

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Influence of surgical margin width on survival rate after resection of intrahepatic cholangiocarcinoma: a systematic review and meta-analysis
AUTHORS	Jiang, Jing-Hua; Fang, Da-Zhang; Hu, Yi-Ting

VERSION 1 – REVIEW

REVIEWER	Fu-yu Li Sichuan University West China Hospital
REVIEW RETURNED	27-Sep-2022

GENERAL COMMENTS	<p>Congratulations for addressing this important question. Nevertheless, the manuscript will benefit from review and editing by a native English speaker to help with usage and grammar. Additionally, the literature included could not be exhaustive, which might be connected to your retrieval approach. Only two studies provide data on DFS in your meta-analysis, and the accuracy of these findings may be in doubt. Radiotherapy and chemotherapy data are still crucial, and the absence of these data may be a critical limitation, despite the fact that this research primarily analyzes the impact of the width of the resection margin on the survival of ICC.</p>
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REVIEWER	Tao-Hsin Tung Cheng-Hsin General Hospital
REVIEW RETURNED	03-Oct-2022

GENERAL COMMENTS	<p>Thank you for the opportunity for reviewing this paper "Influence of surgical margin width on survival rate after resection of intrahepatic cholangiocarcinoma: a systematic review and meta-analysis". This article is interesting, but some issues should be explained more.</p> <ol style="list-style-type: none">1. Please add previous systematic reviews and what are their limitations and what was your rationale for doing this systematic review in the introduction section.2. It will be better to show kappa for the selection and data extraction. Please show the data of kappa of agreement during the systematic searches.3. What are your primary and secondary outcomes?4. Authors should discuss the heterogeneity.5. Its protocol is not registered in the registry such as PROSPERO (https://www.crd.york.ac.uk/PROSPERO/).6. The GRADE tool is suggested.7. Please give readers details about how to apply the findings of this study to clinical practices.
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REVIEWER	Peter Richardson Baylor College of Medicine, Medicine
REVIEW RETURNED	05-Oct-2022

GENERAL COMMENTS	<p>There are several spots where the grammar needs to be corrected. This should get a thorough review by someone else.</p> <p>In a few cases, I think some claims should be stated differently:</p> <p>[1] I did not understand the statement about "contrary evidence"; since I am not a clinician, I don't know what was meant by "surgical margin width did not apply to every ICC patient".</p> <p>[2] On page 5 I would refer to Tierney et al's algorithm instead of the unclear mention of Excel.</p> <p>[3] On page 7, symmetry of funnel plot only suggests a lack of publication bias, it does not establish that none exists.</p> <p>[4] On page 16, I would describe the sensitivity studies as leave-out-one analyses instead of "excluding some studies".</p> <p>[5] Presumably, all 9 included studies involved some covariate adjustment; could you list the adjusters for each study for the reader's benefit?</p> <p>[6] Can you address the general concern about meta-analysis with a small number of studies.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Fu-yu Li

Comments to the Author:

Congratulations for addressing this important question. Nevertheless, the manuscript will benefit from review and editing by a native English speaker to help with usage and grammar. Additionally, the literature included could not be exhaustive, which might be connected to your retrieval approach. Only two studies provide data on DFS in your meta-analysis, and the accuracy of these findings may be in doubt. Radiotherapy and chemotherapy data are still crucial, and the absence of these data may be a critical limitation, despite the fact that this research primarily analyzes the impact of the width of the resection margin on the survival of ICC.

Response:

Thanks to the reviewers' suggestion. Only two studies have examined DFS, which may cause heterogeneity of data and is a limitation of this study. In addition, we have placed data on radiotherapy and chemotherapy in the baseline table. The data on the effect of radiotherapy and chemotherapy on survival after ICC resection have not been analyzed further because of the paucity of data.

Reviewer: 2

Dr. Tao-Hsin Tung, Cheng-Hsin General Hospital

Comments to the Author:

Thank you for the opportunity for reviewing this paper "Influence of surgical margin width on survival rate after resection of intrahepatic cholangiocarcinoma: a systematic

review and meta-analysis". This article is interesting, but some issues should be explained more.

1. Please add previous systematic reviews and what are their limitations and what was your rationale for doing this systematic review in the introduction section.

Response:

Thanks for the suggestion. We have added the previous systematic review in the introduction section, describing their limitations and our rationale for doing this systematic review: " Li et al (PMID: 27338547) evaluated the relationship between surgical margin status and survival benefit in ICC by meta-analysis and found that negative surgical margins are more beneficial for ICC patients' overall survival (OS) and disease-free survival (DFS) after surgical resection, thus emphasizing the importance of R0 resection. In a recent meta-analysis of the effect of surgical margin width on OS in ICC patients, it is similar that ICC patients with R0 ≥ 10 mm have a longer survival benefit than those with < 10 mm [PMID: 27583880]. But this analysis did not provide statistical analysis of DFS, recurrence-free survival (RFS), or a more refined stratification of the range of R0 margin width, making the findings lacking reference value for clinical treatment at the present stage. Therefore, this study was updated from the above meta-analysis to investigate the effect of margin width on OS, DFS, and RFS in ICC patients who underwent R0 surgical resection in recent years, as well as a stratification study of margin width (< 5 mm, 5-9 mm, < 10 mm, and ≥ 10 mm), to provide more evidence-based medical evidence for the determination of surgical margin width in ICC patients." .

2. It will be better to show kappa for the selection and data extraction. Please show the data of kappa of agreement during the systematic searches.

Response:

After a whole-network literature search, the eligible articles were first evaluated for quality, and only 9 articles were of medium to high level. All the data were eventually included without kappa testing.

3. What are your primary and secondary outcomes?

Response:

Thanks for the question. We have clarified the primary and secondary outcome indicators in "1.5 Data Extraction": "Primary outcome indicator: HR and 95% CI for prognostic OS and DFS for patients in each group. Secondary outcome indicator: HR and 95% CI for RFS and lymph node status."

4. Authors should discuss the heterogeneity.

Response:

Thanks for the suggestion. We have added a discussion of heterogeneity to the manuscript: "Second, the presence of single-center and multicenter studies in this study may have contributed to some bias in the results."

5. Its protocol is not registered in the registry such as PROSPERO (<https://www.crd.york.ac.uk/PROSPERO/>).

Response:

Thanks to the reviewer's suggestion. This study is an updated meta. Despite the addition of several recent publications, the effect of the range of margin widths (< 5 mm, 5-9 mm, < 10 mm,

and ≥ 10 mm) on survival after ICC resection is not clear from the analysis. We will continue to study the range, so it is not registered at this time.

6. The GRADE tool is suggested.

Response:

Thanks for the suggestion. A search for relevant information and literature revealed that the GRADE evidence quality assessment tool is mainly used for network meta-analysis and this study was not applicable to the GRADE tool. In addition, the Newcastle-Ottawa Scale (NOS) is a common quality assessment tool applied to case-control studies and cohort studies. The studies included in this study were all cohort studies; therefore, the NOS was appropriate as a quality assessment tool.

7. Please give readers details about how to apply the findings of this study to clinical practices.

Response:

Thanks to the reviewer's suggestion. We have already described how the findings of this study can be applied in clinical practice in "3.6 Conclusion": "In conclusion, the meta-analysis revealed that patients undergoing curative hepatectomy for ICC had a survival advantage for a wide margin of ≥ 10 mm compared with a narrow margin of < 10 mm under certain conditions. But surgeons should determine the margin width in relation to the patient's condition and should not consider < 10 mm as a contraindication to surgery; in addition, lymph node status should be considered during clinical procedures, as it is also an important factor affecting the patient's postoperative survival outcome. In summary, surgical margins of ≥ 10 mm should be achieved as much as possible for ICC patients with negative lymph nodes, but further multicenter study results are still warranted to support this view."

Reviewer: 3

Dr. Peter Richardson, Baylor College of Medicine

Comments to the Author:

There are several spots where the grammar needs to be corrected. This should get a thorough review by someone else.

In a few cases, I think some claims should be stated differently:

[1] I did not understand the statement about "contrary evidence"; since I am not a clinician, I don't know what was meant by "surgical margin width did not apply to every ICC patient".

Response:

We have revised "surgical margin width did not apply to every ICC patient" to "however, another study stated that wide margin hepatectomy does not produce a survival benefit in all ICC patients and is more beneficial for patients without lymph node metastases (PMID: 32044110)".

[2] On page 5 I would refer to Tierney et al's algorithm instead of the unclear mention of Excel.

Response:

Thanks to the reviewer's suggestion. We have made a revision of "(4) With wide margin group as the control, HR and 95% confidential interval (CI) of DFS, RFS, OS in 1-4 mm margin group and 5-9 mm margin group were either available in included studies or can be calculated from HR Excel spreadsheet by using survival curves like Tierney" to "(4) The correlations of surgical margin width with OS, DFS, and RFS were presented in the included studies., i.e., the Hazard Ratio (HR) and 95% confidence interval (CI) could be obtained directly from the literature or could be calculated indirectly.". In addition, the algorithm of Tierney et al. has been briefly described at the end of "1.5 Data Extraction".

[3] On page 7, symmetry of funnel plot only suggests a lack of publication bias, it does not establish that none exists.

Response:

Thank for the suggestions. We have corrected " The publication bias was analyzed by funnel plot. If the funnel plot was symmetrical, there was no publication bias." in "1.7 Statistical Analysis". to "If the funnel plot was symmetrical, indicating a lack of publication bias."

[4] On page 16, I would describe the sensitivity studies as leave-out-one analyses instead of "excluding some studies".

Response:

Thanks to the reviewer's suggestion. We have revised the figure legends of Figure 8 (original Figure 5) and Figure 9 (original Figure 5) according to your suggestion:

Figure 8 Sensitivity analysis of OS after leave-out-one analyses

Figure 9 Sensitivity analysis of RFS after leave-out-one analyses".

[5] Presumably, all 9 included studies involved some covariate adjustment; could you list the adjusters for each study for the reader's benefit?

Response:

Thanks to the reviewer's suggestion. It was not possible to calculate covariates because the included studies could not distinguish between independent and covariate variables.

[6] Can you address the general concern about meta-analysis with a small number of studies.

Response:

Thanks to the reviewers' suggestions. We have added relevant literature in the discussion section to further discuss the problems that may be encountered when ICC patients undergo

R0 resection and the solutions. In addition, these problems are our ongoing focus, and we will try to solve the issues in subsequent studies.

VERSION 2 – REVIEW

REVIEWER	Fu-yu Li Sichuan University West China Hospital
REVIEW RETURNED	11-Jan-2023

GENERAL COMMENTS	<p>The purpose of this study is to clarify that a wide range of surgical procedures can contribute to the prognosis of ICC patients after hepatectomy. 9 articles were included in this meta-analysis study. They found patients with wide margin had a survival advantage. This study provided novel findings but they still have different defects.</p> <p>Major:</p> <ol style="list-style-type: none"> 1. The author defined DFS (disease-free survival) and RFS (recurrence-free survival) and analyzes them respectively. In patients after radical resection, RFS and DFS are replaceable in most cases, discussing the RFS and DFS separately may be unreasonable. Why you discuss the RFS and DFS separately? 2. You discuss the influence of lymph node lesions to OS, can you explain the definition of lymph node lesions? it may require a clearer definition. Besides, what's the difference between lymph node lesions and lymph node invasion? And whether lymphatic invasion is included in lymph node lesions or lymph node invasion also should be explained. 3. The search strategy should include abbreviations, such as ICC. And search strategy should include both the "surgical margin width/length" and "resection margin width/length", but not only one of them. In addition, it may be more reasonable to include "wide margin" and other similar words in search strategy. Your search strategy may lead to incomplete search. 4. The inclusion of the literature may be incomplete. For example, Fig2 of Zhang et al. (Perioperative and Long-Term Outcome for Intrahepatic Cholangiocarcinoma: Impact of Major Versus Minor Hepatectomy) provides the OS and RFS of patients with ICC with R0 resection. These data can be extracted. Can you provide the reason for not including this article? <p>Minor:</p> <ol style="list-style-type: none"> 1. The author defines the inspection level of meta-analysis was set as $\alpha = 0.05$. On analysis of lymph node lesions on OS, $I^2 = 57.5\%$, $P = 0.051$ (> 0.05), you hold that lymph node lesions were detrimental to OS in patients with ICC, it may be inaccurate.
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REVIEWER	Tao-Hsin Tung Cheng-Hsin General Hospital
REVIEW RETURNED	31-Dec-2022

GENERAL COMMENTS	No further comments.
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REVIEWER	Peter Richardson Baylor College of Medicine, Medicine
REVIEW RETURNED	10-Jan-2023

GENERAL COMMENTS	Thank you for your revisions.
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Dr. Tao-Hsin Tung, Cheng-Hsin General Hospital

Comments to the Author:

No further comments.

Response: Thank you for your approval.

Reviewer: 3

Dr. Peter Richardson, Baylor College of Medicine

Comments to the Author:

Thank you for your revisions.

Response: Thanks for your approval of our revised version.

Reviewer: 1

Dr. Fu-yu Li, Sichuan University West China Hospital

Comments to the Author:

The purpose of this study is to clarify that a wide range of surgical procedures can contribute to the prognosis of ICC patients after hepatectomy. 9 articles were included in this meta-analysis study. They found patients with wide margin had a survival advantage. This study provided novel findings but they still have different defects.

Major:

1. The author defined DFS (disease-free survival) and RFS (recurrence-free survival) and analyzes them respectively. In patients after radical resection, RFS and DFS are replaceable in most cases, discussing the RFS and DFS separately may be unreasonable. Why you discuss the RFS and DFS separately?

Response: Thanks for your question. 2 of the 9 papers we included compared patients' DFS and 5 compared patients' RFS. Although the definitions of RFS and DFS are similar, there are still differences between them. If they are analyzed and discussed together, there will be questionable results. The results of the HR summary analysis, which ultimately indicates disease-free survival or recurrence-free survival, need to be harmonized. Therefore, a separate discussion can avoid similar problems.

2. You discuss the influence of lymph node lesions to OS, can you explain the definition of lymph node lesions? it may require a clearer definition. Besides, what's the difference between lymph node

lesions and lymph node invasion? And whether lymphatic invasion is included in lymph node lesions or lymph node invasion also should be explained.

Response: Thanks for questions. Lymph node lesions refer to lymph node sites with increased volume or other obvious signs of deterioration. Lymph node invasion refers to chronic inflammatory cell infiltration at the examined site (locally), and malignant tumor cells then infiltrate into the lymphatic vessels and reach various parts of the body along the lymphatic vessels, causing lymphatic metastasis. When the tumor cells in the lymphatic vessels meet the lymph nodes during metastasis, they will stop to grow and proliferation, resulting in the enlargement of lymph nodes, i.e. lymph node metastasis. Lymph node infiltration and lymph node metastasis are both types of lymph node lesions.

3. The search strategy should include abbreviations, such as ICC. And search strategy should include both the "surgical margin width/length" and "resection margin width/length", but not only one of them. In addition, it may be more reasonable to include "wide margin" and other similar words in search strategy. Your search strategy may lead to incomplete search.

Response: We appreciate for the reviewer's suggestion. In general, in published English-language literature, the full name of the corresponding abbreviation must appear. In addition, we believe that it is more accurate to use the full name search, so we did not search for abbreviations such as ICC. In section 1.1 Study Search Strategy, we listed the main search terms, including "Surgical margin width" and "Length of surgical margin", while in the Supplementary file, we listed the corresponding search strategies in detail, including the "resection margin width" and "resection margin length". As for the term "wide margin" you mentioned, we found that the search results are consistent with the search results of "surgical margin/resection margin", so we think that the literature finally filtered by the search strategy in this study is complete.

4. The inclusion of the literature may be incomplete. For example, Fig2 of Zhang et al. (Perioperative and Long-Term Outcome for Intrahepatic Cholangiocarcinoma: Impact of Major Versus Minor Hepatectomy) provides the OS and RFS of patients with ICC with R0 resection. These data can be extracted. Can you provide the reason for not including this article?

Response: Thanks for the reviewer's question. The inclusion criteria of the literature in this study were that the surgical margin status of patients was all R0 resection, while the patients included in PMID: 28744741 included R0 and R1 resection, and it was impossible to distinguish the OS and RFS of patients with R0 resection in Figure 2, so this literature was extracted in our study.

Minor:

1. The author defines the inspection level of meta-analysis was set as $\alpha = 0.05$. On analysis of lymph node lesions on OS, $I^2 = 57.5\%$, $P = 0.051$ (>0.05), you hold that lymph node lesions were detrimental to OS in patients with ICC, it may be inaccurate.

Response: Thanks for the reviewer's suggestion. $P = 0.051$ (>0.05) was considered moderately heterogeneous, although $\alpha = 0.05$ was defined as the inspection level for the meta-analysis. In addition, based on $I^2 = 57.5\%$ ($>50\%$), we used the random effects model analysis and subsequently found that $HR = 1.44$ (>1 indicating harmful). Therefore, we believe that lymphadenopathy is a risk factor for ICC patients.