

Wide surgical margins improve prognosis for HCC with microvascular invasion

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Abstract. – OBJECTIVE: Hepatocellular carcinoma (HCC) is the sixth leading cause of malignant tumors worldwide. Liver resection is a pivotal treatment modality for HCC. Surgical margin plays an important role in decreasing recurrence and improving prognosis for HCC patients.

MATERIALS AND METHODS: This paper aimed to perform a systematic review of the literature in regard to surgical margin in HCC patients with microvascular invasion (MVI).

RESULTS: Residual MVI due to insufficient surgical margins is the main origin of postoperative recurrence and metastasis in HCC patients. A wide surgical margin (WSM) significantly improves oncological outcomes and long-term survival in HCC patients with MVI. Progress in the preoperative prediction of MVI may contribute to precise surgical decision-making in the future.

CONCLUSIONS: WSM was associated with better outcomes in HCC patients with MVI. WSM is recommended for well-preserved liver function HCC patients who are predicted to have a high risk of MVI preoperatively.

Key Words:

Hepatocellular carcinoma, Microvascular invasion, Surgical margin.

Abbreviations

WSMs: wide surgical margins; NSMs: narrow surgical margins; HCC: hepatocellular carcinoma; OS: overall survival; RFS: recurrence-free survival; MVI: microvascular invasion.

Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death and ranks as the sixth leading cause of malignant tumors worldwide¹. Surgical resection remains the mainstay of treatment and a potential curative modality for HCC patients². The postoperative recurrence rate is still as high as 70% after initial

curative hepatectomy for HCC despite significant progress in surgical techniques and perioperative management for hepatectomy³.

The surgeon can impact the prognosis and relapses thanks to surgical margin in HCC patients⁴. Surgical resection of a primary liver tumor should involve resection of the lesion with enough margin to prevent recurrence to best ensure prolonged survival. Although a consensus on R0 resection for HCC has been well established, the optimal width of the operative margin in liver resection for HCC remains controversial to date⁵. On the other hand, microvascular invasion (MVI) has been considered one of the most critical risk factors contributing to recurrence and poor prognosis after liver resection for HCC⁶. Early recurrence depends on the biological aggressiveness of the primary tumor, particularly the likelihood for MVI and satellitosis⁷. Therefore, a wide surgical margin (WSM) can decrease recurrence and improve prognosis by sufficiently eradicating the entire tumor burden and adjacent hepatic areas at high risk of intrahepatic micrometastasis or MVI⁸. Moreover, not all HCCs may require a uniform margin size, but lesions with aggressive biological behaviors, such as those with positive MVI status, which determines the risk of intrahepatic and extrahepatic metastases of malignant cells, should potentially be cured with a wider margin⁶. However, the significance of MVI on surgical decision-making has been less appreciated.

Materials and Methods

In this review, we summarize recent findings on clinical relevance of MVI, its association with surgical margin, and progress on the preoperative prediction of MVI.

Our goal with this paper was to conduct a systematic review of the literature about comparing outcomes between WSM and narrow surgical

margin (NSM) in resectable HCC patients with MVI and outline the latest progress in preoperative prediction of microvascular invasion for HCC patients.

A comprehensive literature search of PubMed, Embase, Web of Science, and the Cochrane Library was performed from January 1990 to April 2022. The medical subject heading (MeSH) “Hepatocellular carcinoma” and the following terms were used: (“mvi” OR “microvascular invasion” OR “microscopic vascular invasion”) AND (“liver resection” OR “hepatectomy” OR “hepatic resection” OR “laparoscopic hepatectomy” OR “anatomical resection” OR “non-anatomical resection” OR “wide margin” OR “narrow margin” OR “surgical margin” OR “resection margin” OR “surgical margin width”). Additionally, we reviewed the references of included studies and related systematic reviews to identify additional studies.

All the retrieved results were evaluated according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement⁹. The inclusion criteria were as follows: (1) study population: HCC patients with pathologically diagnosed MVI after initial radical hepatectomy; (2) intervention: resection with WSM vs resection with NSM; (3) outcomes: at least one outcome validated among the primary outcomes (recurrence-free survival (RFS), disease-free survival (DFS) and overall survival (OS)); (4) study design: RCTs or observational studies including cohort or case-control studies. The following were excluded: (1) patients with pathologically diagnosed non-HCC, such as intrahepatic cholangiocarcinoma or recurrent HCC; (2) absence of a distinct width of surgical margin; and (3) abstracts from conferences, case reports, noncomparative studies, and non-English articles.

Results

According to the abovementioned search protocol, 2,695 articles were identified from the online database from January 1990 to April 2022. Three citations were obtained by manually searching the reference list and reviewed articles. Among the 2,698 records included, 2,454 were screened after removing duplicates. Then, 2,396 records were excluded after viewing the title and abstract. 58 articles were included for full-text review, 47 of which were excluded for various reasons. Finally, 11 studies were included in this

review (Figure 1). The characteristics and demographics of the included studies are summarized in Tables I and II.

Discussion

Clinical Relevance of MVI

Postoperative recurrence is one of the most important risk factors for poor prognosis in HCC patients after curative hepatic resection²¹. Seventy percent of patients will develop a recurrence after curative hepatectomy within 5 years. Outcomes for liver transplant are slightly better, with a 5-year recurrence rate of 10-20%²². Recurrence can occur secondary to micrometastasis of the primary tumor or *de novo* cancer formation, and intrahepatic recurrence mainly arises from micrometastasis around the primary tumor²³. MVI, which is defined as “a cancer nest with >50 cells in the endothelial vascular lumen under “microscopy”, accounts for the majority of micrometastasis around the primary HCC tumor²⁴. Although MVI is mainly detected in intratumoral microvessels, it can invade beyond the capsules of HCC tumors²⁵. MVI is highly correlated with aggressive biological markers, including elevated serum AFP and DCP, large tumor size, and high grade^{26,27}. Residual MVI due to insufficient surgical margins is the main origin of postoperative recurrence and metastasis in HCC patients⁶. Lauwers et al²⁸ and Cucchetti et al²⁹ demonstrated that the presence of MVI contributed significantly to postoperative recurrence, especially early recurrence (defined as recurrence less than 2 years after initial therapy) and poor prognosis in HCC patients undergoing liver resection. Furthermore, Lim et al³⁰ found that the presence of MVI more accurately predicted recurrence and long-term survival outcomes than factors included in the Milan criteria by assessing outcomes in 454 HCC patients after curative hepatectomy.

Effect of Surgical Margin

It is a critical clinical consideration to completely eradicate MVI around the primary tumor and reduce postoperative recurrence by optimizing surgical modalities (anatomic vs. nonanatomic resection or wide vs. narrow surgical margin resection)³¹. Although numerous studies³²⁻³⁴ have compared anatomic vs. nonanatomic hepatectomy and most of them have suggested a survival benefit among patients undergoing anatomic resection, this approach is feasible only in a few patients.

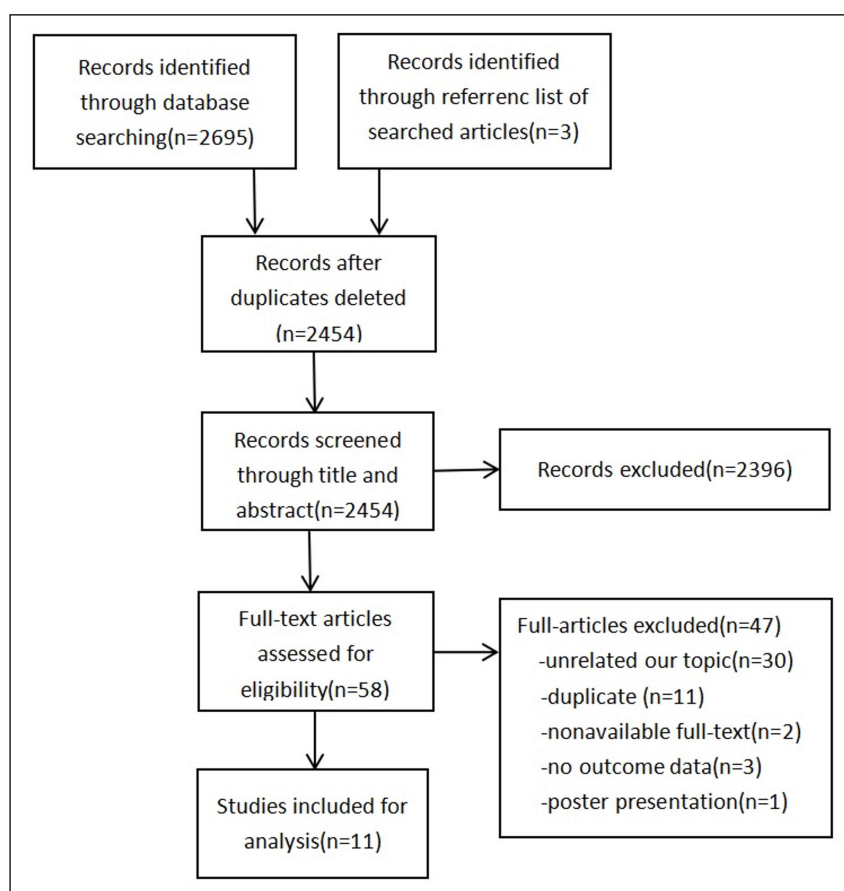


Figure 1. A flow diagram of the inclusion criteria of studies eligible for review.

The significance of the surgical margin on outcomes remains controversial in HCC patients undergoing curative hepatectomy³⁵. Theoretically, a wider surgical margin can effectively decrease local recurrence by eliminating micrometastasis around the primary tumor. Numerous studies³⁶⁻⁴⁰

have shown that a WSM was correlated with a lower recurrence rate or improved survival as compared to a NSM. In contrast, many studies⁴¹⁻⁴⁴ and one meta-analysis⁴⁵ have demonstrated that a WSM was not associated with long-term survival benefit and resulted in a high incidence of

Table I. Characteristics of the selected studies comparing WSM with NSM for HCC with MVI.

Studies	Year	Country	Intervention	Study Period	Study Type
Yamashita et al ¹⁰	2012	Japan	WSM vs. NSM	1995-2010	Retrospective
Hirokawa et al ¹¹	2014	Japan	WSM vs. NSM	2000-2010	Retrospective
Liu et al ¹²	2016	China	WSM vs. NSM	2012-2013	Retrospective
Shin et al ¹³	2018	Korea	WSM vs. NSM	2006-2015	Retrospective
Yang et al ¹⁴	2018	China	WSM vs. NSM	2000-2013	Retrospective
Han et al ¹⁵	2019	China	WSM vs. NSM	2007-2016	Retrospective
Shi C et al ¹⁶	2019	China	WSM vs. NSM	2011-2013	Retrospective
Tsilimigras et al ¹⁷	2020	USA	WSM vs. NSM	1998-2017	Retrospective
Wang et al ¹⁸	2020	China	WSM vs. NSM	2009-2010	Retrospective
Chen et al ¹⁹	2020	China	WSM vs. NSM	2009-2012	Retrospective
Nitta et al ²⁰	2021	France	WSM vs. NSM	1994-2014	Retrospective

WSM indicates wide surgical margin; NSM indicates narrow surgical margin.

Table II. Characteristics of the selected studies comparing WSM with NSM for HCC with MVI.

Studies	No. of Patients	Age (Mean or ≤ 65 yrs%)	Sex (Female%)	Tumor characteristics	Cut-off of width	Period of Follow-up (Mean or Range, mo)
Yamashita et al ¹⁰	20/23	NA	NA	Solitary and ≤ 2 cm	5 mm	NA
Hirokawa et al ¹¹	10/10	NA	NA	Solitary and 1.5-21 cm	10 mm	24-144
Liu et al ¹²	17/15	NA	NA	Solitary and multiple	10 mm	NA
Shin et al ¹³	7/10	NA	NA	Solitary and ≤ 3 cm	10 mm	6.4-143.3
Yang et al ¹⁴	194/194*	92.8/94.3	12.9/14.4	Solitary and Both ≤ 5 cm and ≥ 5 cm	10 mm	3.0-167.4
Han et al ¹⁵	192/158	50.6 \pm 9.9/ 50.8 \pm 10.6	11/9	Solitary and Both ≤ 5 cm and ≥ 5 cm	10 mm	56.3
Shi et al ¹⁶	52/61	NA	NA	Solitary and ≤ 10 cm	10 mm	19-89
Tsilimigras et al ¹⁷	28/90	NA	NA	Solitary and 3-8 cm	10 mm	11.6-53.5
Wang et al ¹⁸	136/130*	NA	NA	Solitary and ≤ 5 cm	2 mm	≥ 60
Chen et al ¹⁹	418/826	NA	NA	Solitary and multiple	10 mm	≥ 60
Nitta et al ²⁰	24/71	NA	NA	Solitary and Both ≤ 3 cm and ≥ 3 cm	7 mm	30

WSM indicates wide surgical margin; NSM indicates narrow surgical margin. Data were described as (WSM/NSM) in most blank. *Indicates after PSM.

perioperative morbidity and mortality in HCC patients. A prospective randomized study⁴⁶ suggested that a wide margin was associated with a survival benefit; however, such survival benefit was only evident among patients with small HCC tumors (≤ 2 cm), and a margin greater than 2 cm margin was feasible only in a few cases of major liver resection, which accounted for less than 10% of the cases in their study. A meta-analysis also indicated a survival benefit for a wide margin in HCC patients; nevertheless, this conclusion was difficult to interpret due to the inconsistency in their results⁴⁷. One of the important factors causing these mixed results is that most of these studies³⁶⁻⁴⁴ did not stratify for inherent tumor biological factors, which may have a complicated impact on recurrence and prognosis in HCC patients after hepatectomy. On the other hand, the wider margin inevitably results in reduced remnant liver volume, which is significantly unfavorable in patients with underlying liver disease⁴⁸. Eighty percent of HCC cases were associated with underlying liver disease, such as chronic HBV infection and cirrhosis, which significantly limited the extent of liver resection for HCC⁴⁹. Therefore, it is rational and feasible to achieve individualized surgical margin under the premise of R0 resection by striking a balance between recurrent risk and remnant liver function.

Wide Surgical Margin for HCC with MVI

MVI, which is noted in approximately two-thirds of large, high-grade HCCs and up to 25% of small HCCs (≤ 3 cm), is one of the critical characteristics of HCC with a more aggressive biology⁵⁰. Many studies^{28,51,52} have demonstrated that a positive MVI status is highly correlated with adverse outcomes in HCC patients after curative hepatectomy. It has been proved that residual MVI due to insufficient surgical margins is the main origin of postoperative recurrence, especially early recurrence (defined as recurrence less than 2 years after initial therapy) and metastasis in HCC patients⁶. In order to clarify the effect of surgical margin for HCC with MVI, we conducted a comprehensive literature search and eleven studies¹⁰⁻²⁰ were identified for analysis. All those studies¹⁰⁻²⁰ demonstrated that WSM significantly benefits not only RFS but also OS in HCC patients with MVI after initial curative hepatectomy. Interestingly, all those studies indicated that a wide margin had no advantage in either RFS or OS in HCC patients without MVI undergoing radical liver resection. Furthermore, two studies^{14,15} showed that a wide margin significantly decreased intrahepatic recurrence in HCC patients with MVI. The results suggest that a wide operative margin can

significantly improve locoregional oncological outcomes and long-term survival by effectively eradicating residual MVI in HCC patients with MVI and that MVI is one of the important factors that should be considered in determining surgical margins.

Although a wide surgical margin has been recommended for curative liver resection in HCC patients, the optimal width of the operative margin remains controversial³¹. Historically, 1-cm resection margins have been extensively explored by most of the researchers, although the zero and 2-cm surgical margins have already been investigated³¹. Zhou et al⁵³ demonstrated that the farthest distances of histological micrometastasis around primary tumors were 3.5 mm, 5.3 mm, and 6.0 mm in 95%, 99%, and 100% of HCC cases, respectively. Nakashima et al⁵⁴ also reported that the distance between primary lesions and intrahepatic micrometastasis or portal vein microinvasion was less than 10 mm in 79.2% of HCC patients with lesions less than 3 cm. These results suggest that 10 mm resection margin is essential to sufficiently eradicate MVI around the primary tumor, and an operative width of greater than 10 mm is proposed in further studies comparing wide and narrow margins in HCC patients with MVI.

Progress on the Preoperative Prediction of MVI

Undoubtedly, the prerequisite is the accurate preoperative diagnosis of the presence of MVI if decision-making on surgical margins depends on the presence of MVI before liver resection in HCC patients. Although precise methods for the diagnosis of MVI are currently lacking, great progress has been achieved in the preoperative prediction of MVI during the past decade. Multiples of predictive methods have been proposed: biomarkers, such as AFP, DCP, and gene tags⁵⁵⁻⁵⁷; advanced imaging techniques^{58,59}; and predictive models, such as MVI nomogram^{60,61}. More recently, Wang et al⁶² developed a preoperative prediction model for MVI, including tumor size, number of tumors, neutrophils, and serum AFP. The concordance index of the model was 0.79 (95% CI: 0.74-0.84) and 0.81 (95% CI: 0.74-0.89) in the training and validation cohorts respectively. Accumulating evidence indicates that it is becoming possible to identify HCC patients at high risk of MVI. Therefore, it is feasible and possible to individualize the optimal resection margin based on the MVI status before hepatectomy in HCC patients.

Conclusions

In conclusion, our study suggests that WSM is superior to NSM in terms of RFS and OS among HCC patients with MVI undergoing curative hepatectomy. A WSM should be recommended in highly selected patients with well-preserved liver function and HCC patients who are predicted to be at high risk of MVI preoperatively.

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Authors' Contributions

Study conception and design: WDL and ZSS. Material preparation, data retrieval, and analysis: WDL, C J, KPW, and. Interpretation of the results: WDL, YFF and CYP. Paper writing: WDL and KPW. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Availability of Data and Materials

All data are available from the corresponding author.

Ethics Approval

Not applicable.

Informed Consent

Not applicable.

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