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Validation of American Joint Committee on Cancer eighth staging system for gallbladder cancer and its lymphadenectomy guidelines

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ABSTRACT

Background: For gallbladder cancer (GBC), the American Joint Committee on Cancer eighth edition (AJCC 8) staging system classifies lymph node (LN) stage by the number of positive LN and recommends sampling of ≥6 LNs. We evaluated the prognostic capability of the AJCC 8 for patients undergoing resection and the current national trends in LN staging in the context of these new recommendations for nodal (N) sampling.

Methods: Utilizing the National Cancer Data Base, we identified all gallbladder adenocarcinoma patients treated with surgical resection in 2004-2014. Cox regression modeling was used to calculate the concordance index of AJCC 8 in predicting overall survival. N sampling and positivity rates were analyzed over the study period.

Results: In our cohort, predicted 5-year overall survival by AJCC 8 was: stage I, 62.5%; II, 50.2%; IIIA, 25.7%; IIIB, 22.1%; IVA, 15.7%; IVB, 6.7% ($P < 0.01$). The concordance index for the staging system was 0.832. Only 50.7% of the patients had any LN sampling to determine the N stage. LN sampling rates improved from 45.6% in 2004 to 55.1% in 2013 ($P < 0.001$). However, only 24.5% of patients with any LN sampling had ≥6 LNs resected (12.4% of eligible cohort), with a median LN sample of two.

Conclusions: AJCC 8 offers adequate discrimination for GBC staging, especially for node-positive patients. With actual GBC LN sampling rates at 50.7%, and far short of the ≥6 LN threshold, quality improvement measures may need to focus on requiring any LN sampling before raising the minimum to six LNs.

The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the deidentified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

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Introduction

Gallbladder cancer (GBC) ranks as the sixth most common gastrointestinal cancer and accounts for 80%-95% of biliary tract cancers worldwide.[1] While GBC is a relatively rare disease in the United States with annual incidence of approximately 3700 cases, it is a lethal disease that accounts for about 2000 deaths annually and confers a 5-year overall survival (OS) rate of approximately 20%.[2] The poor prognosis associated with GBC is likely due to aggressive tumor biology and nonspecific symptoms that result in advanced stages at diagnosis.

The American Joint Committee on Cancer (AJCC) Staging Manual is the standard reference for classifying patients and provides prognostic information and also guides treatment decisions. The manual and its recommendations are created by expert consensus, based on best available data on staging of cancers of all disease sites and were most recently updated in late 2016. In this latest eighth edition AJCC Staging Manual, the AJCC Hepatobiliary Task Force made two notable changes for GBC.[3] First, the T2 category (stage II) was divided into T2a (stage IIA) and T2b (stage IIB), based on tumor location on the peritoneal or hepatic side of the gallbladder, respectively. This was based on a recent multi-institutional study, which showed that tumor location was predictive of recurrence and survival after resection of T2 GBC.[4] Second, the nodal (N) category has been converted from an anatomic location-based system to a number-based system, and the definition of regional lymph node (LN) disease has been changed. In American Joint Committee on Cancer eighth edition (AJCC 8), metastatic LNs along the cystic duct, common bile duct, hepatic artery, and/or portal vein are classified into N1 and N2 stages, depending on involvement of 1-3 LNs and $\geq$4 LNs, respectively. Metastatic LNs to periaortic, pericaval, superior mesenteric artery, and/or celiac artery LNs, considered an N2 stage in the previous AJCC seventh edition (AJCC 7), are now classified as distant metastasis (M1).[5] Finally, the AJCC 8 now recommends resection of $\geq$6 LNs in patients with T1b tumor or greater. Previous retrospective studies have suggested that removal of $\geq$6 LNs can improve risk stratification and staging quality.[6,7]

In the context of these new LN sampling guidelines, the goal of this study was to provide an external validation of the new AJCC 8 for GBC using a large national cancer database and evaluate its new lymphadenectomy guideline of removing at least six LNs. Our hypothesis was that while the new AJCC 8 would provide improved prognostication over AJCC 7 for resected GBC, the majority of patients would not meet the new lymphadenectomy guideline of $\geq$6 LNs.

Patients and methods

Data source

This study was granted an exemption by The University of Texas MD Anderson Cancer Center institutional review board because it utilized a publicly available deidentified patient dataset. This was a retrospective analysis using the National Cancer Data Base (NCDB), which is a nationwide oncology outcomes database jointly sponsored by American College of Surgeons Commission on Cancer and the American Cancer Society.[8] As of 2016, NCDB captures more than 70% of all cancer cases in the United States and has more than 34 million patient records, which makes it the largest clinical oncology database in the world. The available variables in the NCDB have been described by Boffa *et al*.[9] The specific GBC/biliary cancer NCDB participant user file 2014 was obtained by the principal investigator after a formal application process.

Study cohort

There were a total of 29,893 GBC patients in the NCDB between 2004 and 2014. Of those, we identified adenocarcinoma patients utilizing histology codes 8140, 8480, and 8481. We only included patients who underwent resection of their GBC, defined by simple surgical removal of primary site, total surgical removal of primary site, grossly positive margin resection (labeled "debulking" in NCDB), and radical surgery. Although we had surgical data on patients up to calendar year 2014, we excluded patients diagnosed in 2014, due to limited follow-up, as well as patients with missing survival data. Patients with missing tumor and LN variables were excluded. Because we wanted to examine the frequency of lymphadenectomy, we included patients who were categorized "Nx" in our overall cohort. After excluding five patients who were not staged with AJCC sixth edition (AJCC 6) or AJCC 7, we had 10,559 patients in our overall cohort. (Fig. 1).

During survival analysis, we excluded Nx patients as having incomplete staging information. In addition, we excluded patients who were staged using AJCC 6 due to discrepancy in N-staging rules between AJCC 6 and AJCC 7. In AJCC 6, N stage was defined as either N0 or N1, with N1 for hilar, celiac, periduodenal, peripancreatic, and superior mesenteric nodes. AJCC 6 N1 stage was regionally divided into N1 and N2 in the AJCC 7. It is not possible to covert the AJCC 6 cohort to AJCC 7 due to lack of granular surgical anatomical information in the NCDB. Therefore, 3354 patients were included in our survival analysis according to AJCC 7 using available staging information in the NCDB. We then reclassified patients according to AJCC 8, utilizing the available lymphadenectomy variables in NCDB. We utilized the participant user file data items "REGIONAL-NODES_EXAMINED" and "REGIONAL_NODES_-POSITIVE" to define N stage for our cohort according to AJCC 8. Codes 01-89 defined the number of LNs that were examined or positive. During the conversion to AJCC 8, 554 patients were excluded for N stage discrepancy (e.g., categorized as N0 in NCDB but not having any LNs examined and therefore Nx), which left us with 2800 patients who were restaged according to AJCC 8 (Fig. 1). Currently, the NCDB does not provide data on the tumor location within the gallbladder (peritoneal *versus* hepatic surface), which precludes further stratification of T2a *versus* T2b as defined in AJCC 8.

For our lymphadenectomy analysis, we excluded 813 patients from our overall cohort, who had less than T1b disease because lymphadenectomy is only required for patients with $\geq$T1b disease. Therefore, 9746 patients were included in our final lymphadenectomy analysis (Fig. 1).