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SURVIVAL BENEFIT OF LYMPHADENECTOMY FOR INTRAHEPATIC CHOLANGIOCARCINOMA: IT MIGHT BE GOLD EVEN IF IT DOES NOT GLITTER

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Regional lymphadenectomy (LND) is an essential part of the surgical procedure for many cancers. According to the different histotypes, retrieval of an adequate number of regional lymph-nodes (LNs) determines the correct staging of the disease. A correct nodal staging allows for prognostic prediction and often dictates whether adjuvant treatment will be offered. In terms of long-term oncologic outcomes, the beneficial effect of regional LND is more controversial and strongly depends on the primary disease. For instance, current level 1 evidences confirm better cancer-related survival from D2 LND (over D1) in gastric cancer[1,2], suggest better regional control but similar long-term outcomes in melanoma[3] and exclude any benefit from axillary lymphadenectomy in breast cancer with positive sentinel lymph-node[4]. In intrahepatic cholangiocarcinoma (ICC), the AJCC/UICC Cancer Staging recommends retrieval of at least 6 regional nodes for adequate staging[5]. Given that adjuvant therapy is currently indicated for all resected ICC regardless the stage[6], in principle the only purpose of adequate LND would be better prognostic stratification and eligibility for clinical trials. Considering that LND has been repeatedly associated with increased postoperative morbidity[7], why should we perform it during surgery for ICC? Can we foresee an oncologic benefit of LND?

In a recent issue of Journal of Hepatology[8] we reported the results of a large retrospective series of patients operated for clinically node-negative ICC at 5 tertiary Italian Centers. With the acknowledged limitations of a retrospective nonrandomized study, we observed a noteworthy benefit in overall survival (OS) and disease-free survival (DFS) deriving from an adequate LND (AD-LND) according to AJCC, in patients finally found respectively node negative (pN0) and node positive (pN1) at final pathology. These results raised some criticisms, which we feel are worthy of further discussion and analysis.

Koerkamp et al.[9], in their accompanying Editorial, rightly observed that the benefit of AD-LND in pN0 patients is likely a consequence of an understaging of patients receiving inadequate LND (NAD-LND). This is known as the Will Rogers phenomenon, described since 1985 in oncology and already acknowledged in the papers' discussion. Koerkamp et al. also challenge the finding of an oncologic benefit in pN1 patients, stating that NAD-LND was probably performed in those with more advanced nodal disease (i.e., more positive LNs), and this explains the inferior survival outcomes. To investigate this issue, we additionally examined our inverse probability of treatment weight (IPTW) study. If Koerkamp's observation is true, NAD-LND patients would have a higher node ratio (i.e. number of positive LNs/total harvested LNs), and outcomes in pN1 patients with AD-LND would be worse with the increasing of number of metastatic LNs. On the contrary, the nodal ratio is almost identical in the two groups: the median (IQR) number of metastatic LNs in patients who had adequate LND (n=165) was 3 (2-4) over 10 (7-13) (ratio=0.3) while that of patients who had inadequate LND (n=51) was 1 (1-2) over 3 (1-4)(ratio=0.33). Moreover, the number of metastatic LNs did not impact on prognosis of pN1 patients who received AD-LND (n=165), as shown in Table1. An ancillary technical detail discussed by Koerkamp et al.: the heterogeneity of treatment effect was taken into account by interaction tests both here and in the original study. All regressions were interactions, i.e. performed by applying the same distribution of weighted variables and not by generating subgroups.

Other criticisms have been raised by Magyar et al.[10], who challenge our results for potential flaws. In particular: a) We agree that longer follow-up would have led to more accurate estimation of overall survival. However, as can be seen in Figure 1 of the original study, survival curves already proportionally divided within the first 12-18 months from the start of the observation. Consequently, the relative effect of grouping can still be considered robust b) The observation that the results can be the consequence of enrolment year is not supported, since the era of surgery was introduced as a confounder when computing IPTW (as can be seen in Table 1 of the study). Thus, it is unlikely for a relevant Hawthorne effect to be present c) Magyar et al. probably misunderstood the approach of IPTW which, differently from propensity score match, did not match the two cohorts but it weighted patients' features to make them comparable. The number of patients simply represents the final sum of generated weights. d) We acknowledge the fact that the surgical approach (mini-invasive vs open) has not been taken into account, however to the best of our knowledge this has never been shown as an independent factor for long-term outcomes, which were the primary endpoints of our study.

A final observation has to be made on the comparison of our results with concepts related to D2 LND (Magyar et al.) and benefits of extended lymphadenectomy in pancreatic cancer (Koerkamp et al.). Both these issues do not appear to fit with the results of our paper, since our aim was to analyse the benefits of an *adequate* LND (which is the retrieval of > 5 LNs as recommended by the AJCC cancer manual). Differently from the Halstedian concept that resection of positive LNs could avoid the development of metastatic disease, in this setting it is likely that an AD-LND (as in the setting of gastric or rectal cancer) exerts its survival benefit as an essential part of surgery with radical intent, particularly at early stages. The preoperative prediction of nodal positivity in ICC is scarcely accurate, thus all patients should be considered potentially node positive, and lymphadenectomy should be performed adequately in all cases. As also demonstrated in our study, this attitude should be balanced with other oncological factors (i.e. tumor size, multifocality, Ca19.9) and with the risks of postoperative complications. We thank the Colleagues for encouraging this important debate: prospective studies are warranted, possibly in the setting of cN0 early stage ICC, to assess whether the benefit of LND in ICC is truly gold even if it does not glitter.

Table 1. IPTW weighted regression of RFS in pN1 patients who underwent AD-LND: the number of positive nodes has no significant impact on outcomes

| | HR (95% CI) | p |
|--|------------------|-------|
| Recurrence-free survival | | |
| 1 N+ | Ref. | |
| 2 N+ | 0.99 (0.37-2.63) | 0.982 |
| > N+ | 1.13 (0.59-2.14) | 0.632 |
| Overall survival | | |
| 1 N+ | Ref. | |
| 2 N+ | 0.76 (0.38-1.50) | 0.321 |
| > N+ | 1.33 (0.60-2.95) | 0.371 |
| Abbreviations: N+: metastatic node; HR: Hazard Ratio; CI: Confidence Interval) | | |

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