

Manuscript ID: World Journal of Gastroenterology-52784

**Title: Extended lymphadenectomy in Hilar cholangiocarcinoma: what it will bring?
An opinion review**

Dear editor, reviewers:

At first, please allow me to thank you with all my heart for the chance of revising my review. I lean a lot from your precious advice, which help me to consummate my review. I am submitting a revised version of my review “Extended lymphadenectomy in Hilar cholangiocarcinoma: what it will bring? An opinion review” (52784). In this revised version, I have addressed the concerns of the reviewers. Thank you for the helpful comments and suggestions.

In response to comments from the reviewers, I have revised the review based on the suggestions and advice of the reviewers. An item-by-item response to their comments in enclosed. I deleted some contents to avoid confusing readers. I hope that these revisions successfully address their concerns and requirements and that this manuscript will be accepted for publication.

Looking forward to hearing from you soon.

With best regards,

Yi-Lei Deng

Reviewer: 1, Reviewer's code: 02683307

Comment 1. This manuscript is well written.

Reply: Thanks for this comment. We are very happy to receive your praise.

Reviewer: 2, Reviewer's code: 03388124

Comment 1. This is essentially a literature review on lymph node dissection in hilar cholangiocarcinoma. The preferred format would be either a meta-analysis, or based on the author's own experience.

Reply: Thanks for this comment. We also prefer to perform a high-quality meta-analysis to investigate the impact of extended lymphadenectomy on the prognosis of hilar cholangiocarcinoma. There are five literatures are related to the impact of lymphadenectomy on prognosis of hilar cholangiocarcinoma so far.¹⁻⁵ However, there is only one literature (Ma et al. 2019) is directly related to this topic,⁵ which would make the meta-analysis low-quality and unreliable.

For our own experience, Ma Wen-Jie and colleagues from West China Hospital are our collaborator. Recently, Ma et al. reported that extended lymphadenectomy significantly increases lymph node retrieval, thereby preventing understaging and improving survival prediction. extended lymphadenectomy may improve overall survival in patients with M0 disease and underwent R0 resection, but does not improve overall survival for M1 patients. Thus, they concluded that extended lymphadenectomy should not be adopted for HCCA patients with intraoperatively confirmed distant lymph node metastases, which is consistent with previous reports⁵. However, as extended lymphadenectomy indicated improvement of overall survival over patients who underwent regional lymphadenectomy in M0 and R0 resection disease before propensity score matching but not after propensity score matching in Ma et al.'s report, they suggested that future studies are required to further assess whether extended lymphadenectomy should be performed in the negative celiac, superior mesenteric, and para-aortic lymph nodes in HCCA patients. We have added above sentence to the

manuscript, which has been highlighted. If it still seems improper, I would revise it again. Thank you.

Reference:

1. Schwarz RE, Smith DD. Lymph Node Dissection Impact on Staging and Survival of Extrahepatic Cholangiocarcinomas, Based on U.S. Population Data. *Journal of Gastrointestinal Surgery*. 2007;11(2):158.
2. Aoba T, Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, et al. Assessment of nodal status for perihilar cholangiocarcinoma: location, number, or ratio of involved nodes. *Annals of surgery*. 2013;257(4):718-25.
3. Guglielmi A, Ruzzenente A, Campagnaro T, Valdegamberi A, Bagante F, Bertuzzo F, et al. Patterns and prognostic significance of lymph node dissection for surgical treatment of perihilar and intrahepatic cholangiocarcinoma. *J Gastrointest Surg*. 2013;17(11):1917-28.
4. Bagante F, Tran T, Spolverato G, Ruzzenente A, Buttner S, Ethun CG, et al. Perihilar Cholangiocarcinoma: Number of Nodes Examined and Optimal Lymph Node Prognostic Scheme. *Journal of the American College of Surgeons*. 2016;222(5):750-9.e2.
5. Ma WJ, Wu ZR, Hu HJ, Wang JK, Yin CH, Shi YJ, et al. Extended lymphadenectomy versus regional lymphadenectomy in resectable hilar cholangiocarcinoma. *Journal of Gastrointestinal Surgery*. 2019;In Press.

Comment 2. HCC is widely used to represent hepatocellular carcinoma, which is also within the purview of hepatobiliary surgeons. Thus, to avoid confusion, a different abbreviations should be chosen. Commonly used abbreviations for hilar cholangiocarcinoma include HC, hCCA, etc.

Reply: Thanks for this comment. We have corrected all HCC to HCCA. If it still seems improper, I would revise it again. Thank you so much for your careful review.

Comment 3. It has been several years since the publication of AJCC 8th edition staging manual, thus the discussion should focus on AJCC 8th, rather than AJCC 7th.

Reply: Thanks for your careful review. We focused on AJCC 7th edition staging manual in section of “**2. Dispute in dissection scope of lymph node of hilar cholangiocarcinoma**”, which discussing the reason why these arguments exist in dissection scope of lymph node of hilar cholangiocarcinoma. In our opinion, the reason is that the accuracy of the 7th AJCC staging system is not enough, which stage the HCCA by the lymph node metastasis site.

In the section of “**3. New definition of lymph node dissection**”, we discussed the origin of 8th AJCC staging system, which may change the practice of lymph node dissection in hilar cholangiocarcinoma and how it will change the practice.

Therefore, we discussed the AJCC 7th and AJCC 8th separately, not focused on AJCC 7th rather than AJCC 8th. Thanks for this comment.

Comment 4. Although the pathologists and medical oncologists typically prefer more lymph nodes for accurate staging of any cancer, the surgeon has to balance other factors, e.g. the anatomic location, difficulty in removing more lymph nodes, intra-operative and long-term complications associated with extensive lymph node dissection, etc. This should be discussed in the review as a separate section.

Reply: Thanks for this careful comment. Recently, Ma et al. reported that incidence of lymphorrhagia, duration of postoperative stay, 30- or 90-day mortality, and other complications were comparable between the traditional regional lymphadenectomy and extended lymphadenectomy groups. Thus, extended lymphadenectomy could be performed in selected resectable hilar cholangiocarcinoma patients.

We have added your suggestion and this response to our manuscript, which has been highlighted. If it still seems improper, I would revise it again. Thank you.

Comment 5. The authors' conclusion of removing 15 lymph nodes for hilar cholangiocarcinoma appears to be too aggressive. Further justification is desired.

Reply: Thanks for your careful review, but we do not find that we concluded removing 15 lymph nodes for hilar cholangiocarcinoma. We just cited Kambakamba et al.'s study¹ which confirming that at least 15 lymph nodes can be obtained by extended lymphadenectomy in radical resection of HCCA. We just conclude that a standardized extended lymphadenectomy may help to more accurately stage the HCCA; Future studies are required to further assess whether extended lymphadenectomy could improve the long-term survival in the negative celiac, superior mesenteric, and para-aortic lymph nodes diseases. We have corrected the sentence mentioned the “15 lymph nodes” to “more lymph nodes” in abstract, which have highlighted, if it still seems improper, I would revise it again. Thank you.

Reference:

1. Kambakamba P, Linecker M, Slankamenac K, DeOliveira ML. Lymph node dissection in resectable perihilar cholangiocarcinoma: a systematic review. The American Journal of Surgery. 2015;210:694-701.

Reviewer: 3, **Reviewer's code: 03475479**

Comments to the Author

Authors reviewed about lymphadenectomy in hilar cholangiocarcinoma. This review was lacking in novelty but well-summarized.

Comment 1. No16 LN metastasis is recognized as distant metastasis because of poor prognosis. For better survival in such cases, effective chemotherapy is essential not but resection. Authors should also discuss about chemotherapies for hilar cholangiocarcinoma with LN metastases.

Reply: Thanks for this comment.

In Ma et al.'s study¹, extended lymphadenectomy did not significantly improve the long-term survival of patients with No 9, 14, and 16 LN metastasis. Therefore, they suggested that extended lymphadenectomy should not be adopted for HCCA patients with intraoperatively confirmed distant LN metastases, which is consistent with your

opinion. Three meta-analysis have suggested the potential benefit for chemotherapy as adjuvant therapy in patients with node-positive disease²⁻⁴. For these patients, radical resection combined with postoperative adjuvant chemotherapy seems to be a better choice.

We have added your suggestion and this response to our manuscript, which has been highlighted. If it still seems improper, I would revise it again. Thank you very much.

Reference:

1. Ma WJ, Wu ZR, Hu HJ, Wang JK, Yin CH, Shi YJ, et al. Extended lymphadenectomy versus regional lymphadenectomy in resectable hilar cholangiocarcinoma. *Journal of Gastrointestinal Surgery*. 2019; In Press.
2. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant Therapy in the Treatment of Biliary Tract Cancer: A Systematic Review and Meta-Analysis. *Journal of Clinical Oncology* 2012; 30(16): 1934-1940 [PMID: 22529261 DOI: 10.1200/jco.2011.40.5381]
3. Ghidini M, Tomasello G, Botticelli A, Barni S, Zabbialini G, Seghezzi S, Passalacqua R, Braconi C, Petrelli F. Adjuvant chemotherapy for resected biliary tract cancers: a systematic review and meta-analysis. *HPB* 2017; 19(9): 741-748 [DOI: <https://doi.org/10.1016/j.hpb.2017.05.010>]
4. Rangarajan K, Simmons G, Manas D, Malik H, Hamady ZZ. Systemic adjuvant chemotherapy for cholangiocarcinoma surgery: A systematic review and meta-analysis. *European journal of surgical oncology* 2019 [PMID: 31761507 DOI: 10.1016/j.ejso.2019.11.499]

Comment 2. Authors partially used HCC as abbreviation of hilar cholangiocarcinoma. The abbreviation and full-spelling were both found. HCC was usually recognized as abbreviation of hepatocellular carcinoma I recommend HC, hilar CC or hICC as abbreviation of hilar cholangiocarcinoma.

Reply: Thanks for this comment. We have corrected all HCC to HCCA. If it still seems improper, I would revise it again. Thank you so much for your careful review.