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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), the issue of progression on treatment has been used at some hepatobiliary centers as a criteria to decide whether resection was justified. In 2004, Rene 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 a 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 the lack of survival benefit. Subsequently, the same authors later softened their recommendations and showed in a series using LiverMetSurvey data² that disease progression only – although being a negative prognostic factor – was associated with a 5-year survival of 53%. In that study of 2146 patients where 8% (n=176) progressed during preoperative chemotherapy, the presence of additional prognostic factors (size >50mm, >3 lesions, CEA >200ng/mL) were contributing to adverse outcomes in that subset of patients, with a high CEA being independently associated with a worse outcome (RR 5.06 (1.72–14.95) p=0.003) with a 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 response (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 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) that progressed within a short time interval off systemic therapy (<8 weeks), with no survivors at 2 years compared to a 2-year OS of 52.4% for patients with stable disease. As 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

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37.5% vs. 48.5%, $p=0.288$, progression vs. 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 interval off treatment and their study emphasizes the need to perform pre-resection 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 are not included in the study. Additionally, the authors focus on liver progression but we feel that new intra-hepatic disease and extra-hepatic 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 in 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 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 the evaluation of response that is 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 terms outcomes – for chemotherapy with or without targeted therapy – such as depth of response, expressed by the maximal percentage of response at peak compared to 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% 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 in order 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 anti-angiogenic treatment. Frentzas and colleagues¹⁰ 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 sub-analysis of lesions that had developed after cessation of chemotherapy demonstrated a 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 the work of Vigano and colleagues as it emphasizes the importance of high quality pre-resection imaging and underlines the concept of careful

patient selection in order 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 the addition of targeted therapy as it allows for a biological test of time based on three sequential computed tomography. Further insights into biology are mandated in order to interpret the multifaceted responses to systemic treatment and guide decision-making in CLM.

References

1. Adam R, Pascal G, Castaing D, et al. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? *Ann Surg*. 2004; 240:1052–1061. [PubMed: 15570210]
2. Vigano L, Capussotti L, Barroso E, et al. Progression while receiving preoperative chemotherapy should not be an absolute contraindication to liver resection for colorectal metastases. *Ann Surg Oncol*. 2012; 19:2786–2796. [PubMed: 22622469]
3. Vigano L, Darwish S, Rimassa L, et al. Progression of colorectal liver metastases from the end of chemotherapy to resection: a new contraindication to surgery? *Ann Surg Oncol*. in press.
4. Chun YS, Vauthey JN, Boonsirikamchai P, et al. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. *JAMA*. 2009; 302:2338–2344. [PubMed: 19952320]
5. Shindoh J, Loyer EM, Kopetz S, et al. Optimal morphologic response to preoperative chemotherapy: an alternate outcome end point before resection of hepatic colorectal metastases. *J Clin Oncol*. 2012; 30:4566–4572. [PubMed: 23150701]
6. Stintzing, S., Modest, DP., von Weikersthal, LF., et al. Independent radiological evaluation of objective response, early tumor shrinkage, and depth of response in FIRE-3 (AIO KKK-0306) in the final RAS evaluable population; *Ann Oncol*. 2014. p. 25<https://doi.org/10.1093/annonc/mdl1438.1099>
7. Cremolini C, Loupakis F, Antoniotti C, et al. Early tumor shrinkage and depth of response predict long-term outcome in metastatic colorectal cancer patients treated with first-line chemotherapy plus bevacizumab: results from phase III TRIBE trial by the Gruppo Oncologico del Nord Ovest. *Ann Oncol*. 2015; 26:1188–1194. [PubMed: 25712456]
8. Suzuki C, Blomqvist L, Sundin A, et al. The initial change in tumor size predicts response and survival in patients with metastatic colorectal cancer treated with combination chemotherapy. *Ann Oncol*. 2012; 23:948–954. [PubMed: 21832285]
9. Zimmiti G, Shindoh J, Mise Y, et al. RAS mutations predict radiologic and pathologic response in patients treated with chemotherapy before resection of colorectal liver metastases. *Ann Surg Oncol*. 2015; 22:834–842. [PubMed: 25227306]
10. Frentzas S, Simoneau E, Bridgeman VL, et al. Vessel co-option mediates resistance to anti-angiogenic therapy in liver metastases. *Nat Med*. 2016; 22:1294–1302. [PubMed: 27748747]
11. Vermeulen PB, Colpaert C, Salgado R, et al. Liver metastases from colorectal adenocarcinomas grow in three patterns with different angiogenesis and desmoplasia. *J Pathol*. 2001; 195:336–342. [PubMed: 11673831]
12. Wagner JS, Adson MA, Van Heerden JA, et al. The natural history of hepatic metastases from colorectal cancer. A comparison with resective treatment. *Ann Surg*. 1984; 199:502–508. [PubMed: 6721600]
13. Scheele J. Hepatectomy for liver metastases. *Br J Surg*. 1993; 80:274–276. [PubMed: 8472130]
14. Gruenberger B, Tamandl D, Schueller J, et al. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. *J Clin Oncol*. 2008; 26:1830–1835. [PubMed: 18398148]