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Prognostic impact of surgical margin in patients with hepatocellular carcinoma

A meta-analysis

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Abstract

Background: Surgical margin is an important prognostic factor in hepatectomy for patients with hepatocellular carcinoma (HCC). But the extent of surgical margins is still controversial. Our study was designed to systematically evaluate the prognosis of different width of resection margin.

Methods: We conducted comprehensive searches of electronic databases including PubMed, MEDLINE, EMBASE, Cochrane, and the ISI Web of Science for relevant studies. A meta-analysis was performed by RevMan 5.3 software.

Results: A total of 7 studies comprising 1932 patients were included. The patients with wider surgical margin were significantly higher than those with narrow surgical margin on 3-year overall survival (odds ratio [OR]: 1.58, 95% confidence interval (95% CI): 1.21–2.06, $P=.0008$), 5-year overall survival (OR: 1.76, 95% CI: 1.20–2.59, $P=.004$), 1-year disease-free survival (DFS)/recurrence-free survival (RFS) (OR: 1.43, 95% CI: 1.12–1.82, $P=.005$), 3-year DFS/RFS (OR: 1.66, 95% CI: 1.35–2.03, $P<.00001$), and 5-year DFS/RFS (OR: 1.69, 95% CI: 1.37–2.08, $P<.00001$). There was no significant difference in the 1-year overall survival rate for the 2 groups (OR: 1.24, 95% CI: 0.89–1.72, $P=.20$).

Conclusion: In comparison with the narrow surgical margin group (<1 cm), the wide surgical margin (≥1 cm) can significantly improve the prognosis in patients with HCC.

Abbreviations: CI = confidence interval, DFS = disease-free survival, HCC = hepatocellular carcinoma, HR = hazard ratio, NOS = Newcastle–Ottawa Scale, OR = odds ratio, OS = overall survival, RFS = recurrence-free survival.

Keywords: hepatocellular carcinoma, meta-analysis, prognosis, surgical margin

1. Introduction

Hepatocellular carcinoma (HCC) is a common malignant tumor in the world, and its incidence rate was fifth in all malignant tumors, while the mortality rate was the highest in the third place.[1,2] At present, hepatectomy is the first choice of treatment.[3] However, the postoperative cumulative recurrence rate is still high, there are studies reported that the cumulative recurrence rate after hepatectomy reach up to 69.4% to 100%, and overall survival (OS) was also poor.[4,5] The main risk factors of postoperative recurrence and survival are as follows: tumor size, tumor stage, microvascular invasion (MVI), surgical margin, and so on.[6,7] For surgical margin, that R0 resection (no cancer cells were found in surgical margin, and tumor was completely resected) can improve the prognosis of patients with HCC has been recognized,[8,9] but the width of surgical margins remains controversial under the premise of R0 resection.[10,11]

One of the principles of hepatectomy is maximum retention of residual liver volume in order to prevent postoperative liver failure. How to solve the contradiction between the width of the surgical margin and the maximum retention of the remaining liver volume, scholars have different academic views. Lazzara et al suggested that 0.5 to 1 cm surgical margin, which would not increase the risk of marginal recurrence and does not decrease OS rate, could be used as a safe margin of resection.[12] However, Lee et al[4] hold the opposite opinion. By searching and reading a large number of literatures, finally, we have made a systematic evaluation between the wide group (0.5 cm ≤ surgical margin <1 cm) and the narrow group (surgical margin <0.5 cm). We found that there was no significant difference on the OS [hazard ratio (HR): 0.63, 95% confidence interval (95% CI): 0.28–1.42, $P=.27$], disease-free survival (DFS) rate (HR: 0.80, 95% CI: 0.64–1.01, $P=.06$), and recurrence rate (HR: 0.76, 95% CI: 0.56–1.05, $P=.10$) between the 2 surgical margin groups.[13–15] In addition, some studies have shown that the surgical margin should be greater than 1 cm, but still inconclusive.[16,17] Moreover, there were few systematic reviews or meta-analyses to verify whether the margin width ≥1 cm is more favorable to the prognosis of patients with HCC under the premise of R0 resection. Therefore, we conducted a meta-analysis to assess the prognosis value between wide surgical margins (≥1 cm) and narrow surgical margins (<1 cm) on survival for patients with HCC.

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FPZ, YJZ, and YL have contributed equally to this work.

The authors solemnly declare that there are no conflicts of interest.

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2. Methods

2.1. Data sources and search strategy

A comprehensive search of MEDLINE, EMBASE, PubMed, Cochrane, and the ISI Web of Science databases from the database inception to April 2017 was performed. The following MeSH terms and free-text words were used in combination: "liver neoplasms" or "HCC" or "hepatocellular carcinoma" or "liver cancer" or "liver tumor" or "liver cell carcinoma," "surgical margin" or "resection margin" or "margin width," "prognostic" or "prognosis" or "outcome " or "survival" or "recurrence." In addition, the references of eligible studies, pertinent reviews, and meta-analyses in this field were screened.

2.2. Inclusion and exclusion criteria

To select relevant and high-quality articles, we designed comprehensive inclusion criteria and exclusion criteria. The following articles were included based on the criteria as follows: HCC were diagnosed clearly based on postoperative pathology; association of wide and narrow surgical margin on OS or DFS or recurrence-free survival (RFS) or contained survival curves. All the patients were primary liver resection and included the most recent or informative report when more than one paper was written by the same author or group based on the same patients population. Original high-quality English articles were included. Exclusion criteria were as follows: case reports, letters, editorials, reviews, conference abstracts, and expert opinion were excluded; articles that lack survival rates or survival curve were excluded; and nonprimary HCC, such as metastatic liver cancer or recurrent liver cancer.

2.3. Data extraction

The following information was captured using data abstraction forms: first author, year, country and journal of publication, number of patients, follow-up, width of surgical margin, and primary endpoints (OS, DFS, or RFS). If the data of OS or DFS/RFS were not directly reported, then the survival data read from Kaplan–Meier curves were read by Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/). To reduce inaccuracy in the extracted survival data, this work was performed by 2 independent investigators.

2.4. Quality assessment

A total of 7 studies were included. The quality evaluation standards of the Newcastle–Ottawa Scale (NOS)[18] were used to assess the quality of the literature. The overall score include 3 categories as follows: the selection of the study groups: 0 to 4 scores; the comparability of the groups: 0 to 3 scores; and the ascertainment of either the exposure or outcome: 0 to 2 scores. The higher scores reflect a better methodological quality. This work was performed independently by 2 investigators. In case of disagreement, we solved through discussion or ruling of third parties.

2.5. Statistical analyses

Review Manager5.3 software was used for Meta-analysis (Cochrane Collaboration, Copenhagen, Denmark). All statistics are calculated 95% CI. Statistical heterogeneity between trials was evaluated by the Chi-square test. In the absence of statistically significant heterogeneity ($P > .05$, $I^2 < 50\%$), the fixed-effect model was used for the meta-analysis, while in the heterogeneity study ($P < .05$, $I^2 > 50\%$), the random-effect model was selected. The odds ratio (OR) and their 95% CI was used to evaluate clinical efficacy. The consolidated result was an average OR and 95% CI weighted according to the standard error of the OR of the trial. $P < .05$ was considered statistically significant difference. Funnel plots were used to assess the publication bias.

2.6. Ethics declarations

Ethics approval and consent to participate are not applicable for meta-analysis.

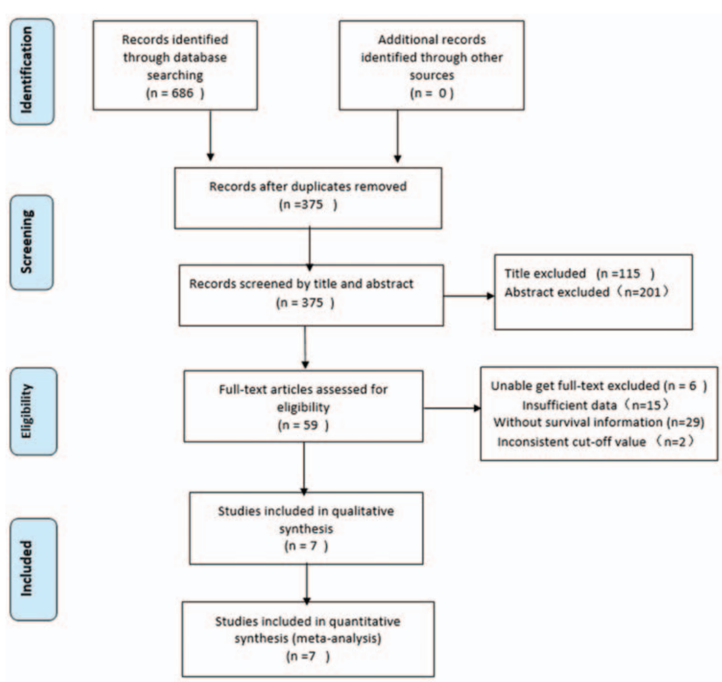

Figure 1. The PRISMA flow diagram of the study selection process.

Table 1

Main characteristics and quality scores of the included studies in the meta-analysis.

Author	Year	Journal	Country	Quality score	Cut-off of surgical margin, cm	Narrow group	Wide group	Primary endpoints	Follow-up
Poon et al[19]	2000	Ann Surg	China	8	Narrow group <1 Wide group ≥1	150	138	OS RFS	27
Shi et al[20]	2007	Ann Surg	China	8	Narrow group<1 Wide group ≥1	84	85	OS RFS	43.7±14.9
Masutani et al[21]	1994	Arch Surg	Japan	7	Narrow group <1 Wide group ≥1	131	54	OS	Unclear
Chau et al[22]	1997	J Surg Oncol	China	7	Narrow group <1 Wide group ≥1	80	85	RFS	Unclear
Shimada et al[23]	2008	AM J Surg	Japan	8	Narrow group <1 Wide group ≥1	85	32	OS RFS	62
Hu et al[24]	2015	Int J Clin	China	8	Narrow group <1 Wide group ≥1	373	228	RFS	30
Lee et al[14]	2012	JFMA	China	7	Narrow group <1 Wide group ≥1	265	142	OS DFS	72.97

DFS = disease-free survival, OS = overall survival, RFS = recurrence-free survival.

3. Results

3.1. Study characteristics

A total of 686 articles were identified after comprehensive searching of the database. After duplicates removal, 375 articles were eligible for screening. Of these, 316 articles were excluded through titles and abstracts. And then, 50 studies did not meet the inclusion criteria and were therefore excluded in the remaining 59 articles. Because the surgical margin cut-off values should be consistent among the articles that we are going to include, 2 of the remaining 9 articles were not included. Ultimately, 7 eligible studies, comprising a total of 1932 patients, were considered eligible for the meta-analysis.[14,19–24] The PRISMA flow diagram of the study selection process is shown in Fig. 1.

Of 7 studies, 5 studies investigated the clinical impact of surgical margin on OS, and 6 studies explored the prognostic impact of surgical margin on DFS/RFS. Characteristics of included studies and literature quality scores are summarized in Table 1.

3.2. Meta-analysis

3.2.1. Overall survival. Five studies included 1166 patients involved in postoperative survival during follow-up 1, 3, 5-year between surgical margin wide group and narrow group. The follow-up 1-year OS rate was not statistically different between wide group and narrow group (OR: 1.24, 95% CI: 0.89–1.72, $P=.20$, Fig. 2A). The follow-up 3-year OS rate was significantly higher in wide group than in narrow group with a combined OR

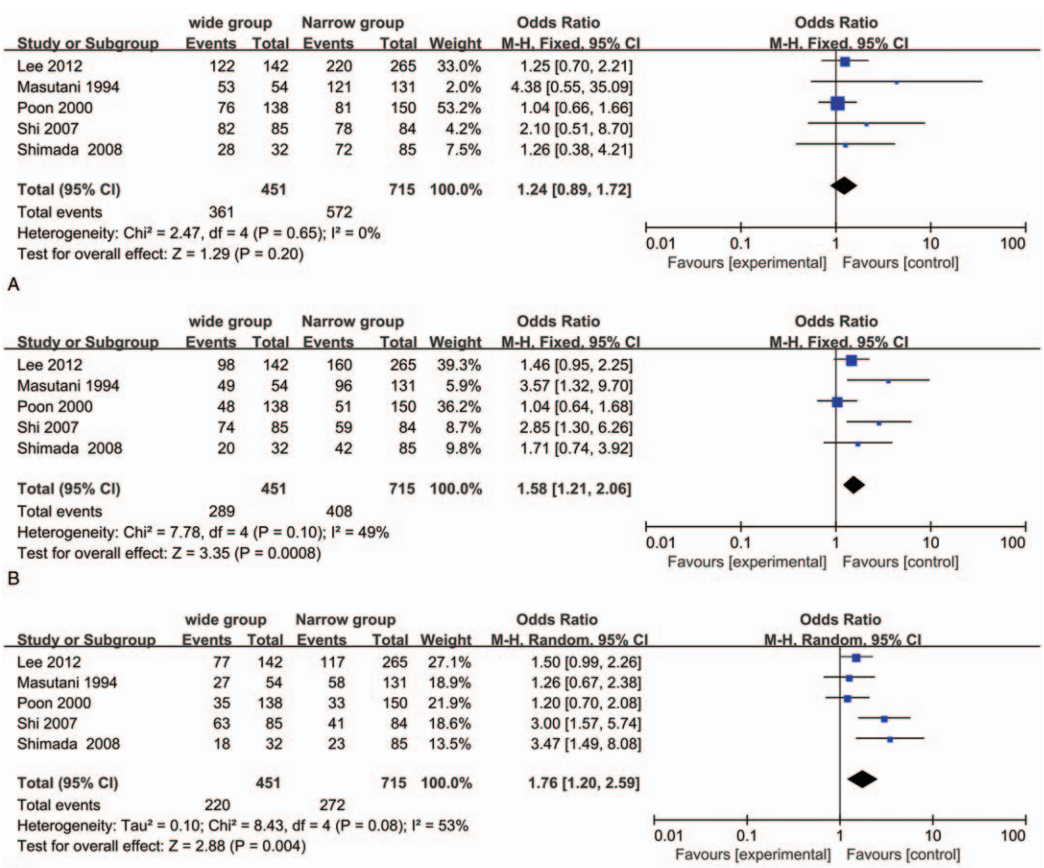

Figure 2. (A) Forest plot for the association between surgical margins and 1-year OS. (B) Forest plot for the association between surgical margins and 3-year OS. (C) Forest plot for the association between surgical margins and 5-year OS.

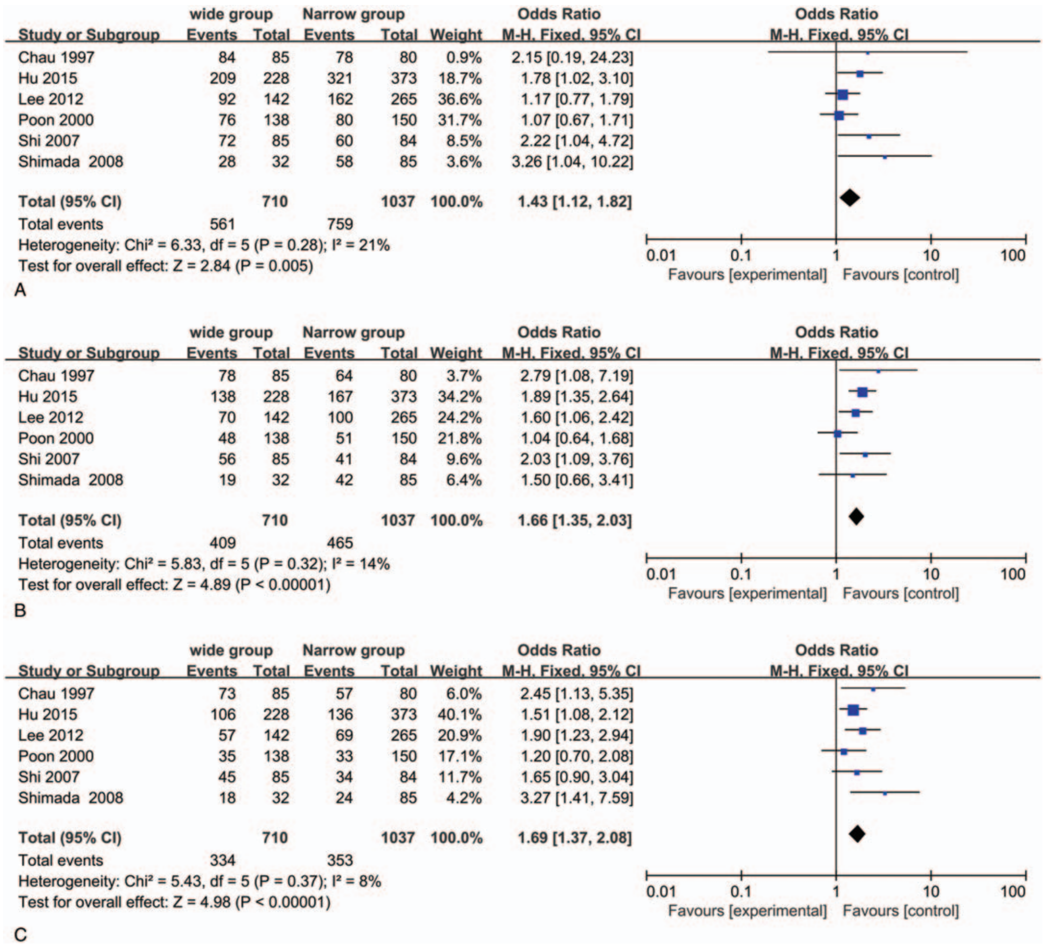

Figure 3. (A) Forest plot for the association between surgical margins and 1-year DFS/RFS. (B) Forest plot for the association between surgical margins and 3-year DFS/RFS. (C) Forest plot for the association between surgical margins and 5-year DFS/RFS.

of 1.58 (95% CI=1.21–2.06, P=.0008, Fig. 2B). The follow-up 5-year OS rate was significantly higher in wide group than narrow group with a combined OR of 1.76 (95% CI=1.20–2.59, P=.004, Fig. 2C).

3.2.2. Disease-free survival/recurrence-free survival. Six studies comprising 1747 patients evaluated the relationship between surgical margin (wide group ≥1 cm and narrow group <1 cm) and DFS/RFS. Compared with the narrow group, the wide group was significantly correlated with better 1-year DFS/RFS (OR: 1.43, 95% CI: 1.12–1.82, P=.005, Fig. 3A), 3-year DFS/RFS (OR: 1.66, 95% CI: 1.35–2.03, P<.00001, Fig. 3B), and 5-year DFS/RFS (OR: 1.69, 95% CI: 1.37–2.08, P<.00001, Fig. 3C).

4. Discussion

Surgery is the only possible effective method for the treatment of liver cancer. At present, there is no uniform consensus on radical resection of HCC. Surgical margin is one of most controversial focus. Not only the radical resection of the tumor, but also the compensatory ability of the residual liver should be taken into account. The resection of excessive liver tissue during the operation will lead to liver dysfunction, especially in patients with liver cirrhosis.[25–27] An appropriate width of surgical margin, which would be most beneficial to the prognosis of patients, is worth exploring.

The pattern of HCC recurrence includes multicentric occurrence, intrahepatic metastasis, margin local recurrence, an so on.[28] The failed excised MVI was the most important factor of intrahepatic metastasis and local margin recurrence.[29,30] However, surgical margin is closely related to the complete resection of microvascular metastasis.[31] Poon et al[19] concluded that the resection margin was not associated with recurrence after hepatectomy; even Lee et al[14] considered that wide surgical margin had worse perioperative outcomes. Besides, some studies showed that surgical margin is an independent prognostic factor for HCC recurrence, but has no significant effect on OS; even they concluded that the margin of >1 mm is safe.[4,32] In view of this, we did this meta-analysis to evaluate the prognostic value of the surgical margin on survival rate and recurrence rate.

Our meta-analysis showed that, although there was no significant difference in short-term OS (1-year OS) in patients between the wide surgical margin (≥1 cm) and the narrow surgical margin group (<1 cm), the former had higher long-term OS and DFS/RFS. According to the study of Sumie et al[33,34] and Shah et al,[35] MVI is more common in the invasion of tumor adjacent liver parenchyma. Even Roayaie et al[36] extend the range of MVI extension to 1 cm apart. Therefore, one of the reasonable explanations for the results of our meta-analysis is that the wide margin group can significantly reduce the incidence of postoperative residual MVI, improve OS, and RFS. Of course, there is a certain limit of the width of the liver surgical margin, and the maximum critical margin needs further study. In addition, to our knowledge, there is currently only 1 meta-analysis that evaluated the relationship between surgical margin and prognosis,[37] and this meta-analysis showed that surgical margin ≥1 cm does not obtain a better prognosis than surgical margin <1 cm, but the serious deficiency of this meta-analysis is its limited sample size and incomplete researches; it is likely to result in errors.

Certainly, several limitations of this meta-analysis should be taken into account. First of all, this study has some significant heterogeneity. Second, only published English literature was included. Third, preoperative tumor size, stage, location, tumor biological characteristics, the general situation, and postoperative treatment measures of patients are not the same; these potential confounders present in individual studies were unavoidable. Fourth, publication bias is inevitable due to the high publication rate of the positive results. Finally, although some related data are independently estimated by 2 investigators from Kaplan–Meier survival curves in OS and DFS/RFS, they still cannot be fully consistent with the reality.

In summary, our meta-analysis confirms that the wide surgical margin (≥1 cm) had higher long-term OS and DFS/RFS compared with the narrow surgical margin group (<1 cm); the former can improve prognosis better in patients with HCC. Of course, high-quality and more large-sample studies are needed to further confirm.

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