

## Positive Margins After Resection of Metastatic Colorectal Cancer in the Liver: Back to the Drawing Board?

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The debate over the relevance of surgical margins in patients undergoing hepatic resection for metastatic colorectal cancer has gone on for decades. For many years a “1-cm margin” rule was recommended. Based on limited and now outdated information, patients with margins closer than 1 cm appeared to have significantly worse survival. As recently as 10 years ago, our group continued to find better outcomes associated with margins greater than 1 cm.<sup>1</sup> More recently, most studies have found that beyond a 1-mm margin, there is no associated prolongation of survival. In fact, some groups have found that a positive margin does not matter at all, although these are typically reported in series where the margin positivity rate is as high as 50%.<sup>2</sup> To add more fuel to the fire, we recently found that compared to a true positive margin (malignant cells at the actual margin), even negative margins <1 mm were associated with improved survival.<sup>3</sup> One thing, however, is common throughout these myriad studies: in the context of multiple tumors, they all reported the surgical margin as that of the tumor with the closest margin.

We and others have questioned whether the oncologic outcomes associated with margins are a reflection of surgical technique or of underlying tumor biology. The issue is complicated, because the pathologist may see one margin but the actual liver may see another. In the case of using instruments like the Cavitron ultrasonic surgical aspirator or the argon beam coagulator, the liver margin may be “enhanced” by thermal ablation or obliteration of tissue that the pathologist never sees. Of course, the surgeon can resect well away from a tumor or get too close or

even truly enucleate a tumor, which could affect outcomes if you believe that technique is the issue. My own anecdotal experience suggests that margins are likely more a reflection of underlying tumor growth patterns and a surrogate for underlying tumor biology. I have seen exposed tumors on the surface of a resection specimen called negative on a pathology report, and I have seen what grossly looks like normal liver tissue called positive on a pathology report. Indeed, our recent analysis demonstrating differences in outcome based on <1-mm margins (not visible to my eye!) is an argument for the “biology” side. How could we technically control for such a small margin? Recent data has supported that idea that growth patterns are probably relevant and may explain the link between margins and outcome.<sup>4,5</sup> The debate has certainly not been laid to rest.

In this issue of the *Annals of Surgical Oncology*, Sazaki et al. question the way margins traditionally have been studied. They specifically ask whether, in the case of multiple tumors, the closest margin of any of the tumors or the margin of the largest tumor is more relevant. The rationale is sound, because some data suggest that the largest tumor is more likely to harbor occult microscopic disease beyond the grossly visible edge of the tumor (ASO Sazaki ref). The authors deserve great credit for asking a unique question that has not been tackled before. Their ultimate conclusion is that the margin of the largest tumor is independently associated with survival, whereas the margin of the tumor with the closest margin is not. There are a few reasons why these data should be interpreted with caution. The rate of positive margins was higher than most series. Of the 250 patients with multiple tumors, 38% had a positive margin. Overall, the numbers of patients and events were small and the follow-up was limited. Among the two groups with positive margins, there were only 45 and 50 patients, respectively. Furthermore, the follow-up was not adequate to document long-term outcomes. If one

reviews the Kaplan–Meier curves, the number of patients at risk after 2 years is less than 10, limiting the ability to make solid conclusions about long-term survival. Furthermore, the analysis of the closest margin (regardless of tumor size) was quite close to being significantly associated with outcomes ( $p$  values of 0.05 on univariate analysis and 0.08 on multivariable analysis). Lastly, it is unclear what the prognostic implications of multiple positive margins are, because there were no such patients in this series. Given the limited number of events, short follow-up, and risk of statistical error, this study must be interpreted with a grain of salt. Whereas Sazaki et al. have posed a unique and potentially valuable question, I believe it has not been fully answered. As I write this, I certainly feel the inspiration to delve into our database to try to analyze this question further. As always, there is work to do.

I am sure that the debate on margins in cancer surgery will continue well into the future. There is much to study regarding the relationship between margins, outcome, and underlying biology. These topics include tumor genetic alterations, histologic growth patterns, and likely other undefined issues. But we must, at this time, ask ourselves a practical question. How should any of this change our practice? It is hard to document much of a benefit to a resection margin of more than 1 mm for patients with metastatic colorectal cancer in the liver. Furthermore, we have been unable to find any specific imaging or clinical characteristics that can predict a positive margin.<sup>1</sup> The nihilist might say that we should just resect the tumor without much regard for gross clearance and consider margins as merely reflective of underlying tumor biology. Others would argue that the surgeon has a singular opportunity to impact outcomes and that a wide margin gives the patient the best chance at an optimal outcome. Of

course, this question comes down to an individualized risk/benefit analysis. For a single tumor on the edge of the liver, a wide margin adds no risk and may help the patient. Of course one should not tempt fate in this situation and simply stay wide of the tumor. On the other hand, if obtaining a wide margin changes a low-risk segmental resection into an extended multisegment resection, the risk substantially increases and the benefit is in doubt. This change in surgical plan would be illogical and, in this case, it probably is best to perform the limited resection. As in all cases in surgical oncology, optimal care depends on a thoughtful analysis that is individualized to the patient and underlying cancer.

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