Original Article

External validation of the 8th American Joint Committee on Cancer staging system for gall bladder carcinoma

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Background: To validate the changes within the American Joint Committee on Cancer (AJCC) 8th staging system for gall bladder carcinoma compared to AJCC 7th staging system.

Methods: Surveillance, Epidemiology and End Results (SEER) database [2004–2014] was queried. Kaplan-Meier survival analyses and Log-rank testing were assessed according to both AJCC 7th and 8th staging systems. Likewise, Cox cancer-specific hazard ratio was evaluated according to both staging systems.

Results: Overall survival was assessed according to the two staging systems; and P values for overall trend (log/rank test) were significant (P<0.001) for both scenarios. Cox regression cancer-specific hazard adjusted for age, gender, histology, gender and surgery was evaluated according to the two staging systems. According to AJCC 7th staging system, the following pair wise hazard ratio comparisons were significant (II *vs.* IIIA; IIIB *vs.* IVA; IVA *vs.* IVB). According to AJCC 8th staging system, the following pair wise hazard ratio comparisons were significant (II *vs.* IIIA; IVA *vs.* IVB). C-statistic was assessed using death from gall bladder carcinoma as the dependent variable; and the findings for the two staging systems were as follows: AJCC 7th staging system: 0.684 (SE: 0.008; 95% CI: 0.667–0.701); AJCC 8th staging system: 0.682 (SE: 0.009; 95% CI: 0.665–0.698).

Conclusions: There is a comparable discriminatory performance for AJCC 8th staging system compared to AJCC 7th staging system. Change form location-based to number-based N category assessment does not improve the overall prognostic performance of the staging system.

Keywords: Gall bladder carcinoma; Surveillance, Epidemiology and End Results (SEER); biliary tract cancer; staging; prognosis

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Introduction

Although gall bladder is generally considered a rare malignancy, it is the most common malignant tumor of the biliary tract (accounting for approximately 80% of total biliary tract cancers) (1). Multiple risk factors were reported in association with gall bladder carcinoma including: gall stones and female sex (2). Moreover, it is far more common in Southeast Asia compared to other parts of the world (3). Although gall bladder carcinoma has been traditionally grouped with other biliary tract cancers, numerous epidemiological, molecular and clinical studies suggest that gall bladder carcinoma is a distinct tumor entity (4).

Treatment paradigms for gall bladder carcinoma

Table 1 Comparisons of the different staging definitions among AJCC 7th and 8th editions

Stage	AJCC 7th	AJCC 8th
I	I: T1N0M0	I: T1N0M0
II	II: T2N0M0	IIA: T2aN0M0 IIB: T2bN0M0
III	IIIA: T3N0M0	IIIA: T3N0M0
	IIIB: T1–3N1M0	IIIB: T1–3N1M0
IV	IVA: T4N0–1M0	IVA: T4N0–1M0
	IVB: any T N2 M0	IVB: any T N2 M0
	Any T any N M1	Any T any N M1

The AJCC 8th provided revised definitions for some TNM stages as follows: T2a, tumor invades perimuscular connective tissue on the peritoneal side without involvement of the serosa; T2b, tumor invades perimuscular connective tissue on the hepatic side without involvement of the liver; N staging, change from location-based to number-based; N1, 1–3 regional lymph nodes; N2, 4 or more regional lymph nodes. AJCC, American Joint Committee on Cancer.

incorporated multiple considerations; these include: mode of presentation, stage of the disease, as well as background medical profile (e.g., co-morbidity and age) (5).

Numerous staging systems were employed for gall bladder carcinoma. The most common staging system is American Joint Committee on Cancer (AJCC) staging system. Successive editions of the AJCC staging system were published, reflecting our increased understanding of the prognosis and treatment approaches for gall bladder carcinoma. The most recent edition of the AJCC staging system is the 8th edition which was published in late 2016. Compared the 7th AJCC, the 8th AJCC updates some T and N. For example, T2 stage is sub-divided into T2a and T2b according to the side of involvement (peritoneal *vs.* hepatic). This change was based on an international multicentre study which proved the prognostic utility of the side of involvement (6). Likewise, N stage is now categorized according to the number of positive lymph nodes rather than the location of positive lymph nodes. AJCC 8th provides also a revised definition of some sub-stages within stage II, III and IV (7). *Table 1* provides a summary of the different stage definitions according to both AJCC 7th and 8th.

The current study tries to validate the performance of the AJCC 8th staging system in a population-based setting. This is done through assessment of the outcomes of gall bladder carcinoma patients included in the Surveillance, Epidemiology and End Results (SEER) database. This validation is done in comparison to AJCC 7th staging system. We selected the SEER database because of its broad coverage and rigorous quality program.

Methods

Objective

To assess the performance of the AJCC 8th staging system compared to the AJCC 7th staging system among patients with gall bladder carcinoma.

Methodology

The SEER-18 registry (with added treatment descriptors) was accessed through the SEER*stat, version (8.3.4) in order to collect eligible records (8).

The current study search was restricted to the period from 2004–2014 (because data about tumor extension were not adequately available in the SEER dataset before 2004). The study population was further limited to those with an ICD-O-3/WHO 2008 disease category of "gall bladder". Patients with inadequate information about primary tumor extension, nodal or distant metastases were not selected. Because nodal staging of the AJCC 8th system relies upon number of positive lymph nodes, patients who did not undergo lymph node surgery and evaluation were not included.

For each record, the following data were collected: age (at diagnosis), gender, race, histology, tumor extension, nodal or distant metastases, radiotherapy, chemotherapy, and surgery, cause of death (if applicable), survival months and vital status. Chemotherapy and radiotherapy information in the SEER database were not detailed enough to be elaborated into survival analysis. AJCC 7th and AJCC 8th stages were constructed through incorporation of basic information about tumor, node and metastases. Because SEER database did not include information about whether the peritoneal or hepatic side of the perimuscular connective tissue was involved, it was not possible to divide stage II into stage IIA or stage IIB. Information about performance and co-morbidities were not available in the SEER dataset.

Statistical considerations

Kaplan-Meier analysis and log-rank testing were then used for comparisons of overall survival according to both the

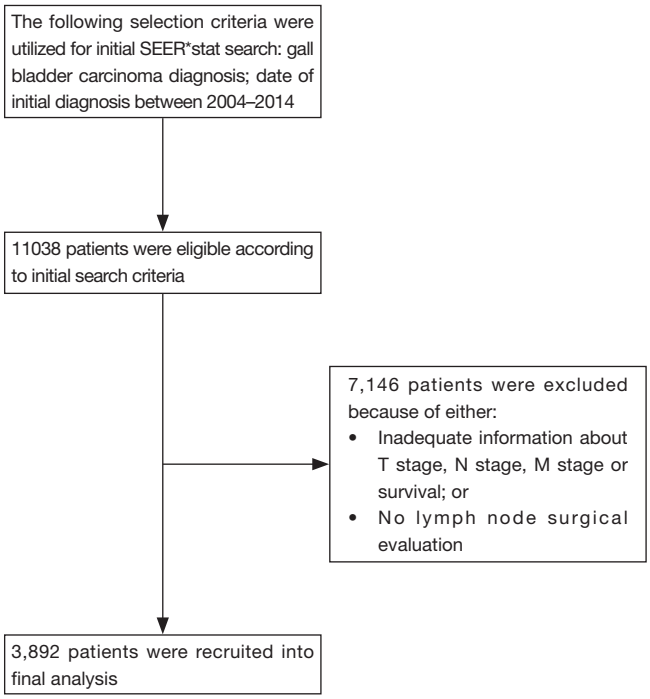


Figure 1 Flow chart of the selection process of the studied cohort.

AJCC 7th and AJCC 8th staging systems. Cox cause-specific hazard with pair wise hazard ratio comparisons were evaluated for the two staging systems (using death from gall bladder carcinoma as the event of interest). Cox hazard ratio calculations were adjusted for age, gender, histology, race and surgical treatment.

C-statistic (concordance index) was then conducted to assess the discriminatory ability of the two staging systems in predicting gall bladder carcinoma-specific mortality. A two-tailed P value <0.05 was required to confirm statistical significance. The statistical analyses were performed using SPSS Statistics 20.0 (IBM, NY, USA).

Results

Figure 1 shows the selection process for included patients in the current study. A total of 3,892 patients with gall bladder carcinoma diagnosed in the period from 2004–2014 were included into the study. Distribution of patients according to AJCC 7th and 8th staging systems was summarized. Other baseline characteristics (including age, gender, race, histology, and received treatments) were detailed in *Table 2*. Detailed technical information about radiotherapy or chemotherapy was not available. Mean follow up time was 20 months and follow up period ranged from 1 to 130 months.

Overall survival was assessed according to the two editions of the staging system; and P values for overall trend (log/rank test) were significant (P<0.001) for both scenarios (*Figure 2A,B*).

Cox regression cancer-specific hazard (using death from gall bladder carcinoma as the event of interest) adjusted for age, gender, histology, gender and surgery was evaluated according to the two staging systems (*Figure 3A,B*). According to AJCC 7th staging system, the following pair wise hazard ratio comparisons were significant (II *vs.* IIIA; IIIB *vs.* IVA; IVA *vs.* IVB). According to AJCC 8th staging system, the following pair wise hazard ratio comparisons were significant (II *vs.* IIIA; IVA *vs.* IVB).

C-statistic was assessed using death from gall bladder carcinoma as the dependent variable; and the findings for the two staging systems were as follows: AJCC 7th staging system: 0.684 (SE: 0.008; 95% CI: 0.667–0.701); AJCC 8th staging system: 0.682 (SE: 0.009; 95% CI: 0.665–0.698).

Analysis of the subset of patients with more than five examined lymph nodes

In order to account for the impact of inadequate number of dissected lymph nodes on the validity of the analysis, an additional subset analysis on the category of patients with more than five dissected lymph nodes (728 patients) was conducted. The cutoff of at least six lymph nodes was obtained according to the guidance of AJCC 8th edition staging manual (7). A multivariate analysis for factors affecting cancer-specific survival was conducted (incorporating age, race, gender, histology, surgery, M status, lymph node location and number of positive lymph nodes). The following factors were associated with worse cancer-specific survival: M1 (P<0.0001) and age ≥69 years old (P=0.009).

C-statistic analysis was also done among the subset of patients with >5 lymph node dissected. It revealed the following C-statistic for AJCC 8th: 0.674 (SE: 0.021; 95% CI: 0.634–0.714); and for AJCC 7th: 0.675 (SE: 0.021; 95% CI: 0.635–0.716).

Discussion

The current study evaluated the newly proposed AJCC 8th staging system for gall bladder carcinomas compared to the AJCC 7th staging system. It showed that both staging systems have comparable discriminatory performance. Moreover, the adoption of a number-based N category

Table 2 Baseline characteristics of included patients in the study (3,892 patients)

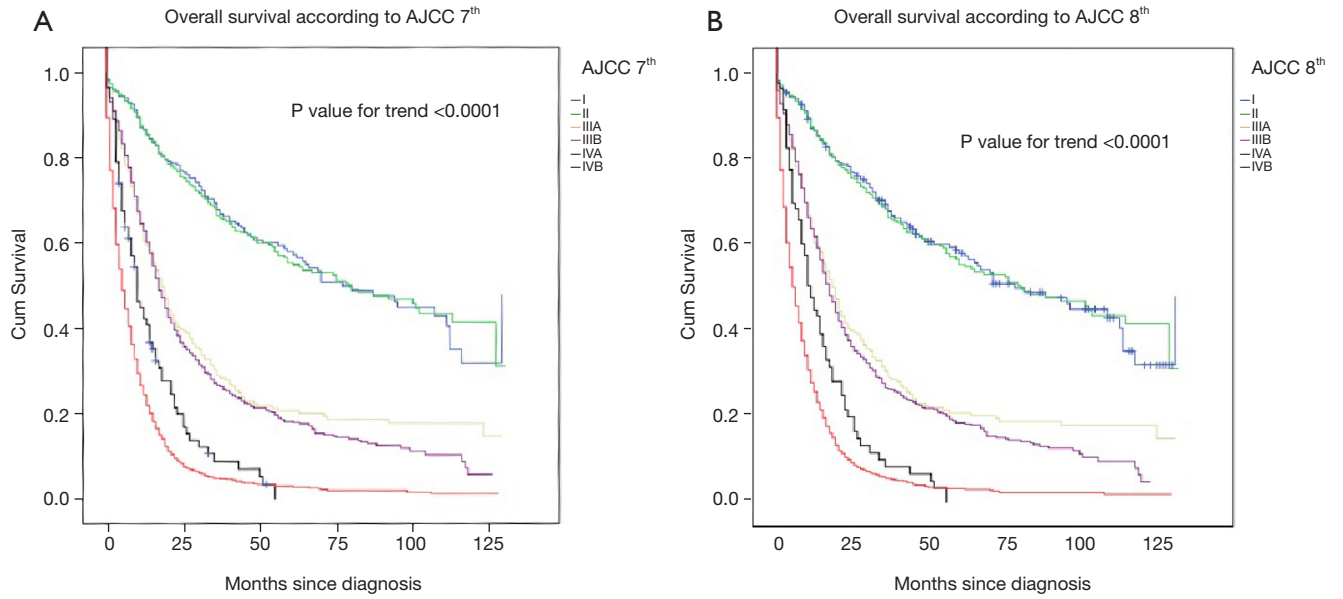
Parameter	Number (%)
Age, years	
<40	63 (1.6)
40–69	1,989 (51.1)
>69	1,840 (47.3)
Race	
White	3,016 (77.5)
Black	462 (11.9)
Others	407 (10.5)
Unknown	7 (0.2)
Gender	
Male	1,153 (29.6)
Female	2,739 (70.4)
Histology	
Adenocarcinoma, NOS	2,913 (74.8)
Other variants	979 (25.2)
Surgical treatment	
Radical surgery	3,044 (78.2)
No radical surgery	848 (21.8)
Chemotherapy	
Yes	1,575 (40.5)
No/unknown	2,317 (59.5)
Radiotherapy	
Yes	798 (20.5)
No/unknown	3,094 (79.5)
AJCC stage groups 7th edition	
I	319 (8.2)
II	648 (16.6)
IIIA	339 (8.7)
IIIB	1,007 (25.9)
IVA	82 (2.1)
IVB	1,497 (38.5)
AJCC stage groups 8th edition	
I	319 (8.2)
II	648 (16.6)
IIIA	339 (8.7)
IIIB	977 (25.1)
IVA	81 (2.1)
IVB	1,528 (39.3)
Distant metastases**	
Bone	29
Brain	6
Liver	395
Lung	41

**, for patients diagnosed starting from 2010. AJCC, American Joint Committee on Cancer.

assessment in the 8th edition (compared to a location-based N category assessment) did not improve the overall discriminatory performance of the staging system.

A number of population-based studies were recently published in order to establish the best N category assessment approach. Overall, they showed that a number-based may provide a better assessment of N category (provided an adequate number of lymph nodes were dissected) (9-12). Some of them also suggested that lymph node ratio may play an important role in N category assessment.

Potential weaknesses in this analysis include the fact that information about co-morbidities as well as performance score was absent; therefore, the analysis was performed for both overall and cancer-specific survival to mitigate any confounding effect resulting from non-cancer death. Likewise, there are insufficient systemic ad radiation treatment details in the evaluated dataset; therefore, treatment factors could not be integrated in survival analysis. Similarly and as noted above, the SEER database did not include the information of gall bladder carcinoma invasions to the peritoneal or hepatic side; thus stage II patients in this study could not be sub-grouped into stage IIA or stage IIB. Additionally, the total number of patients in the current analysis is relatively small. Although this is understandable given the rarity of the disease, this might still have affected the outcomes. Moreover and given the fact that SEER data are usually derived from multiple



Number at risk	0 months	50 months	100 months	150 months
I	319	189	48	0
II	648	386	83	0
IIIA	339	166	37	0
IIIB	1007	524	123	0
IVA	82	44	6	0
IVB	1497	633	120	0

Number at risk	0 months	50 months	100 months	150 months
I	319	189	48	0
II	648	386	83	0
IIIA	338	166	37	0
IIIB	978	510	119	0
IVA	81	43	7	0
IVB	1528	648	123	0

Figure 2 Kaplan-Meier curve of overall survival according to: (A) AJCC 7th staging system; (B) AJCC 8th staging system. AJCC, American Joint Committee on Cancer.

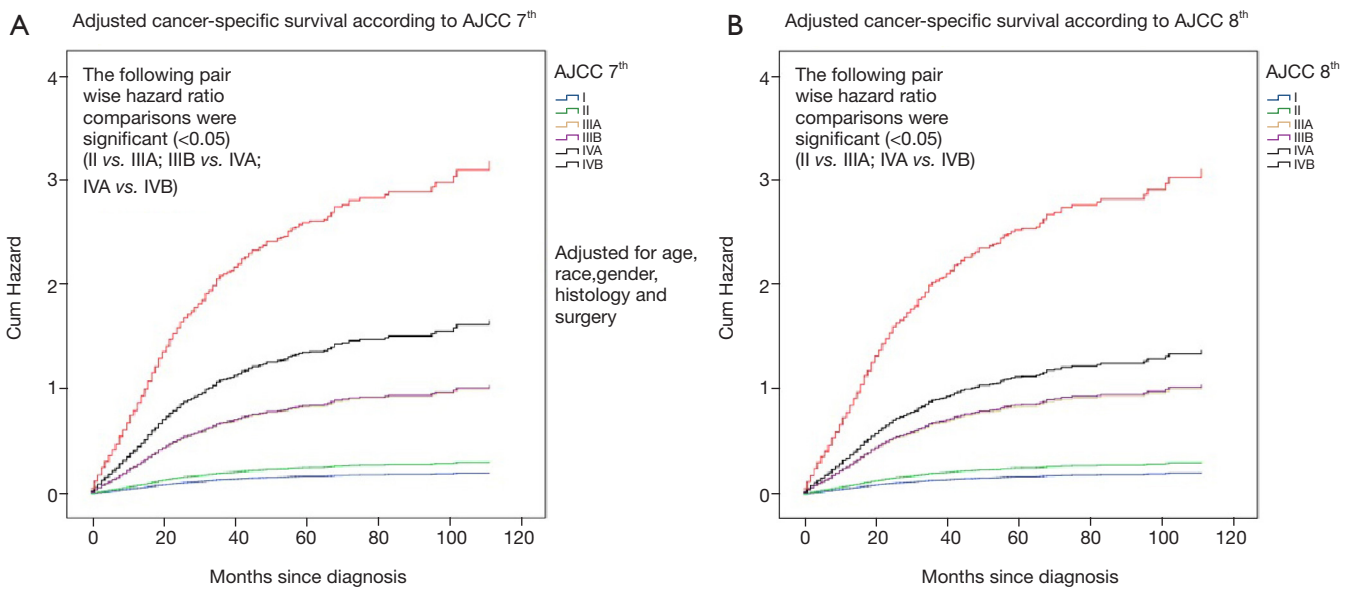


Figure 3 Cox cancer-specific hazard plot according to: (A) AJCC 7th staging system; (B) AJCC 8th staging system. AJCC, American Joint Committee on Cancer.

institutes, the surgeons' performance and professional skill are expected to be heterogeneous and this might have affected the outcomes of the analysis.

The change of the method of N category assessment (from location-based to number-based) would mean there should be a minimum number (more than three) for the dissected regional lymph nodes in order to ensure proper nodal staging.

In order to confirm that the results of the current analysis are applicable to radically resected patients, the analysis was repeated for patients with more than five examined lymph nodes and the results were similar to the overall cohort.

Although the current analysis provides an insight into the performance of the AJCC staging system among patients who underwent radical surgery, it stands short of assessing patients who were diagnosed following biopsy only or following incidental histological discovery of adenocarcinoma in cholecystectomy specimens. A number of interventions were suggested to improve the staging of those patients. These include thorough staging laparoscopy as well as second radical resection following incidental histological diagnosis (13,14).

A plethora of recent studies suggested that molecular and gene expression profiling may play an important role in prognostication and treatment selection for gall bladder cancer (15,16). Given the recent interest of AJCC staging systems in gene expression profiling in some solid tumors (e.g., breast cancer), these molecular signatures might prove useful for the staging algorithm for gall bladder cancer and might be introduced at a later version of the AJCC.

In conclusion, there is a comparable discriminatory performance for AJCC 8th staging system compared to AJCC 7th staging system. Change form location-based to number-based N category assessment does not seem to improve the overall prognostic performance of the AJCC staging system.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This article does not contain any studies with human participants or animals performed by the authors. As this study is based on a publicly available database without identifying patient information, informed consent was not needed.

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