

Assessment of nodal status for perihilar cholangiocarcinoma: does the extent of lymphadenectomy make a difference?

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Over the last several decades aggressive surgical resection has changed the prognosis for perihilar cholangiocarcinoma, transforming an unresectable tumor with certain mortality to a curable disease with almost 50% 5-year survival in high volume centers with R0N0 resections (1). The field continues to evolve, pushing boundaries and improving outcomes by extending resection to include vascular resections and pancreaticoduodenectomy to achieve negative margins. The Nagoya group has been instrumental in advocating an aggressive approach to this disease and is considered one of the most experienced and aggressive surgical centers for treatment of cholangiocarcinoma. However, no matter how aggressive the surgery, the risk of lymph node metastases at the time of resection remains 24-50% (2) and lymph node involvement remains one of the most significant negative prognostic factors for recurrence and survival after resection after margin status.

To date, there has not been any conclusive evidence that increasing the extent of lymphadenectomy impacts survival in cholangiocarcinoma (3), or other gastrointestinal (GI) malignancies, including gastric (4) and pancreatic cancer (5,6). The current Union for International Cancer Control (UICC), TNM staging system (7th edition) for perihilar cholangiocarcinoma classifies regional lymph nodes (hilar and pericholedochal nodes in the hepatoduodenal ligament) to be N1 and considers all other nodes, including the common hepatic artery lymph node and periaortic nodes to be distant metastases included in the M1 classification. In general, current recommendations are that resection is not carried out for metastatic cholangiocarcinoma with the implication that if lymph nodes classified as M disease are identified resection would not be carried out.

The UICC suggests the minimum requirement for

lymph nodes is 15 for resection of cholangiocarcinoma. Recent publications on other GI malignancies demonstrate that not only location, but number of lymph nodes and the ratio of involved nodes (LNR) improve the accuracy of staging (7,8). In their recent paper the Nagoya (2) group retrospectively reviewed their large experience and evaluated the nodal status of 320 patients who underwent resection for perihilar cholangiocarcinoma over a decade. This included 26 resections done between 2000-2005 when periaortic lymph node dissections were routinely performed. The total lymph node count (TLNC) per resection was a median of 12.9 nodes, and that 45.6% of patients had lymph node involvement at the time of resection. Not surprisingly, the TLNC increased with periaortic lymph node dissection.

As expected, nodal involvement was a strong prognostic factor with 5-year survival 59.6%, 19.2% and 11.5% for N0, N1 and M1 disease respectively. Survival was worse for M1 compared to the N1 disease but this was not significant with a P-value of 0.058. There are some difficulties with this analysis however. Only 26 patients underwent an M1 node dissection with resection, and by the authors report they stopped periaortic lymph node dissection in 2005 because of what was felt to be conclusive data that extended lymphadenectomy does not impact survival. It is hard to comment on the 294 patients that underwent resection without periaortic node dissection since staging bias is introduced and we do not know those patients true status. Due to the small number of patients resected for M1 disease, the risk of type II error is also high. Additionally, resection in M1 patients was only pursued in patients with low risk for morbidity or mortality from the liver resection, which may be selecting patients with less aggressive/ extensive disease for resection.

Patients who had disseminated disease at resection or were unresectable had a 0% survival at 5 years. Patients with a single metastasis fared better than patients with multiple metastases with a 5-year survival of 26% compared to 14.3%. However, there was no difference in survival if the multiple metastases were regional or distant in location. In univariate analysis, all three nodal factors were statistically significant, but only number of nodes was significant in multivariate analysis.

LNR was inversely proportional to the TLNC. In this series the median TLC was 12.9, but in other comparable series ranges from 3-7 (9,10). The Nagoya group felt that LNR was not a useful tool because of the low number of nodes recovered. This is contrary to other recently published data on LNR and cholangiocarcinoma that found LNR to be highly prognostic (10,11), similar to studies in other cancers like gastric and pancreatic cancer (7,8). The authors also suggest TLNC >5 is necessary for accurate clinical staging, but a TLNC of 15 as recommended by UICC may be unrealistic without peri-aortic node dissection.

The authors conclude that number and not location is the most important negative prognostic factor for perihilar cholangiocarcinoma. Against conventional wisdom the authors recommend not only proceeding with liver resection with positive periaortic lymph nodes, but including a periaortic lymphadenectomy to increase the number of nodes retrieved and the accuracy of the staging. In their hands long-term survival is possible in this patient population with metastatic nodal disease and they are considered for resection.

There is no doubt that results from the experienced Nagoya group are excellent. Including the periaortic lymph nodes to improve staging and possibly stratify patients for additional modes of therapy is a relatively low risk endeavor with potential benefit. However further confirmation of the utility of proceeding with the resection in the face of positive periaortic lymph nodes would appear to be needed before generalizing this approach. Performing liver and bile duct resection in patients with positive periaortic nodes cannot yet be considered standard of care. However, it is clear from this series that surgeons should endeavor to perform as complete a lymphadenectomy as possible to improve staging.

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