U-shaped relationship of age at diagnosis and cancer-specific mortality in primary urachal adenocarcinoma: a cohort study

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Background: To examine the association between age at diagnosis and cancer-specific mortality (CSM) in primary urachal adenocarcinoma.

Methods: The data was obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results program (SEER). A total of 393 patients were included in the study. Smooth curve fitting and two-piecewise Cox proportional hazards models were used to identify the nonlinearity between the age at initial diagnosis and cancer-specific survival rate. Survival time between different groups was compared using Kaplan-Meier survival curves and the log-rank test.

Results: Using smooth curve fitting we found that the relationship between age at diagnosis and cancer-specific survival takes on a U-shaped curve. The inflection point that we identified for the age at initial diagnosis was 60 years. The log-likelihood ratio test (P<0.05) indicated that the two-piecewise Cox regression model was more appropriate for fitting the correlation of age at diagnosis and CSM. The two-piecewise Cox regression model showed that when the age was <60 years, reduced risk of CSM was significantly associated with increased age (HR: 0.95, P=0.0002). Conversely, when age was >60 years, increased risk of CSM was significantly associated with increased age (HR: 1.05, P=0.0499).

Conclusions: In summary, our study suggested that the relationship between age at diagnosis and cancer-specific survival is nonlinear, and takes on a U-shaped curve. Both younger and older age at initial diagnosis age were associated with increased CSM.

Keywords: U-shaped curve, Primary Urachal Adenocarcinoma, cancer-specific mortality, surveillance epidemiology and end results

Introduction

Bladder cancer is the most common cancer of the urinary system, with urothelial carcinoma constituting greater than 90% of pathological types. Urachal cancer is a rare form of tumor associated with a high degree of malignancy, late staging and poor prognosis, accounting for approximately 0.2–0.5% of all malignant tumors of the bladder (1-3). Adenocarcinoma is the most common histological subtype of urachal carcinoma (4,5). Primary urachal adenocarcinoma has been rarely studied due to its low incidence. Case series provide most of the available evidence in the medical literature. It has previously been observed that several disease-specific factors (e.g., stage of the disease (1,5-7),

1074

Yu et al. U-shaped relationship of age and CSM

histologic subtype (6), presence of positive margins after surgery (8,9), pathological tumor grade (5,10), presence of positive lymph nodes and type of surgery (8) were closely related to the prognosis.

Age is known to be an important predictor in many tumors (11-14). However, the influence of age at diagnosis on outcomes in patients with primary urachal adenocarcinoma remains unclear. Ashley *et al.* analyzed the 50 years data from Mayo Clinic and concluded that older age was associated with malignant cell in a urachal mass (8). Wright *et al.* evaluated 151 patients in the National Cancer Institute's Surveillance, Epidemiology, and End Results program (SEER) database and demonstrated that age was not an independent prognostic factor in urachal adenocarcinoma (6).

Understanding the association of age at diagnosis and outcomes may not only have prognostic implications but may also have important therapeutic significances for the development of molecular targeted cancer therapy and personalized medicine (13). In our study, we evaluated data from a large, nationwide, population-based database to investigate the effect of age at initial diagnosis on cancer-specific mortality (CSM) of primary urachal adenocarcinoma patients. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tau-19-863).

Methods

We used a retrospective cohort study design. The data was obtained from the National Cancer Institute's SEER program, which includes approximately 28% of the U.S. population. We used the International Statistical Classifications of Diseases for Oncology, 3rd edition (ICD-O-3) site codes C677 and histology codes 8140–8147 and 8255–8490 to identify primary urachal adenocarcinoma. Additional inclusion criteria were as follows: (I) urachal adenocarcinoma that was the first malignancy; (II) patients for whom information about CSM, duration of survival (in months), and therapy provided were available; and (III) diagnosis was by histological confirmation only. Cases diagnosed by clinical presentation, radiography, or autopsy alone were excluded.

Ethical statement

We were granted permission from the National Cancer Institute USA to access the SEER dataset for research purposes only (reference number: 18015-Nov2017). All the data from the SEER database were de-identified, and the extracted data did not require informed consent.

Statistical analysis

Continuous variables such as age are presented as median and interquartile range median (IQR). Categorical variables such as race are presented as counts and percentages. Two-sample *t*-test was used for continuous variable analysis, and chi-square test was used for continuous variable analysis. Univariate Cox regression analysis was performed to identify potential risk factors. After factors were identified, we explored the nonlinear relationship between age at diagnosis and cancer-specific survival using a smoothing plot. Using a trial method, the inflection point of age at diagnosis at which the relationship began to change was identified. The trial inflection point was moved along a predetermined interval to detect the inflection point to obtain the maximum model likelihood (15,16). Survival time between the different groups was compared using Kaplan-Meier survival curves. The X-tile software was used to identify the best cutoff value in the Kaplan-Meier curves. Then we used multivariate Cox regression model and a two-piecewise Cox regression model to explore the relationship of age at diagnosis on cancer-specific survival according to the smoothing plot. The log-rank test was used to compare the two curves. Data were analyzed using the statistical package R (the R foundation; http://www.r-project.org;version3.4.3) and EmpowerStats software (www.empowerstats.com, X&Y solutions, Inc. Boston MA).

Results

Demographic Characteristics

A total of 393 patients were included in the analysis according to the criteria described above (*Figure 1*). The demographic and clinicopathological characteristics of study patients are presented in *Table 1*. The median age was 45 years (range, 19 to 91 years), The majority of the patients were White (303 patients, 77.10%), 216 (54.96%) were male and 250 (63.61%) were married. The median follow-up time was 41 months (range, 0 to 394 months), and 205 (52.16%) patients died before the last follow-up, of which 155 (39.44%) patients died due to primary adenocarcinomas of the urachus.
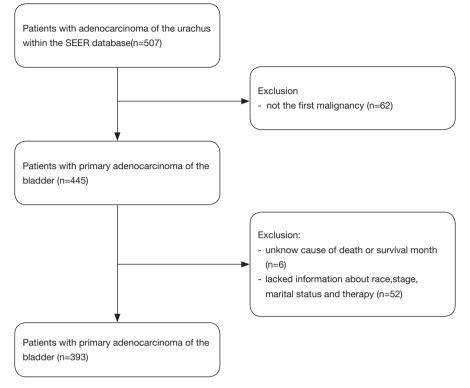
Figure 1 Flow chart of participant selection.

Pathologic and clinical characteristics

Considering the tumor the stage and grade, a majority of patients (210, 57.07%) had tumors that were staged as regional and the tumors of 137 (47.90%) patients were graded as moderately differentiated (Grade II). Staging data was missing in 25 (6.36%) patients and our analysis showed that these data met the "missing at random" hypothesis. In general, 361 (91.86%) patients underwent cancer-directed surgery. Among them, 46 (11.70%) patients had transurethral resection, 250 (63.61%) had partial cystectomy, and 45 (11.45%) had cystectomy. A small number of patients received chemotherapy (106, 26.97%) or radiation treatment (42, 10.69%).

Correlation between age at diagnosis and cancer specific death

Univariate Cox regression analysis was performed to identify potential risk factors associated with CSM, as shown in *Table 2*. Patients with Signet ring cell adenocarcinoma (HR: 2.03, P=0.0213), poorly differentiated cells (HR: 3.44, P=0.0002), regional stage (HR: 2.16, P=0.0226), distant

stage (HR: 8.34, P<0.0001), have received radiotherapy (HR: 2.29, P=0.0001), had received chemotherapy (HR: 2.13, P<0.0001) were associated with worse prognosis. Patients who had undergone surgery (HR: 0.26, P<0.0001 for transurethral resection; HR: 0.14, P<0.0001 for partial cystectomy; HR: 0.23, P<0.0001 for cystectomy; HR: 0.23, P=0.0001 for other surgical methods), had a better prognosis than those who were not surgical patients.

The independent correlation between age at diagnosis and cancer-specific survival rate

After possible confounders were identified using univariate Cox regression analysis, smooth curve fitting was performed after adjusting all variables. The curve showed a two-stage change and one inflection point (*Figure 2*) , meaning that there was an inverse association between age at initial diagnosis and cancer-specific survival when age was before the inflection point, and there was a positive relationship between age and cancer specific survival rate when age was after the inflection point. The inflection point that we identified for age at initial diagnosis was 60 years. Kaplan–Meier analyses showed that in patients <60 years of age,

Table 1 Clinical characteristics of the 393 patients with primary adenocarcinoma of the urachus

Variable	<60 (n=231)	≥60 (n=162)	Total (n=393)	P-value
Age at diagnosis, median (IQR), year	47 (41–53)	67.5 (63–73)	56 (45–65)	<0.001***
Sex, n (%)				0.8310
Male	128 (55.41)	88 (54.32)	216 (54.96)	
Female	103 (44.59)	74 (45.68)	177 (45.04)	
Race, n (%)				0.1900
White	172 (74.46)	131 (80.86)	303 (77.10)	
Black	28 (12.12)	11 (6.79)	39 (9.92)	
Other	31 (13.42)	20 (12.35)	51 (21.98)	
Grade, n (%)				0.4600
Well differentiated; Grade I	27 (15.88)	24 (20.69)	51 (17.83)	
Moderately differentiated; Grade II	80 (47.06)	57 (49.14)	137 (47.90)	
Poorly differentiated; Grade III	56 (32.94)	29 (25.00)	85 (29.72)	
Undifferentiated; anaplastic; Grade IV	7 (4.12)	6 (5.17)	13 (4.54)	
Histologic type, n (%)				0.3740
Adenocarcinoma NOS	87 (37.66)	72 (44.44)	159 (40.64)	
Mucinous adenocarcinoma	126 (54.55)	74 (45.68)	200 (50.89)	
Signet ring cell adenocarcinoma	11 (4.76)	9 (5.56)	20 (5.09)	
Other adenocarcinoma subtypes	7 (3.03)	7 (4.32)	14 (3.56)	
SEER historic stage A, n (%)				0.2100
Localized	27 (12.16)	26 (17.81)	53 (14.40)	
Regional	136 (61.26)	74 (50.68)	210 (57.07)	
Distant	56 (25.23)	43 (29.45)	99 (26.90)	
Unstaged	3 (1.35)	3 (2.05)	6 (1.63)	
Radiation, n (%)				0.8200
Yes	24 (10.39)	18 (11.11)	42 (10.69)	
None/unknown	207 (89.61)	144 (88.89)	351 (89.31)	
Chemotherapy, n (%)				0.3940
Yes	66 (28.57)	40 (24.69)	106 (26.97)	
None/unknown	165 (71.43)	122 (75.31)	287 (73.03)	
Surgery, n (%)				0.5050
No cancer-direct surgery	16 (6.93)	16 (9.88)	32 (8.14)	
Transurethral resection	26 (11.26)	20 (12.35)	46 (11.7)	
Partial cystectomy	152 (65.80)	98 (60.49)	250 (63.61)	
Cystectomy	28 (12.12)	17 (10.49)	45 (11.45)	
Other surgery type	9 (3.90)	11 (6.79)	20 (5.09)	
Marital status at diagnosis, n (%)				<0.001***
Married	148 (64.07)	102 (62.96)	250 (63.61)	
Never married	62 (26.84)	20 (12.35)	82 (20.87)	
Other[a]	21 (9.09)	40 (24.69)	61 (15.52)	

Statistically significant *P<0.05, **P<0.01, ***P<0.001. IQR, interquartile range; Localized, confined entirely to the organ of origin; Regional, has extended 1) beyond the limits of the organ of origin directly into surrounding organs or tissues; 2) into regional lymph nodes by way of the lymphatic system; or 3) by a combination of extension and regional lymph nodes; Distant, has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis; Unstaged, unknow stage. [a]Other includes divorced, separated, widowed and unmarried or domestic partner.

Table 2 Univariate Cox regression analysis of prognostic factors for cancer-specific mortality in primary urachal adenocarcinoma

Variable	Level	HR	95% CI	P value
Age at diagnosis (years) median (IQR), year	56 (45–65)	1.00	(0.99–1.01)	0.6497
Sex, n (%)				
Female	177 (45.04)	Reference		
Male	216 (54.96)	0.99	(0.72–1.36)	0.9483
Race, n (%)				
White	303 (77.10)	Reference		
Black	39 (9.92)	1.29	(0.79–2.13)	0.3087
Other	51 (12.98)	1.49	(0.96–2.31)	0.0786
Grade, n (%)				
Well differentiated; Grade I	51 (17.83)	Reference		
Moderately differentiated; Grade II	137 (47.90)	1.42	(0.73–2.78)	0.3019
Poorly differentiated; Grade III	85 (29.72)	3.44	(1.79–6.64)	0.0002***
Undifferentiated; anaplastic; Grade IV	13 (4.55)	2.84	(0.98–8.20)	0.0535
Histologic type, n (%)				
Adenocarcinoma NOS	159 (40.46)	Reference		
Mucinous adenocarcinoma	200 (50.89)	1.05	(0.74–1.47)	0.7927
Signet ring cell adenocarcinoma	20 (5.09)	2.03	(1.11–3.72)	0.0213*
Other adenocarcinoma subtypes	14 (3.56)	0.99	(0.40–2.48)	0.9877
SEER historic stage A, n (%)				
Localized	53 (14.40)	Reference		
Regional	210 (57.07)	2.16	(1.11–4.20)	0.0226*
Distant	99 (26.90)	8.34	(4.28–16.27)	<0.0001***
Unstaged	6 (1.63)	2.31	(0.51–10.56)	0.2792
Radiation, n (%)				
No/unknow	351 (89.31)	Reference		
Yes	42 (10.69)	2.29	(1.50–3.50)	0.0001***
Chemotherapy, n (%)				
No/unknow	287 (73.03)	Reference		
Yes	106 (26.97)	2.13	(1.53–2.95)	<0.0001***
Surgery, n (%)				
No cancer-direct surgery	32 (8.14)	Reference		
Transurethral resection	46 (11.70)	0.26	(0.15–0.46)	<0.0001***
Partial cystectomy	250 (63.61)	0.14	(0.09–0.22)	<0.0001***
Cystectomy	45 (11.45)	0.23	(0.13–0.41)	<0.0001***
Other surgery type	20 (5.09)	0.23	(0.11–0.49)	<0.0001***
Marital status, n (%)				
Married	250 (63.61)	Reference		
Never married	82 (20.87)	1.12	(0.75–1.67)	0.5722
Other[a]	61 (15.52)	1.40	(0.91–2.15)	0.1219

Statistically significant *P<0.05, **P<0.01, ***P<0.001. CI, confidence interval; HR, hazard ratio. [a]Other includes divorced, separated, widowed and unmarried or domestic partner.
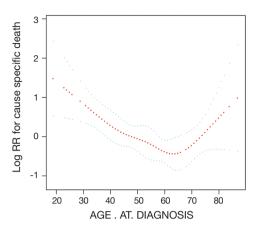
1078

Yu et al. U-shaped relationship of age and CSM

Figure 2 The relationship between age at diagnosis and cancer-specific mortality. A nonlinear relationship was observed after adjusting for race, sex; histologic type, grade, stage, radiation, chemotherapy, marital status, surgery, year of diagnosis.

worse prognosis was associated with younger age (P=0.0007; *Figure 3A*). In patients ≥60 years of age, worse prognosis was associated with older age (P=0.0025; *Figure 3B*). These results confirm the association identified by smooth curve fitting. Then we used a Cox regression model and a two-piecewise Cox regression model to fit the association between age at diagnosis and CSM, respectively. The log likelihood ratio test (P<0.05) indicated that the two-piecewise Cox regression model was more appropriate for fitting the correlation of age at diagnosis and CSM, as shown in *Table 3*. The two-piecewise Cox regression model showed that when the age was <60 years, reduced risk of CSM was significantly associated with increased age (HR: 0.95, P=0.0002). Conversely, when age was ≥60 years, increased risk of CSM was significantly associated with increased age (HR: 1.05, P=0.0499).

Discussion

The urachus is a remnant of the allantois and forms the medial umbilical ligament after birth. Urachal carcinoma occurs mostly in the patent urachal duct (17). Urachal cancer is a rare malignant tumor, first described by Begg in 1930 (18), representing less than 1% of bladder cancers. The median diagnosis age is 52 years which is earlier than that of non-urachal adenocarcinoma (8,10,19).

Patients with urachal adenocarcinoma are more likely to be male and have the mucinous subtype. In this study, most patients were male (216, 54.96%) and had the mucinous

adenocarcinoma subtype (200, 50.89%). These results are similar to those reported by Szarvas *et al.* 2016 (19). Previous studies have shown that compared with patients with non-urachal tumors, those with primary urachal adenocarcinoma had a higher risk of suffering from non-organ-confined disease (6). In this study, 309 (78.63%) patients had a regional or distant stage. This may be due to the intramural growth of the adenocarcinoma leading to late onset hematuria, urinary tract irritation and other symptoms, and thus, a late stage of diagnosis (20). What is surprising is that when compared with patients with non-urachal adenocarcinoma of the bladder, individuals with urachal adenocarcinoma still had a better survival outcome. The reported five-year survival rates were 48% and 35% for patients with urachal and non-urachal adenocarcinoma, respectively (4,6).

Several staging approaches have been proposed for urachal cancer (e.g., the Sheldon system and the alternative Mayo, Ontario, and TNM systems). However, no staging system has been verified (7,8,10). In this study, we used the SEER historic stage A (localized, regional, distant and unstaged) classification system because it is the only staging system that was used continuously throughout the study period from 1973–2015. Several studies have shown that the presence of an advanced stage is associated with a poor prognosis (1,6,7).

At present, the main treatment of urachal adenocarcinoma is radical surgery (21). However, there is no significant survival advantage between complete cystectomy and partial cystectomy (20,22). Adenocarcinoma is not sensitive to radiotherapy or chemotherapy (23,24). Szarvas *et al.* (19) and Tatli *et al.* (23) believed that chemotherapy regimens containing 5-FU can improve the prognosis in patients with adenocarcinoma of the bladder, while others have indicated that radiotherapy, neo-adjuvant chemotherapy, or adjuvant chemotherapy have not proven to be efficacious in treatment of adenocarcinoma of the bladder (21,25-27).

In this study we found that the relationship between age at diagnosis and mortality is nonlinear and takes on a U-shaped curve. Both younger and older ages at initial diagnosis were associated with increased CSM. The risk of cancer-specific death in older patients (≥60 years) was markedly increased, which may be expected considering the possibility of less healthy patients, decreased overall life expectancy, and inability to tolerate invasive surgery or other regimens. Survival outcomes are not necessarily improved in younger patients, although they are generally
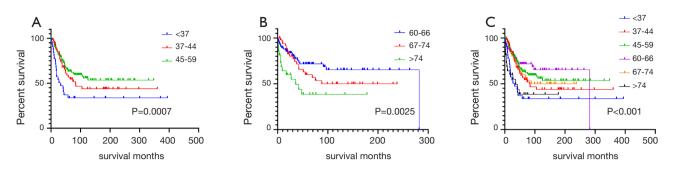
Figure 3 Kaplan-Meier curves of cancer-specific mortality in patients <60 years old (A); ≥60 years old (B); in the entire cohort (C).

Table 3 Threshold effect analysis of age at diagnosis on cancer-specific mortality using two-piecewise Cox regression

Inflection point of age at diagnosis	Odds ratio	95% CI	P value
<60	0.95	(0.93–0.98)	0.0002***
≥60	1.05	(1.00–1.10)	0.0499*
Log-rank test			0.004**

Statistically significant *P<0.05, **P<0.01, ***P<0.001. CI, confidence interval; HR, hazard ratio. Two-piecewise Cox regression hazards models were also adjusted for race; sex; histologic type; grade; stage; radiation; chemotherapy; marital status; surgery; year of diagnosis.

healthier and have fewer comorbidities than older patients, which may reflect differing biology. This finding is contrary to results of previous studies in which age at diagnosis was not an independent covariate associated with CSM in patients with primary urachal adenocarcinoma (6). A possible explanation for this might be that the non-linear association is difficult to identify using a single-piecewise cox regression model. In the era of molecular targeted cancer therapy and personalized medicine, our finding may have both important prognostic and therapeutic implications (28).

We should admit that there are some limitations in our research. First, our research was retrospective, which is inevitably associated with selection bias. Second, the distinction between urachal and non-urachal primary adenocarcinoma has always been a challenge problem in clinically and pathology (29-31). Therefore, there is a potential misclassification bias. Considering this situation, we performed an additional analysis after excluding the primary site of dome lesions; however, there was no significant change in our result (not shown in the article). Third, the SEER database lacks information about treatment strategies, family history, occupation, tumor markers, biochemical factors and immunological factors, which may cause bias. However, this is a real-world study based on a large sample, and these limitations do not

weaken our conclusions.

In summary, our study suggested that the relationship between age at diagnosis and cancer-specific survival is nonlinear and takes on a U-shaped curve. Both younger and older ages at initial diagnosis were associated with increased CSM. Further studies are needed to evaluate the actual role of age at diagnosis in CSM as well as the underlying biological mechanism.

Acknowledgments

Footnote

1080

Yu et al. U-shaped relationship of age and CSM

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. We were granted permission from the National Cancer Institute USA to access the SEER dataset for research purposes only (reference number: 18015-Nov2017). All the data from the SEER database were de-identified, and the extracted data did not require informed consent.

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