Published in final edited form as:

J Gastrointest Surg. 2017 January ; 21(1): 196–198. doi:10.1007/s11605-016-3253-5.

Positive Resection Margin and Outcome After Resection of Colorectal Cancer Liver Metastases

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Introduction

Historically, resectable colorectal cancer liver metastases (CRLM) were defined as 3 tumors or less, with mandatory 1cm margins, and without extrahepatic disease. The criteria for resection have expanded to include any extent of liver-confined disease that can be resected with negative margins, and leaving 2 or more contiguous liver segments, with vascular inflow, vascular outflow, and biliary drainage, and an adequate sized future liver remnant.¹ With the development of these guidelines, more extensive resections are carried out to include patients with widespread bilobar hepatic metastatic disease. While a greater burden of disease portends worse outcomes, the potential for long-term survival after resection still exists. Furthermore, with the evolution of hepatic surgery towards more parenchymal-sparing resections, morbidity and mortality have continued to decrease without impacting survival or recurrence.^{2,3} As such, closer margins may be more frequently encountered during resection in attempts to spare healthy parenchyma and clear higher burdens of disease. The impact of positive margins and margin width following resection of CRLM are discussed below. It should be noted that many studies have evaluated the impact of margins on survival following CRLM. However, for the purposes of this brief discussion, only the largest series are highlighted below.

The Impact of Positive Margins on Survival

To date, there have been no prospective randomized controlled data evaluating the impact of close or positive margins on survival following resection of CRLM. Such a trial would not

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The authors have no conflicts of interest, financial or otherwise, to disclose.

This paper was originally presented as part of the SSAT/AHPBA/E-AHPBA Joint Symposium: Extending the Limits of Resection for Colorectal Liver Metastases at the SSAT 57th annual meeting, May 2016, in San Diego, California. The other articles presented in the presentation are:

Extending the Limits of Resection for Colorectal Liver Metastases

Ernst Klar

Extending the Limits of Resection for Colorectal Liver Metastases

ENHANCED ONE STAGE SURGERY

Guido Torzilli, MD, PhD, FACS, Matteo Maria Cimino, MD

Extending the Limits of Resection for Colorectal Liver Metastases

ALPPS for colorectal liver metastases

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Extending the Limits of Resection for Colorectal Liver Metastases

Bilateral Disease

Thomas A. Aloia

be easily designed or performed and may not be technically feasible. Therefore, a trial evaluating margins and outcome in resection of CRLM is unlikely to ever occur.

In this review, we will analyze several large-scale retrospective studies that have evaluated the prognostic impact of margin width following resection of CRLM. In a recent study from our institution, we evaluated the impact of margin width on overall survival (OS) by evaluating the relationship between resection margin and OS using high-resolution histologic distance measurements.⁴ By using the prospectively maintained database at the Memorial Sloan Kettering Cancer Center, we identified a total of 4,915 patients who underwent initial complete resection of CRLM between 1992 and 2012. R1 resection was defined as tumor cells at the resection margin (0mm), and R0 margins were divided into 3 categories: 0.1–0.9mm (submillimeter), 1–9mm, and ≥10mm. Half of the patients presented with synchronous disease and 43% had solitary metastases, with a median tumor size of 3.4cm. The median OS for the R1, submillimeter, 1–9mm, and ≥10mm were 32, 40, 53, and 56 months, respectively ($p < 0.001$). There was no statistical difference in OS between the 1–9mm and ≥10mm groups. The data demonstrated that a clear resection margin, when adjusted for confounders, was independently associated with OS and that wide margins beyond 1mm were not associated with further prolongation of survival. We concluded that wide margins should be the goal, when safe, to ensure a clear margin. Furthermore, given that even submillimeter negative margins were associated with improved survival, resection should not be precluded where narrow margins are anticipated, particularly since the ability to reliably predict a positive margin preoperatively is not possible. We also interpreted the prolonged OS observed with submillimeter margins to most likely be a surrogate for tumor biology, rather than the result of surgical technique.

In another important study evaluating the effect of surgical margins following resection of CRLM, authors from the MD Anderson cancer center evaluated the impact of margin status on OS following the administration of preoperative chemotherapy.⁵ A total of 378 patients who were treated with preoperative chemotherapy followed by hepatectomy were identified, of whom 52 had undergone R1 resection. In this study, a positive resection was defined as a margin <1mm. Five-year survival was 26% among patients who had R1 resections compared with 55% in those with negative margins ($p = 0.017$). Multivariate analysis identified R1 resection and minor pathologic response to systemic therapy as the 2 independent factors associated with worse OS. In a subset analysis, there was no difference in OS between R0 and R1 resection in patients who had an optimal morphologic response on imaging follow-up or major pathologic response after systemic chemotherapy. Given the importance of a positive microscopic margin on OS on multivariate analysis, the authors concluded the negative margins remain an important determinant of survival and should still be the sought goal of resection.

An older study from the same institution by Pawlik and colleagues had previously noted the adverse effect of a positive resection margin in 45 R1 CRLM patients among 557 total patients identified during the study period.⁶ Median OS was 49 months in patients with positive margins but had not yet been reached in patients with negative margins. In this study, survival was not different when a negative margin was categorized into 1–4mm, 5–

9mm, or 10mm categories. However, the authors were able to demonstrate an increased rate of surgical margin recurrence in patients who underwent R1 resection ($p = 0.003$).

Finally, in a French study by de Haas and colleagues from the Hôpital Paul Brousse, the authors compared long-term outcomes of R0 versus R1 liver resections for CRLM treated by preoperative and/or postoperative chemotherapy and resection.⁷ A total of 436 patients were identified, of whom 202 underwent R1 resection (46%). Five-year OS was similar between the 2 groups (61% in R0 group compared with 57% in R1 group; $p = 0.27$). There was also no difference in recurrence-free survival between the 2 groups. R1 resection was not found to be an independent predictor of survival in this series. Whether the use of perioperative chemotherapy may have accounted for this finding, particularly given the subgroup analysis of the MD Anderson study above, is unknown. However, it is important to note that the effect of systemic chemotherapy has not been reproduced in several other studies, including the above study from the Memorial Sloan Kettering Cancer Center.⁴ The high rate of margin positivity (46%) may account for the unique finding in this study as most other studies have R1 resection rates of approximately 10 to 15%. Similar to most other studies, de Haas and colleagues noted a higher rate of intrahepatic, but not margin, recurrences in patients who underwent R1 resection. This also may support the contention that margin status could be a surrogate for underlying tumor biology.

Re-Resection of Margins

In a small but interesting study by Wray and colleagues, the authors retrospectively evaluated recurrence and survival in CRLM patients who underwent margin re-resection for a macroscopically positive or suspicious margin evaluated with frozen section analysis. The patients were divided up into 3 groups: margins >1 cm, margins <1 cm, and those who underwent re-resection to margins >1 cm. They found that in patients with initial margins >1 cm, the rate of both liver and distant recurrences were significantly lower than in patients who underwent re-resection.⁸ Overall disease-free survival was also significantly higher in patients who achieved >1 cm margin following initial resection. These findings additionally support the theory that narrow and/or positive surgical margins are more likely to be a harbinger of aggressive tumor biology, which may be the most important determinant of survival. In a similar but more recent study by Margonis and colleagues, margin re-resection from R1 to R0 was also not shown to improve long-term outcomes.⁹

Conclusion

Strategies for resection of CRLM should continue to include resection with wide margins when possible. However, close margins are not a contraindication to resection since close but negative margins are associated with improved survival and are not easily predicted on preoperative planning. Given that most recurrences occur outside the surgical margin and in a disseminated and/or distant pattern, it is important to recognize that positive margins are most likely a surrogate of aggressive tumor biology, which ultimately may be the most important determinant of long-term survival.

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