metastases (CLM), progression on treatment has been used at some hepatobiliary centers as a criterion to determine whether resection was justified. In 2004, Adam et al. reported the outcomes of patients exhibiting disease progression during preoperative chemotherapy in a series of 131 resected patients with ≥ 4 metastases and showed 5-year survival of only 8% for this subgroup.[1] This led to the conclusion that disease progression during preoperative chemotherapy may represent a contraindication to resection due to lack of survival benefit. Subsequently, the same authors later softened their recommendations and showed in a series using LiverMetSurvey data[2] that disease progression only, although a negative prognostic factor, was associated with 5-year survival of 53%. In that study of 2146 patients of whom 8% ($n = 176$) progressed during preoperative chemotherapy, presence of additional prognostic factors [size > 50 mm, > 3 lesions, carcinoembryonic antigen (CEA) > 200 ng/mL] contributed to adverse outcomes in that subset of patients, with high CEA being independently associated with worse outcome [relative risk (RR) 5.06 (1.72–14.95), $p = 0.003$] with 10% 3-year overall survival.

In the current issue of *Annals of Surgical Oncology*,[3] Vigano et al. further address the issue of tumor control in the preoperative period in a study focusing on the time interval off preoperative chemotherapy prior to resection. The authors report the outcomes of 128 patients who were resected after an initial (stable or partial) response to preoperative chemotherapy. All patients included were imaged three times, including before and after chemotherapy and prior to resection (> 4 weeks after chemotherapy cessation). Using Response Evaluation Criteria in Solid Tumors (RECIST) measurement, Vigano et al. report that 25% ($n = 32$) had disease progression in the interval between chemotherapy and resection. After stratification by different time intervals off treatment, the group with worse outcome consisted of a small subset of patients ($n = 8$) who progressed within a short time interval off systemic therapy (< 8 weeks), with no survivors at 2 years, compared with 2-year overall survival (OS) of 52.4% for patients with stable disease. As the time interval increased, the survival gap between patients with progression versus stable disease became narrower (3-year OS 25.0% vs. 53.7%, $p = 0.009$), until no differences in outcomes were found for longer (> 16 weeks) time intervals off chemotherapy (3-year OS 37.5% vs. 48.5%, $p = 0.288$, progression versus stable disease, respectively). The authors concluded that disease progression upon cessation of preoperative chemotherapy may be a contraindication to surgery given the markedly poor outcomes. The authors rightly focused on short time intervals off treatment, and their study emphasizes the need to perform preresection imaging to risk-stratify patients and reevaluate the disease after cessation of preoperative therapy.

A shortcoming of the study is the lack of denominator, as patients who progressed to the point of unresectability were not included in the study. Additionally, the authors focus on liver progression, whereas we feel that new intra- and extrahepatic disease is as equally if not more concerning than hepatic progression of known hepatic disease. In addition to the relatively small number of patients in the series, an issue with the study of Vigano et al. is the disease assessment by RECIST, which is known to have some limitations and no association with survival especially in

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the context of targeted therapy.[4] Hence, the authors did not find an association between progression after treatment cessation and preoperative chemotherapy response, but since 59% of these patients received targeted therapy, morphologic criteria[4,5] would provide an additional tool for response evaluation more reflective of disease biology.

Based on the limitations of size-based tumor evaluation, alternative parameters of response have been developed and validated as predictors of long-term outcomes—for chemotherapy with or without targeted therapy—such as depth of response, expressed by the maximal percentage of response at peak compared with baseline,[6,7] and early tumor shrinkage, defined by a 10% decrease in tumor burden in the first 2 months after initiation of first-line chemotherapy.[8] Molecular profiling is also increasingly integrated in the evaluation of patients with CLM, and chemotherapy response is related to RAS mutation status, with the wild type being more likely to have optimal morphologic response [odds ratio (OR) 4.38; 95% confidence interval (CI) 1.45–13.2] with chemotherapy and bevacizumab, as shown in a recent series of 184 patients.[9] Altogether, several characteristics need to be considered to fully account for the disease biology and the multifaceted behavior of CLM.

The findings of Vigano et al. confirm previous reports indicating that progression of CLM during or after cessation of preoperative chemotherapy may be mediated by intrinsic tumor characteristics that respond differently to systemic therapy, particularly with antiangiogenic treatment. Frentzas and colleagues[10] recently demonstrated that CLM utilizing a different vascularization process known as vessel co-option (as opposed to relying on angiogenesis) are prone to neoadjuvant treatment resistance and thereby associated with worse oncological outcomes after surgical resection. This more aggressive subtype of liver metastasis is represented pathologically by a replacement histological growth pattern, where the tumor interface infiltrates the normal liver, "replacing" surrounding hepatocytes.[11] Interestingly, a subanalysis of lesions that developed after cessation of chemotherapy demonstrated significant enrichment of this replacement histological growth pattern, suggesting that co-opting lesions may mediate disease progression in this context.[10]

In conclusion, we congratulate Vigano and colleagues on this work, as it emphasizes the importance of high-quality preresection imaging and underlines the concept of careful patient selection to optimize survival outcome. The results of the study are equivalent to the traditional off of chemotherapy historical "test of time" described by Johannes Scheele in Germany and Martin Adson of Mayo Clinic[12,13] to discriminate patients with unfavorable biology, which we believe is valuable and represents a novel aspect in preoperative decision-making. We typically use an interval off of therapy of 5 weeks prior to resection[14] regardless of addition of targeted therapy, as it allows for a biological test of time based on three sequential computed tomographies. Further insights into biology are mandated to interpret the multifaceted responses to systemic treatment and guide decision-making in CLM.

Disclosure None of the authors have declared any conflict of interest.

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