

Assessment of nodal status for perihilar cholangiocarcinoma location, number, or ratio of involved nodes

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Abstract: Surgical treatment of perihilar cholangiocarcinoma (PCC) is the treatment of choice that can achieve long term results. Unfortunately the presence of lymph node metastases is frequent and it is one of the major negative prognostic factors in patients submitted to surgery. In literature there are few data about the prognostic significance of location, number and ratio of involved nodes. Moreover guidelines about the extent of lymph node dissection are not available. In this commentary the data of literature about prognostic significance of lymph node involvement are described and analysed.

Keywords: Cholangiocarcinoma; surgery; lymphnodes metastases



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Perihilar cholangiocarcinoma (PCC) is a rare tumor but its incidence is increasing worldwide, this tumor originates from bile ducts at the level of hilar bifurcation. Surgical resection, with radical intent, is the treatment of choice and can achieve long-term survival. Among different prognostic factors evaluated in literature the presence of lymph-node (LN) metastases is one of the most relevant and poor survival after resection in PCC is closely related with LN status (1,2). The frequency of positive LNs is variable in literature and it ranges from 19% to 53% in PCC (3-5). Several clinical studies have described poor survival in patients with positive LNs, with an expected 5-year survival between 0% and 25% (1,6-8) compared to 30-50% in N0 patients; therefore, some authors suggest that patients with positive LNs should be excluded from surgical resection (9,10).

Recently, the importance of the lymph-node ratio (LNR) in cholangiocarcinoma was confirmed in different surgical series, and this variable has been shown to better stratify patients with positive LNs (11,12). However, the extent of LN dissection and its prognostic value is still under debate (3,13).

In the recent study of Aoba *et al.*, the Authors analyzed

the prognostic significance of lymph node status in resected PCC in order to clarify the prognostic role of number, location of LN metastases and LNR (14).

This study from Nagoya Clinical Centre includes one of larger single centre surgical series and they collected 320 patients during a 20 years period with PCC who underwent surgical resection.

They investigated this population with a multivariate analysis and they confirmed that the presence of LN metastases is the strongest negative prognostic factor. This study has a great clinical significance due to the large number of patients collected in a single surgical centre.

Moreover this study analysed the prognostic role of number, location and ratio of LN metastases. This issue has not been extensively analysed in literature and it is still matter of debate.

These authors focused on the prognostic significance of location of lymph node metastases, they reported that survival for patients with distant lymph node metastasis (pM1) was not significantly shorter compared to pN1 patients. The prognostic value of the distribution of positive LNs among different stations according to the JSBS classification has not been adequately evaluated in

the literature. In a previous study of the same surgical group, Kitagawa *et al.* analyzed 110 patients who underwent surgical resection for hilar cholangiocarcinoma with lymph node dissection including both the regional and paraaortic nodes. They found no significant differences in survival between patients with pN1 and pN2 disease (3-year survival, 23.1% *vs.* 37.1%; 5-year survival, 23.1% *vs.* 13.9%; median survival, 29.2 *vs.* 25.0 months). While in patients with positive pN3 (paraaortic nodes) the prognosis was significantly worse (0% at 5 years) and comparable to unresected patients (6).

These data suggest that the presence of paraaortic nodes metastases is related with worse prognosis but survival in these patients is similar to those with regional LN metastases. The prognosis seems to be related to the presence of LN metastases per se and not by their location.

Aoba *et al.* analyzed another debated issue of surgical treatment of PCC: the number of positive LN and they confirmed that the number of positive nodes is related with survival (14). This data was previously reported by Schwarz *et al.* in a multi-institutional study who reported 5-year survival rates of 36% and 12% in patients with up to 2 and with 3 or more positive LNs, respectively (15).

Also the LNR was analyzed, Aoba *et al.* confirmed the prognostic value in patients with <0.2 showing longer survival compared to LNR >0.2 (14). They underlined the intrinsic bias of LNR due to its strong relationship to Total Lymph Node Count (TLNC). Different cut-off values were used in the literature and were typically between 0.1 and 0.3 (11,16-18). Oshiro reported similar results for patients with extrahepatic cholangiocarcinoma, with 5-year survival rates of 44%, 10% and 0% for patients with an LNR =0, between 0 and 0.20 and more than 0.20, respectively (19). In our previous study we evaluated, in a series of 62 patients with perihilar cholangiocarcinoma, we identified that LNR with cut-off value of 0.25 has a strong prognostic value in PCC (12).

The TLNC and its prognostic role is debated in literature since in PCC is not adequately defined the minimal LN count for adequate staging.

The TLNC seem to be related to survival, but the UICC/AJCC TNM Staging System and the JSBS classify regional LNs in different manners. Due to the different classifications and the lack of published data about lymph node dissection, consensus statement regarding the extent of LN dissection is still not available.

In this study of Aoba the, average TLNC in the 320 patients study was 12.9 (median: 11), the average TLNC in

43 patients who underwent periaortic node dissection was 24.6 and 11.0 in the remaining 277 (14).

Aoba *et al.* criticized the seventh edition of UICC TNM classification in which the minimum number of harvested nodes was increased from 3 to 15, the Authors underlined that following UICC TNM guidelines only 29% of patients were correctly staged and for this reason this requirement can not be fulfilled in normal clinical practice. They suggested that the realistic number would be “around” 5 (14).

Multi-institutional studies including more patients may clarify this issue, identifying the “magic number” of adequate lymph node dissection. However the data of literature suggest to retrieve more LN as possible in order to improve the staging of patients since a clear therapeutic role of LN dissection is difficult to demonstrate as occurs in other gastrointestinal tumors (16-18). Also in our recent study we confirm the prognostic significance on TLNC in PCC (20).

In conclusion the study of Aoba *et al.* adds a significant contribution to our knowledge of the prognostic factors of PCC after surgical, it confirmed that LN metastases is the most important prognostic factor and the role of LN dissection in the treatment of this tumor. The extent of LN dissection is still not clear and the study of Aoba *et al.* underlined and confirmed the need of further studies in order to provide new guidelines in this field.

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