

# Intraoperative margin re-resection for colorectal cancer liver metastases

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**Abstract:** One of the basic tenets of surgical oncology is the achievement of margin-negative resection. The importance of surgical margins in hepatic resection for colorectal cancer liver metastases (CRCLM) is reflected in the abundance of literature written about this topic. However, the definition of the ideal surgical margin has evolved in parallel with advances in systemic chemotherapy, biologic therapy and surgical technology. A better understanding of the biology of liver metastasis is of critical importance in the context of surgical strategy for CRCLM. The value of intraoperative margin re-resection to achieve R0 status for CRCLM is addressed, taking into consideration current understandings of cancer biology.

**Key Words:** Colorectal cancer liver metastasis; intraoperative margins; colorectal cancer; margin re-resection; liver metastasis



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## Background

Over 143,000 individuals are estimated to be diagnosed with colorectal cancer (CRC) in the United States in 2012, with nearly 52,000 secondary deaths (1). CRC represents the most common gastrointestinal malignancy globally, and it is believed that of the 1.2 million people afflicted each year, 609,000 will die (2). The liver represents the most common site of initial clinical metastasis and approximately 60% patients develop colorectal cancer liver metastasis (CRCLM) during their primary or recurrent presentation (3). Approximately 20% of these patients will be eligible for hepatic resection with curative intent and with careful selection 5-year overall survival rates up to 25-58% can be reached (4-10). Advances in surgical technique, surgical series defining favorable clinical characteristics, and modern systemic chemotherapies have all contributed to these favorable outcomes. Despite these encouraging numbers, caution should be exercised in interpretation of the data because the benefits of resection are not based on prospectively randomized data but rather on retrospective series showing survival benefits compared to

historical controls.

Over the last quarter century, the question of appropriate surgical margins in CRCLM has come to the forefront of debate. Surgical opinion regarding margin management in CRCLM has evolved but has been hindered somewhat by the lack supporting level 1 data. During the 1980s and 1990s, it was claimed that at least a 1-cm margin was required for hepatectomy to minimize disease recurrence and optimize survival (11-15). This led to a substantial period during which a requirement for resectability was the ability to achieve a 1-cm margin. However, this argument was weakened by the retrospective nature of the supporting data, which included studies that were underpowered, had suboptimal patient stratification, and lacked multivariate analysis. Near the turn of the last century, reports that questioned the necessity of 1-cm as the minimal resection margin began to appear. Surgeons from North America, Europe, and elsewhere reported large institutional series showing that outcomes in recurrence and survival depended more closely on the achievement of microscopically negative margins rather than a 1-cm negative margin (16-21). More

recently, several groups have begun to question whether negative margins are in fact absolutely necessary in surgical resections (22-25). These most recent studies have shown that positive microscopic margins may still result in equivalent overall survival and recurrence as patients with negative margins. Given this changing notion of the appropriate surgical margin, the question of whether intraoperative margin re-resection is of benefit in CRCLM becomes even more interesting.

### Surgical margins

In 1986 Ekberg and colleagues from Sweden presented their data regarding outcomes after surgical resection for CRCLM (11). In this now-classic retrospective series of 72 patients, they concluded that it is “essential to obtain a margin of resection that is 10 mm or more” because this clinical variable was associated with a favorable overall survival. During this time period, the experience of several other groups was similar and thus the “standard of care” for liver resections in CRCLM was to consider patients for curative resection only if 1-cm margins could be achieved (11-15).

This viewpoint began to change around the turn of the century. The largest retrospective series to question the 1-cm margin paradigm was by Pawlik and colleagues (16). This international, multi-institutional retrospective series comprised of 557 patients stratified margin status by positive margins and negative margins of either 1-4 mm, 5-9 mm and >10 mm. All patients with negative margins had similar overall recurrence rates, but patients with positive margins had a significantly poorer median overall survival (5-year overall survival of 17.1% *vs.* 63.6%,  $P=0.01$ ) and were more likely to have surgical margin recurrence (38.6% *vs.* 51.1%,  $P=0.04$ ). Furthermore, patients with positive recurrence margins tended to have more metastatic lesions and a higher preoperative CEA level. This study concluded that subcentimeter, negative surgical margins were sufficient for liver resections. Equally important, it also suggested that a different tumor biology driving metastasis, rather than surgical technique, accounted for a positive margin. Several investigators have also shown that subcentimeter negative margins of resection provide similar clinical outcomes as patients undergoing hepatectomy with greater than 1-cm margins (17-21).

The belief that even microscopically negative margins are absolutely necessary for CRCLM has recently been challenged. De Haas and colleagues reviewed 436 patients undergoing hepatectomy for CRCLM with either an R1

or R0 margin of resection on patients operated between 1990-2006 (22). They showed that patients undergoing R0 and R1 resections had no significant difference in 5-year overall survival (61% *vs.* 57%,  $P=0.27$ ) and median disease-free survival ( $P=0.12$ ). Although patients with R1 resections had higher numbers of intrahepatic recurrences, when the investigators looked specifically at surgical margin recurrence, they found both groups to have equivalent surgical margin recurrence. Predictors of poor overall survival were not microscopically positive margins, but rather tumors greater than 3 cm and bilobar distribution. These data also strongly suggest that there are inherent biological differences in tumor behavior in patients undergoing R0 and R1 resections. Interestingly, this difference in tumor biology among positive and negative margins is similar to the conclusions implied in the study by Pawlik *et al.*, which notably drew different conclusions about surgical margins. It is plausible to conceive that when liver resections are performed by experienced hepatopancreatobiliary surgeons, differences in tumor biology rather than surgical technique are responsible for differences in margin status.

It is not a coincidence that evolution of surgical opinion regarding margins has paralleled advances in systemic chemotherapy and biologic therapy in CRC. We have seen substantially improved outcomes in metastatic CRC as more modern systemic therapies have been introduced. In 1993 when systemic chemotherapy with fluorouracil-based therapy was first shown by the Scheithauer and colleagues to improve the overall survival compared to palliative care, therapeutic options were limited (26). This landmark trial reported prolonged median overall survival to 11 months, but it was not until much later that oxaliplatin- and irinotecan-containing regimens were shown in prospective trials to prolong median overall survival to 19 months. Most recently the introduction of biologic agents (*i.e.*, bevacizumab, cetuximab) has further increased median survival data to 24 months (27,28). Not only has survival improved in widely metastatic CRC, but also groups of patients with CRCLM that were initially deemed unresectable have become resectable after systemic chemotherapy, such as demonstrated in a French retrospective series of 701 patients (29). Interestingly, a Dutch group reported a series of 264 patients undergoing hepatectomy for CRCLM and found no differences in clinical outcome in patients receiving neoadjuvant chemotherapy between those with R0 and R1 resections (25). However in patients that did not receive upfront chemotherapy, R1

resection was associated with a worse clinical outcome. Thus, significant advances in systemic therapies have become part of the multidisciplinary care of CRC patients and will continue to influence the outcome of liver surgery.

As ideas about the importance of margin status have evolved, so too has the role of intraoperative margin re-resection to achieve R0 status during hepatectomy for CRCLM. Unfortunately, the issue of margin re-resection is even less well informed by the surgical literature. When surgeons are confronted with positive intraoperative margins, many will perform re-resection when feasible or ablation with cautery or radiofrequency when re-resection is not feasible, yet these practices are not supported by data (12,16). There is only one study that specifically addressed this topic. Wray and colleagues from the University of Cincinnati reported in 2007 a retrospective single-institution review of 118 surgically resected cases of CRCLM over a 13-year time span (30). Clinical outcomes were compared between patients undergoing intraoperative margin re-resection and patients with resection margins greater or less than 1-cm. Their study showed that patients with >1 cm margins after intraoperative margin re-resection had higher local recurrence rates and worse overall survival than those individuals initially undergoing >1 cm margin resection ( $P<0.05$ ). They also showed that initial margins >1 cm were associated with favorable disease-free survival (39.2 vs. 22.9 mo,  $P=0.023$ ).

The results of this study suggest several points. First, and probably most important, tumor biology plays a dominant role in patient outcome. Intraoperative margins requiring re-resection to achieve margins >1 cm resulted in higher local recurrence and lower disease-free survival than individuals with initial margins greater than 1 cm. If margin status were the absolute determining factor for survival, one would expect similar outcomes in both groups. The observation that this was not the case suggests that it is tumor biology and not margin that drives clinical outcome. For example, it is plausible to conceive that a rate-limiting factor precluding an initial R0 resection may be an infiltrative growth pattern near major vascular or biliary structures indicative of aggressive cancer. If one analyzes the recent French and Dutch studies on surgical margins in the context of the University of Cincinnati, the dominant role of tumor biology on clinical outcome is undeniable.

Second, preoperative computed tomography and/or magnetic resonance imaging and intraoperative ultrasonography are critical imaging modalities for the surgeon to utilize in operative planning for hepatectomy. The fact that margin re-resection does not convey the same

favorable disease-free survival as an initial negative margin implies that careful preoperative surgical planning and intraoperative ultrasound are important tools for the surgeon to utilize to maximize the chance for an initial margin negative resection. However if intraoperative margin re-resection is performed, the surgeon and medical oncologist must appreciate that the patient is at higher risk for local recurrence and may benefit from additional chemotherapy.

Other points concerning intraoperative margin re-resection relate to surgical technology and specimen interpretation by the pathologist. Surgeons must use caution when interpreting results of intraoperative frozen sections because accurate assessment of surgical margin in liver surgery can be difficult. Intraoperative interpretation of frozen sections may overestimate the true positive margin rate because the commonly used ultrasonic dissector partly aspirates liver parenchyma between tumor and normal tissue. This may decrease the resection margin up to 2-mm, potentially overestimating the proportion of R1, rather than R0, resections. Also the remnant cut section of the liver in contact with the previously removed specimen is commonly treated with argon beam coagulation “sterilizing” another 1 to 2 mm of hepatic tissue. Some surgeons now incorporate radiofrequency energy to coagulate along the margins of the tumor prior to resecting the liver (31). Thus, tumors interpreted as “margin-positive” may incorrectly receive this designation because of failing to take into consideration the false positives secondary to modern surgical technology.

Finally, more effective chemotherapy regimens could reduce the proportion of R1 resections that develop secondary liver metastases, thus minimizing residual micrometastatic disease. It seems that the microscopic margin of resection is less important when effective modern systemic therapy is applied to treat residual occult disease. This concept is supported by recent studies showing R0 resections are not required to achieve optimal outcomes given the efficacy of modern systemic agents (22-25).

The substantial improvements in the effectiveness of newer agents for systemic therapy in metastatic CRC should be taken into account when there is surgical consideration of intraoperative margin re-resection. Re-resection should be performed for an R2 resection since, at minimum, an R1 resection should always be sought for optimal clinical outcomes. However intraoperative margin re-resection is probably of no value in the setting of R1 or sub-centimeter R0 resection. Recent studies show no outcome differences between negative sub-centimeter and >1 cm margins, and between negative and microscopically positive margins. Effective modern chemotherapy, false positives from

ultrasonic dissectors, and coagulation necrosis from argon beam coagulators and radiofrequency energy favor this approach. However if margin re-resection is required clinicians must be wary that this represents a marker for more aggressive cancer and consideration should be made for prolonged systemic therapy.

In summary, definitive surgical resection is critical to the treatment of appropriately selected patients with CRCLM. The definition of what constitutes an ideal margin resection has evolved, with current evidence indicating similar outcomes with R1 or R0 resections with use of modern systemic therapies. Intraoperative margin re-resection should be used selectively and may play less of a role in the current practice of liver surgery in light of modern systemic therapies, imaging modalities that allow careful operative planning, and advances in surgical technology. When margin re-resection is undertaken, it should be with the understanding that margin status can be skewed by surgical technique, and that regardless of margin status, margin re-resection is associated with worse clinical outcome. Perhaps the most important point regarding intraoperative margin re-resection is not necessarily whether or not it should be done, but rather that it is an indicator of more aggressive tumor biology and higher rates of local recurrence.

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