



## Underutilization of Lymphadenectomy for Gallbladder Cancer: A Persistent Problem with Dire Consequences

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The importance of performing portal lymph node dissection for patients with resectable gallbladder cancer that has invaded the muscular layer (T1b) is widely endorsed by the American Joint Committee on Cancer (AJCC), Americas Hepato-pancreato-biliary Association (AHPBA), and National Comprehensive Cancer Network (NCCN). Having a positive portal lymph node is associated with worse long-term survival and, for many clinicians, is one of the main reasons for offering adjuvant systemic therapy. Despite this, data from actual clinical practice suggest the rates of performing portal lymphadenectomy (LAD) are low. Although the impact of portal LAD for gallbladder has been examined, which patients are offered it and its association with survival are not well studied.

In this issue of *Annals of Surgical Oncology*, in a paper entitled “Rates, Predictors, and Outcomes of Portal Lymphadenectomy for Resectable Gallbladder Cancer,” Kemp Bohan and colleagues utilize the National Cancer Database (NCDB) to carry out a deeper investigation into the prognostic value of, and who receives, portal lymph node dissection for gallbladder cancer.<sup>1</sup> The authors identified 2302 patients from 2006 to 2015 who underwent resection of gallbladder cancer, of whom only 58.3% also had portal lymph node dissection. When portal LAD was performed, only 23.9% ( $n = 310$ ) had  $\geq 6$  lymph nodes retrieved. Over the study period, the frequency of performing node dissections increased from 51.6% in 2006 to 64.2% in 2015, and it was more often performed in younger patients, those

with private insurance, at academic centers, and in those with higher T stages. They also found that patients undergoing LAD were more likely to receive chemotherapy (46.2% versus 26.6%,  $p < 0.001$ ). As expected, patients who underwent LAD with no positive lymph nodes had the best overall survival (OS), but interestingly, patients who had positive nodes or did not undergo LAD had similar, poor OS. This was also seen on multivariate analysis, where having a lymph node dissection was associated with improved OS for pT2 and pT3 tumors, regardless of nodal status.

This study confirms the disheartening reality that, despite widespread recommendations by the AHPBA, AJCC, and NCCN, portal lymph node dissection is not routinely performed in clinical practice for muscle invasive gallbladder cancer.<sup>2,3</sup> What is consistently seen in NCDB studies is that failure to perform a portal LAD is associated with worse OS, and in this study, not performing a LAD was as bad as having a positive lymph node.<sup>2,4</sup> The question that has not, and cannot, be answered with this study is: why? This study showed that patients who have a positive lymph node are more likely to receive adjuvant therapy, while those who do not are likely to be understaged and not receive survival improving therapy. Although a cause-and-effect relationship cannot be determined from retrospective database studies, the OS benefit seen with LAD was likely not simply associated with those patients receiving adjuvant therapy alone, since less than half of the LAD group received chemotherapy. There are likely unrecognized confounders and selection bias towards higher-risk patients being offered adjuvant therapy based on variables not available in the NCDB.

During the period of this study (2006–2015), there were limited level 1 data on the value of adjuvant therapy. Prior to 2015, the only phase III trial available to guide adjuvant therapy was by Takada et al. published in 2002.<sup>5</sup> This

multiinstitutional Japanese study included randomized patients with gallbladder cancer and cholangiocarcinoma to adjuvant mitomycin-C and 5-fluorouracil versus surgery alone. The trial found an improvement in 5-year OS for gallbladder cancer (26.0% versus 14.4%,  $p = 0.0367$ ) but not cholangiocarcinoma. Although this study supported adjuvant systemic therapy, the mitomycin-C regimen was not routinely used in the USA.<sup>6</sup>

Since that original trial, lymph node status may hold greater prognostic value based on more recent level 1 data. The BILCAP trial, published in 2019, examined adjuvant capecitabine versus observation in patients with muscle invasive gallbladder cancer and cholangiocarcinoma.<sup>7</sup> The study was met with mixed reactions as it did not find an improvement in the primary endpoint of OS in the intention-to-treat analysis (HR 0.81, 95% CI 0.63–1.04;  $p = 0.097$ ) but did in the per-protocol population (HR 0.71 (95% CI 0.55–0.92;  $p = 0.010$ ). An important detail of the trial is that the investigators did have a preplanned sensitivity analysis of OS in the intention-to-treat population for identified prognostic factors. They found that there was an improvement in OS when adjusting for nodal status, disease grade, and sex (HR 0.71, 95% CI 0.55–0.92,  $p = 0.01$ ). Despite the controversy surrounding the results, the American Society of Clinical Oncology practice guidelines recommend use of adjuvant capecitabine for resected biliary cancers.<sup>7,8</sup> No matter how clinicians decide to interpret these data, node positivity was identified as an adverse prognostic factor in BILCAP, suggesting this patient population would likely derive the greatest benefit from adjuvant therapy and stressing the importance of performing a complete lymph node dissection.

What really sets this study apart is the investigation into which patients are most likely to undergo LAD. The authors found that being female, being White non-Hispanic, and having insurance were the strongest factors associated with LAD. These data shed light on the disproportionate care for patients with gallbladder cancer. Previous studies have similarly discussed these underlying disparities and have suggested that, unfortunately, they may be more pronounced over time.<sup>9</sup> This study also found that patients treated at academic medical centers were most likely to undergo LAD. This was not purely reflective of more patients being seen at academic centers, as Comprehensive Cancer Centers performed the most resections in total. Although many studies have discussed the importance of regionalization of care for better patient outcomes, we do not know how many patients were referred to academic centers for this purpose and whether inability to refer was secondary to disparities in care.

Using the NCDB is not without its limitations, but despite these, it does provide a snapshot into practice patterns in the USA over a given period. This insight can help identify areas to improve, such as the need to perform LAD, and guide in building future clinical trials.

The timing of this manuscript is fitting with the recent activation of the long-awaited optimal perioperative therapy for incidental gallbladder cancer (OPT-IN) study through the Eastern Cooperative Oncology Group (ECOG-ACRIN), NCT 04559139.<sup>10</sup> This is a phase II/III study for patients with incidental T2 and T3 gallbladder cancer who will be randomized to perioperative (neoadjuvant and adjuvant) versus adjuvant chemotherapy consisting of gemcitabine and cisplatin. This trial will specifically focus on the same T-stages that derived the greatest benefit from LAD based on results from this NCDB study, and results from this trial will shape future treatment.

Gallbladder cancer is plagued with low rates of patients with resectable disease, high rates of distant failure, and controversy regarding the best adjuvant regimen. Data that can help guide clinical practice to improve patient survival are desperately needed. In this study, the authors highlight the importance of portal lymph node dissection, which patients undergo the procedure, and its impact on survival. While we anxiously wait for prospective trials to be completed, data from hypothesis-driven studies, such as those carried out by Kemp Bohan et al., can help inform clinical practice for patients with resectable gallbladder cancer.

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