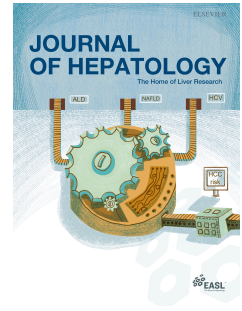


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*Letter to the Editor*

**Survival benefit of adequate lymphadenectomy in patients undergoing liver resection  
for clinically node negative intrahepatic cholangiocarcinoma – Letter to the editor**

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CTJM: data interpretation, wrote the manuscript; GB: data interpretation, critical revision; VB:  
data interpretation, critical revision.

## Discussion

To the Editor,

It was with great interest that we read the Italian multicenter retrospective cohort study by Sposito et al. on adequate lymphadenectomy in patients for clinically node negative intrahepatic cholangiocarcinoma[1]. The study was able to demonstrate that in 45% of the patients radiologically negative lymph nodes, cancer cells were found in histological workup in the lymph nodes. Several questions arise with regard to the current multicenter study and we would like to emphasize the following points:

We would like to challenge that the study is potentially flawed for several reasons. The occurrence of the major oncological outcome manifests itself after the median follow-up period (FU) (overall survival median 39 months; follow-up duration median 33 months) and thereby is not sufficiently powered. Neither type nor duration of (adjuvant) chemotherapy was described. As the cohort encompasses a twenty years study period, the aspect of the systematic therapeutic options are likely to be evolved over time. Details on the frequency of the use of radiological screening tools (computed tomography vs. magnetic resonance imaging [MRI] vs. positron emission tomography [PET]) are neither mentioned in the preoperative diagnostics phase nor in the FU period. This might relevantly contributed to an ascertainment bias. Additionally, a relevant Hawthorne-effect might be possible due to a (most likely) increase of use of PET and/or (liver-specific) MRI over time. Detailed, but relevant surgical aspects (laparoscopic vs. open resection) and postoperative treatment and complication rates were not mentioned / taken into account in this study. Surgical technique has developed and changed during the past twenty years, and the superiority of a laparoscopic approach has been previously shown [2,3]. Brustia et al. were able to show, that severe postoperative complications are predictors for overall survival (hazard ratio: 10.5, 95% confidence interval [1.01-109] p-value = 0.049) and tumor recurrence alike (hazard ratio: 4.07, 95% confidence interval [1.15-14.4] p-value = 0.030) [3]. Moreover, 54.1% of recurrences in the adequate lymphadenectomy (AD-LND) group occurred in the liver only. No explanation on how additional extra-hepatic surgical resection impacts intra-hepatic oncological was given. This might be partially due to the R1 resection status, but further discussion and possible explanations need to be sought. The necessity of the used statistical method of stabilized inverse probability of treatment weights is either questionable as only few cases (0.96% [n=4] in AD-LND and 1.73%

[n=5] in NAD-LND) were excluded from further analysis or these few patients are fundamentally surgically or biologically different from the rest of the cohort. This corresponds to the possible limitation of a retrospective cohort study as discussed by Sposito and colleagues.

Moreover, some discrepancies exist in numbers between text, tables and figures (e.g. Suppl. Table 1 adequate group n=191 vs. text n=195; Suppl. Table 1  $103/191=53.9\%$  and not  $54.1\%$ ).

In conclusion, we would like commend the authors on addressing a clinically relevant issue. At the same time the readers need to consider the still limited scientific evidence that would be required to routinely perform D2 lymph node dissection for clinically node negative intrahepatic cholangiocarcinoma. Future studies are warranted in which the afore mentioned (possible) co-factors and biases taken into account and adjusted for accordingly.

**References**

- [1] Sposito C, Ratti F, Cucchetti A, Ardito F, Ruzzenente A, Di Sandro S, et al. Survival benefit of adequate lymphadenectomy in patients undergoing liver resection for clinically node negative intrahepatic cholangiocarcinoma. *J Hepatol* 2022.  
<https://doi.org/10.1016/j.jhep.2022.10.021>.
- [2] Sahakyan MA, Aghayan DL, Edwin B, Alikhanov R, Britskaia N, Brudvik KW, et al. Laparoscopic versus open liver resection for intrahepatic cholangiocarcinoma: a multicenter propensity score-matched study. *Scand J Gastroenterol* 2022:1–8.  
<https://doi.org/10.1080/00365521.2022.2143724>.
- [3] Brustia R, Laurent A, Goumard C, Langella S, Cherqui D, Kawai T, et al. Laparoscopic versus open liver resection for intrahepatic cholangiocarcinoma: Report of an international multicenter cohort study with propensity score matching. *Surgery* 2022;171:1290–302.  
<https://doi.org/10.1016/J.SURG.2021.08.015>.