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Reply to: Does lymphovascular invasion really associate with decreased overall survival for patients with resected cholangiocarcinoma?



We thank Ma et al. [1] for commenting on our recent publication describing the roles of lymphovascular invasion (LVI) and nodal status as predictors of oncologic outcome in patients undergoing curative intent surgery for hilar (pCCA) and intrahepatic (iCCA) cholangiocarcinoma [2] and like to congratulate the Chinese group for having their large cohort published recently. While we fully agree with Ma et al. that our results have to be interpreted within the limitations of a single-center cohort and are also influenced by the analyzed sample size, we do however disagree with other claims of their letter.

First, our results do not show a multivariate association between LVI and overall survival (OS) in iCCA as indicated in their letter but instead for nodal status. We also did not correlate the presence of LVI with nodal status in these particular patients but discussed the potential role of LVI as a first step to lymphatic metastases [3].

Second, we agree with Ma et al. that the role of LVI in CCA remains controversial and warrants further research as already stated in our paper. However, LVI has already been identified as an important prognostic factor in patients with breast, esophageal and rectal cancer [4,5]. Of note, LVI and peritumoral lymph vessel density are associated with nodal metastases in iCCA, suggesting LVI-dependent tumor cell dissemination through the lymphatic system in CCA [6]. We further disagree with Ma et al. that the single common feature of the quoted literature, which explains the controversy in the results, is sample size. Ma et al. quote studies from three different continents having different incidence rates and comprising patients with differing genetical heritage and oncological and surgical standards which has to be taken into account when making claims about the potential role of LVI. Furthermore, we are to some extent surprised by the critic on our findings by the Chinese group. While we were not able to find reference 2 of their letter to the editor (“Ma WJ et al. Extended lymphadenectomy versus regional lymphadenectomy in resectable hilar cholangiocarcinoma. *Journal of Gastrointestinal Surgery* 2019; In Press”) and look at their cohort in detail, we found the recently published paper of Peng et al. from the same department [7] (not PubMed listed). Here, Peng et al. evaluate oncologic outcome in 244 patients who underwent radical resection for Bismuth type IV pCCA and develop a scoring system to predict early disease recurrence. Based on their multivariate analysis, they conclude, that “a simple scoring system using CA19-9 level, N category, resection

margin and LVI could predict early recurrence, and thus might direct post-operative surveillance and adjuvant therapy for patients with type IV pCCA.”

Third, the main goal of surgical therapy in patients with pCCA is the achievement of a R0 resection. However, the prognostic role of margin status has already been questioned in other oncologic entities such as colorectal liver metastases [8]. Interestingly, the Nagoya group has recently published their experience with Bismuth type IV tumors comprising 332 patients and found no association of margin status with OS in univariate and multivariable analysis [9]. As a possible explanation, we speculated that the findings of the Nagoya Group and our paper might be attributed to the more common use of adjuvant therapy. The suggestion of Ma et al. to differentiate between R0 wide and R0 narrow is indeed very interesting and should be evaluated in upcoming studies. However, several authors have already evaluated the importance of the length of the resection margin. Yoo et al. analyzed survival data of 96 consecutive patients with pCCA and found no difference in survival among R0 resections with a narrow (<5 mm) and a wide (>5 mm) margin [10]. Also, the width of a negative margin had neither impact on long-term survival nor the probability of tumor relapse in a multicenter analysis comprising 434 patients with iCCA [11]. We therefore believe, that there is enough evidence in the currently available literature to consider a microscopically confirmed R0 status as radical resection and subsequently do not see a benefit in re-analyzing our data with respect to the length of the resection margin.

Conflict of interest statement

The authors report no conflict of interest.

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interest regarding the manuscript. All authors acknowledge that the conflict of interest disclosures are complete for both themselves and their co-authors, to the best of their knowledge.

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