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Original Article

Different patterns in the prognostic value of age for bladder cancer-specific survival depending on tumor stages

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Abstract: To compare the pathological features and long-term survival of bladder cancer (BCa) in young patients with elderly counterparts. Using the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) population-based data, we identified 93115 patients with non-metastatic bladder cancer diagnosed between 1988 and 2003. Patients were categorized into young (50 years and under) and elderly groups (over 50 years of age). The overall and five-year bladder cancer specific survival (BCSS) data were obtained using Kaplan-Meier plots. Multivariable Cox regression models were built for the analysis of long-term survival outcomes and risk factors. There were significant differences between the two groups in primary site, pathologic grading, histologic type, AJCC stage ($p<0.001$). The overall and 5-year cancer specific survival rates were 88.1% and 90.8% in young group, 64.8% and 81.3% in elderly group, which had significant difference in both univariate and multivariate analysis ($p<0.001$). Further analysis showed this significant difference existed across all the AJCC stage patients. The study findings show different patterns in the prognostic value of age for determining BCSS, depending on the tumor stages. Compared with elderly patients, young patients with bladder cancer surgery appear to have unique characteristics and a higher overall and cancer specific survival rate.

Keywords: Prognostic value, age, survival, bladder cancer

Introduction

Bladder cancer (BCa) is the 7th most common malignant cancer in men and the 17th in women, and is ranked as the second most common cancers in the urologic field [1, 2]. The highest rates of BCa were reported in Europe, Australia and North America [3]. In the year 2012, 73,510 BCa cases were expected to occur and nearly 14,880 will die from this cancer [4]. In 2013, an estimated 72,570 adults in the United States were diagnosed with BCa [4]. Approximately 70% to 80% of newly diagnosed BCa patients are non-muscle-invasive. Among of these patients, an estimated 50% to 70% cases had a high rate of recurrence and progression [5, 6]. Transitional cell carcinoma accounts for about 90% of BCa, histologically, the less common types are squamous cell carcinoma (3-5%) and adenocarcinoma (0.5 to 2%) [7]. This malignancy exhibits a remarkable gender disparity in male patients than women [8]. Therefore, the prevalence of BCa places a major economic burden on global health care systems.

Smoking, dietary factors, genetic susceptibility, occupational exposure to carcinogens, and infection with schistosomiasis are the established causal risk factors for bladder cancer, as well as age [2, 9, 10]. In many solid tumors, age has a prognostic implication, such as liver cancer (LC) [11-13], colorectal cancer (CRC) [14, 15]. Regarding BCa, various studies have reported that elderly BCa patients have higher mortality than younger ones [16, 17]. However, some studies have argued that while young BCa patients have unfavorable clinicopathologic characteristics, the natural history of BCa in the younger groups resembles that in elder patients [18, 19]. Most studies on BCa are limited sample sizes or single-institution experiences. To further clarify the issue of age on BCa prognosis, we used data from the Surveillance, Epidemiology and End Results (SEER) registries to analysis age role on BCa long time survival after surgery.

Table 1. Characteristics of Patients from SEER Database by age

	Total	Young Group	Elderly Group	*p* value
Characteristic	93115	8193	84922	
Media follow up (mo)		142	95	P<0.001
(IQR)		104-193	34-135	
Years of diagnosis				0.049
1988-1993	22566	2022	20544	
1994-1999	28464	2573	25891	
2000-2003	42085	3598	38487	
Sex				0.917
Male	70807	6234	64573	
Female	22308	20349	22308	
Race				P<0.001
Caucasian	84699	7194	77505	
African American	4375	553	3822	
Others*	4041	446	3595	
Primary site				P<0.001
Trigone of bladder	5643	542	5101	
Dome of bladder	3352	238	3114	
Lateral wall of bladder	20293	1942	18351	
Anterior wall of bladder	1710	116	1594	
Posterior wall of bladder	8392	660	7732	
Bladder neck	2715	232	2483	
Ureteric orifice	4612	572	4040	
Urachus	136	54	82	
Overlapping lesion of bladder	11261	790	10471	
Bladder, NOS	35001	304	31954	
Pathological grading				P<0.001
High/Moderate	50438	5479	44959	
Poor/undifferentiation	35948	2092	33856	
Unknown	6729	622	6107	
Histological Type				P<0.001
squamous cell carcinoma	1213	115	1098	
Transitional cell carcinoma	90949	7905	83044	
Adenocarcinoma	953	173	780	
AJCC Stage				P<0.001
I	70827	6662	64165	
II	7172	399	6773	
III	4922	321	4601	
IV	7532	564	6968	
unstaged	2662	24	2415	

*including other (American Indian/AK Native, Asian/Pacific Islander) and unknowns.

Materials and methods

Ethics statement

Our study was approved by an independent ethical committee/institutional review board of Bayi Hospital, Nanjing, China. The data released by the SEER database do not require informed patient consent because cancer is a reportable disease in every state of the United States. And patient records/information was anonymized and de-identified prior to analysis.

Patients

The SEER Cancer Statistics Review (http://seer.cancer.gov/data/citation.html), a report on the most recent cancer incidence, mortality, survival, prevalence, and lifetime risk statistics, is published annually by the Data Analysis and Interpretation Branch of the National Cancer Institute, (Bethesda, MD, USA). The current SEER database consists of 17 population-based cancer registries that represent approximately 26% of the population in the United States. SEER data contain no identifiers and are publicly available for studies of cancer-based epidemiology and survival analysis.

Cases of invasive bladder cancer (C67.0-67.9) diagnosed between 1998 and 2005 were extracted from the SEER database (SEER*Stat 8.1.5) according to the Site Recode Classifications. Histological type were limited to squamous cell carcinoma (8052/3, 8070/3, 8071/3, 8072/3, 8074/3), transitional cell carcinoma (8120/3, 8122/3, 8130/3, 8131/3), and adenocarcinoma (8140/3, 8310/3, 8480/3, 8481/3, 8255/3, 8260/3). Only patients who underwent surgery with an age at diagnosis of between 18 and 85 years were included. Patients diagnosed after 2006 were excluded to ensure an adequate follow-up time. Other exclusion criterions were as follows: incomplete staging, distant metastasis (M1), no evaluation of histological type, or follow up. Adjuvant chemotherapy was not evaluated as the SEER registry does

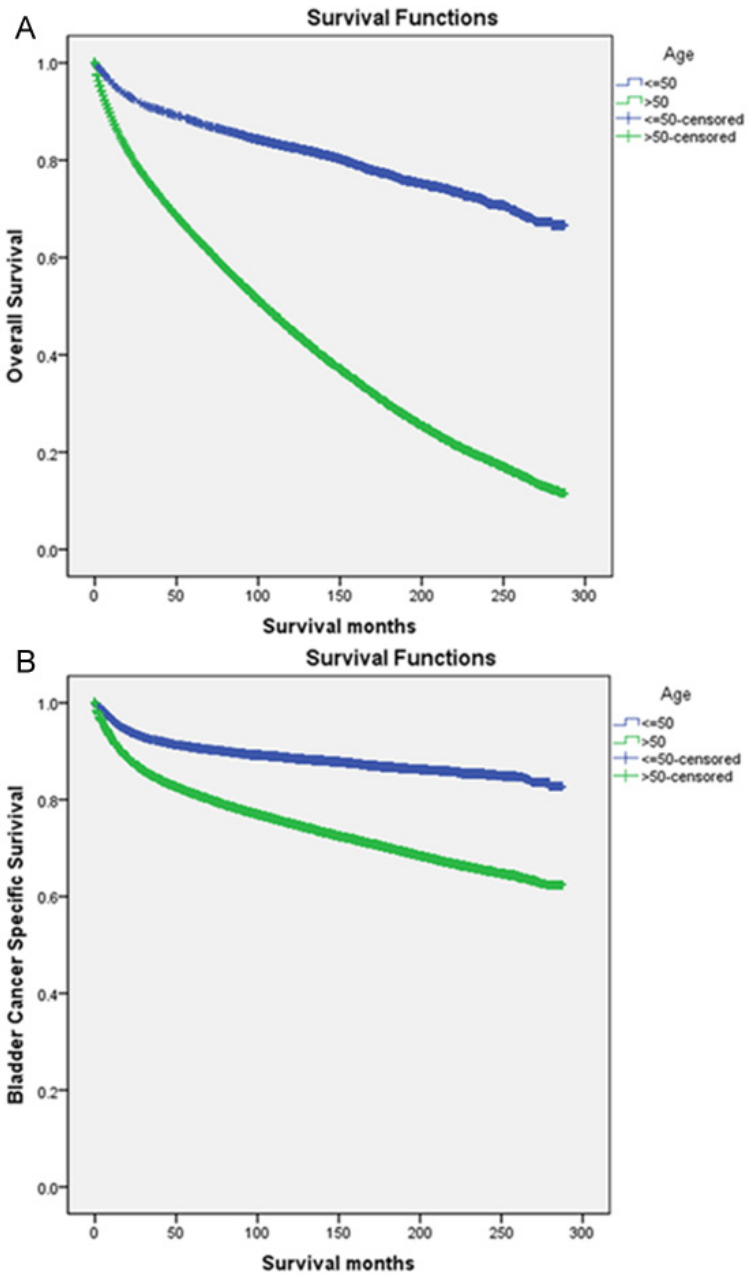

Figure 1. Survival curves in BCa patients according to different age groups. A: Bladder cancer-specific survival. Young group vs. Elderly group, χ^2=820.938, p<0.001. B: The overall survival. Young group vs. Elderly group, χ^2=4670.049, p<0.001.

not include this information. The primary endpoint of the study is BCSS, which was calculated from the date of diagnosis to the date of cancer specific death. Deaths were treated as events and deaths from other causes were treated as censored observation.

This study was based on public data from the SEER database; we obtained permission to access research data files with the reference number 13526-Nov2013.

Statistical analysis

The association of age (young and elderly) with clinicopathological parameters was analyzed by the chi-squared (χ^2) test. Continuous variables were analyzed using the Student's t-test. Survival curves were generated using Kaplan-Meier estimates; differences between the curves were analyzed by log-rank test. Multivariable Cox regression models were built for analysis of risk factors for survival outcomes. All statistical analyses were performed using the statistical software package SPSS for Windows, version 17 (SPSS Inc., Chicago, IL, USA). Results were considered statistically significant when a two-tailed test of a *p*-value of less than 0.05 was achieved.

Results

Patient characteristics

We identified 93115 eligible patients with BCa during the 15-year study period (between 1988 and 2003) in the SEER database. There were 70807 (76.04%) males and 22308 (23.96%) females. The median age was 43 in the younger age group and 70 in the older age group. The median follow-up period was 99 months. Patient demographics and pathologic features are summarized in **Table 1**.

Clinicopathological differences between groups

As shown in **Table 1**, there were significant differences observed between the two groups. Compared with the older age group, the younger age group demonstrated differences with regards to the calendar years of diagnosis (more frequent in 2000-2003, p<0.001), race

Table 2. Univariate survival analyses of BCa patients according to various clinicopathological variables

Variable	n	5-year BCSS (%)	Log rank χ^2 test	P
Years of diagnosis			15.872	P<0.001
1988-1993	22566	82.7%		
1994-1999	28464	82.6%		
2000-2003	42085	81.7%		
Sex			132.693	P<0.001
Male	70807	83.4%		
Female	22308	76.8%		
Age			820.938	P<0.001
≤50	8193	90.8%		
>50	84922	81.3%		
Race			608.618	P<0.001
Caucasian	84699	82.8%		
African American	4375	68.5%		
Others*	4041	83.6%		
Primary site			1868.737	P<0.001
Trigone of bladder	5643	82.2%		
Dome of bladder	3352	77.5%		
Lateral wall of bladder	20293	88.3%		
Anterior wall of bladder	1710	76.3%		
Posterior wall of bladder	8392	86.4%		
Bladder neck	2715	77.5%		
Ureteric orifice	4612	91.2%		
Urachus	136	62.1%		
Overlapping lesion of bladder	11261	72.0%		
Bladder, NOS	35001	80.8%		
Pathological grading			10828.094	P<0.001
High/Moderate	50438	93.5%		
Poor/undifferentiation	35948	65.8%		
Unknown	6729	82.2%		
Histological Type			3403.630	P<0.001
Squamous cell carcinoma	1213	34.6%		
Transitional cell carcinoma	90949	83.1%		
Adenocarcinoma	953	53.8%		
AJCC Stage			35834.452	P<0.001
I	70827	92.4%		
II	7172	60.1%		
III	4922	51.1%		
IV	7532	25.4%		
unstaged	2662	74.2%		

*including other (American Indian/AK Native, Asian/Pacific Islander) and unknowns.

(less frequent in Caucasians, p<0.001), primary site (more frequent in bladder, NOS, p<0.001), pathologic grade (less high/moderate in grade, p<0.001), histologic type (more frequent in adenocarcinoma, p<0.001), stage (less stage I, p<0.001). As regard to sex (p=0.917), no significant differences between two groups were found.

Impact of age on BCa survival outcomes

The overall 5-year survival was 88.1% in young group and 64.8% in elderly group, which had significant difference (p<0.001) (**Figure 1A**). And the univariate log-rank test showed that the overall 5-year bladder cancer specifi survival (BCSS) was 90.8% and 81.3% in the younger and elderly groups, respectively (**Figure 1B**). Moreover, an latter year of diagnosis (2000-2003), female, African-American race, urachus, poor /undifferentiated grade, squamous cell carcinoma, higher AJCC stage (p<0.001), were regarded as significant risk factors for a poorer prognosis by univariate analysis (**Table 2**). Multivariate analysis was also performed by the Cox regression model. The following eight factors were found to be independent prognostic factors (**Table 3**), including year of diagnosis (1994-1999, hazard ratio (HR) 1.007, 95% confidence interval (CI) 0.971-1.045; 2000-2003, HR 1.053, 95% CI 1.017-1.090), gender (female, HR 1.444, 95% CI 1.370-1.522), age (>50, HR 2.222, 95% CI 2.084-2.368), race (African-American, HR 1.444, 95% CI 1.370-1.522; others, HR 0.818, 95% CI 1.763-0.878), primary site (dome of bladder, HR 0.870, 95% CI 0.798-0.949; lateral wall of bladder, HR 0.781, 95% CI 0.732-0.834; anterior wall of bladder, HR 0.908, 95% CI 0.817-1.010; posterior wall of bladder, HR

Table 3. Multivariate Cox model analyses of prognostic factors of BCa

Variable	Hazard Ratio	95% CI	P
Years of diagnosis			0.004
1988-1993	1		
1994-1999	1.007	0.971-1.045	
2000-2003	1.053	1.017-1.090	
Sex			P<0.001
Male	1		
Female	1.444	1.370-1.522	
Age			P<0.001
≤50	1		
>50	2.222	2.084-2.368	
Race			P<0.001
Caucasian	1		
African American	1.444	1.370-1.522	
Others*	0.818	1.763-0.878	
Primary site			P<0.001
Trigone of bladder	1		
Dome of bladder	0.870	0.798-0.949	
Lateral wall of bladder	1.781	0.732-0.834	
Anterior wall of bladder	0.908	0.817-1.010	
Posterior wall of bladder	0.817	0.758-0.881	
Bladder neck	1.022	0.933-1.120	
Ureteric orifice	0.789	0.716-0.869	
Urachus	0.921	0.700-1.211	
Overlapping lesion of bladder	1.056	0.990-1.127	
Bladder, NOS	1.022	0.963-1.085	
Pathological grading			P<0.001
High/Moderate	1		
Poor/undifferentiation	2.216	2.138-2.297	
Unknown	1.758	1.658-1.864	
Histological Type			P<0.001
squamous cell carcinoma	1		
Transitional cell carcinoma	0.447	0.415-0.482	
Adenocarcinoma	0.595	0.527-0.671	
AJCC Stage			P<0.001
I	1		
II	2.935	2.806-3.069	
III	3.532	3.363-3.710	
IV	8.190	7.878-8.514	
unstaged	2.227	2.063-2.403	

*including other (American Indian/AK Native, Asian/Pacific Islander) and unknowns.

0.817, 95% CI 0.758-0.881; bladder neck, HR 1.022, 95% CI 0.933-1.120; ureteric orifice, HR 0.789, 95% CI 0.716-0.869; urachus, HR 0.921, 95% CI 0.700-1.211; overlapping lesion of bladder, HR 1.056, 95% CI 0.990-1.127; bladder, NOS, HR 1.022, 95% CI 0.963-1.085), pathologic grading (poor/undifferentiated, HR 2.216, 95% CI 2.138-2.297), histological type (transitional cell carcinoma, HR 0.447, 95% CI 0.415-0.482; adenocarcinoma, HR 0.595, 95% CI 0.527-0.671), AJCC stage (stage II, HR 2.935, 95% CI 2.806-3.069; stage III, HR 3.532, 95% CI 3.363-3.710; stage IV, HR 8.190, 95% CI 7.878-8.514).

Stratified analysis of age on cancer survival based on different stages

We further analyzed of age on 5-year BCSS in different stages. The univariate analysis of age on BCSS showed that younger patients had an better 5-yearBCSS than elderly patients across several subgroups (**Table 4**). Multivariate Cox regression analyses were performed for different stages; age was validated as an independent predictor of survival in these AJCC stages (p=0.302) (**Table 5**).

Discussion

The prognosis between the younger and their elderly counterparts are controversial, as well as the definition of young BCa patients. The inconsistent data may due to the heterogeneity among these studies. Despite some studies defined the young BCa patients as less than 40 years [20, 21], while a cutoff of younger than age 70 also has been used in other studies [22, 23]. However, BCa is uncommon below the age of 50 [24], and the Polish National Cancer Registry data showed that only 48 cases were found in patients aged below 40 years and 191 cases in patients aged 40-49 years in 5820 newly diagnosed bladder cancers in Poland [25]. Since lack of a unified standard definition makes it difficult to make meaningful comparisons between different studies. We defined 50 years as the cutoff for younger age, as most studies reported. In our study, the proportion of

Table 4. Univariate analysis of Age on BCSS based on different stages

Variable	n	5-year BCSS (%)	Log rank χ^2 test	P
I				
Age			679.830	P<0.001
≤50	6662	97.8%		
>50	64165	91.8%		
II				
Age			65.849	P<0.001
≤50	399	80.3%		
>50	6773	58.8%		
III				
Age			28.332	P<0.001
≤50	321	63.8%		
>50	4601	50.2%		
IV				P<0.001
Age			20.080	
≤50	564	30.8%		
>50	6968	24.9%		

Table 5. Multivariate Cox model analyses of prognostic factors of BCa on different stages

Variable	Hazard Ratio	95% CI	P
I			
Age			P<0.001
≤50	1		
>50	3.451	3.093-3.850	
II			
Age			P<0.001
≤50	1		
>50	2.168	1.787-2.629	
III			
Age			P<0.001
≤50	1		
>50	1.545	1.289-1.852	
IV			P<0.001
Age			
≤50	1		
>50	1.321	1.191-1.466	

P values were adjusted for years of diagnosis, sex, age, race, primary site, pathological grading, histological type, AJCC Stage as covariates between the two groups.

elderly patients with BCa accounted for almost 90% from the year of 1988-1993 to the year of 2000-2003, which was consistent with the epidemiological features.

Age is now widely accepted as a strong and independent risk factor of BCa. This cancer is primarily considered a disease of the middle-aged and elderly. However, various studies have reported that age plays a paradoxical role in many solid cancers. Elderly patients with breast and gastric cancer have a better prognosis than young ones [26, 27]. Conversely, Cho et al. demonstrated that young HCC patients had a poorer survival rates than elderly patients [28]. Regarding the biological and clinical aggressiveness of BCa in young and elderly patients, the results are still inconclusive. Linn et al. and Fitzpatrick et al. demonstrated that when compared to elderly patients, young patients less than 40 years of age presented with well differentiated lesions and present a more indolent manner [17, 29]. Similar results were reported by Resorlu et al. [30]. It is well known that transitional cell carcinoma and highly differentiated tumors tend to have a better prognosis compared to poorly and undifferentiated tumors. Our study showed that the younger group had a better overall and 5-year BCSS than the older age group. 5-year BCSS of squamous cell carcinoma, transitional cell carcinoma and adenocarcinoma was 34.6%, 83.1% and 53.8%, respectively. Squamous cell carcinoma was at extremely low rate.

Compared with the patients over 50 years of age, young BCa patients had a better 5-year BCSS across several stages. The results were confirmed by both univariate and multivariate analysis. A total of 8193 younger BCa patients and 84922 elderly ones were included in our study, the largest sample size up to now, which made our results more convincing. Differences in prognosis between the younger and their elderly counterparts might result from a combination of a relatively lower stage. Young patients have a better survival, which is compensated by the better overall function, faster postoperative recovery and the administration of more aggressive and effective therapies. Clinicians are more likely to gain all therapeutical options in young patients because of better tolerated toxicities associated with chemotherapy. Hence, to improve survival, aggressive treatment may be an option for younger BCa patients. We also verified the 5-year BCSS in the ureteric orifice was the highest among all the BCa (91.2%). And the cancer in the urachus had the lowest survival (62.1%).

Although our sample size is large, our study also has limitations. First, the SEER database only include the treatment information (e.g., surgery and radiotherapy), other detailed treatment information does not record, which makes further investigation regarding age and clinical outcome impossible. Second, this database also lacks BCa predisposing factors (e.g., smoking, dietary factors, occupational exposure to carcinogens). Thus, our analyses could not adjust for these potential confounding factors. Importantly, its retrospective nature rather than prospective may introduce biases of the analysis. Despite these potential limitations, our study was based on a large population and multiple centers, and has its convincing power.

In conclusion, our analysis shows that, compared to elderly patients, young patients with BCa aged 50 and below appears to have a higher BCSS after surgery. Future studies should pay more attention to this interesting phenomenon and clarify the underlying mechanism of age's effect on survival.

Disclosure of conflict of interest

None.

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