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Characteristics of arsenic-related bladder cancer: A study from Nationwide Cancer Registry Database in Taiwan

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ABSTRACT

Objective: To investigate the clinical and pathological characteristics of arsenic-related bladder cancer.
Methods: From 2008 through 2011, data on 7699 patients with bladder cancer were extracted from the Taiwan Cancer Registry Database. A diagnosis of bladder cancer (International Statistical Classification of Diseases and Related Health Problems, 9th Revision: 188) was confirmed in all patients. Using birth residency codes, patients were divided into three groups: the core zone (CZ; an arsenic endemic area with well water arsenic levels of 350–1100 ng/mL); zone 1 (Z1; an area with well water arsenic levels of ≥ 350 ng/mL but not a blackfoot disease-endemic area); and zone 2 (Z2; an area with well water arsenic levels of < 350 ng/mL). Clinicopathological characteristics and survival outcomes were compared between the three groups.
Results: In this cohort, 119 (1.5%), 1145 (14.9%), and 6435 (83.6%) patients were born in the CZ, Z1, and Z2, respectively. A higher proportion of female patients (35.3%, 31.4%, and 27.5%; $p = 0.014$) and lower smoking rates (29%, 34.8%, and 35.9%; $p = 0.694$) were noted in the CZ compared with Z1 and Z2. CZ patients had more high-grade differentiated (80.9%, 69.9%, and 63.0%; $p < 0.001$) and high clinical stage (stages II–IV, 52.8%, 38.1%, and 31.8%; $p < 0.001$) tumors compared with Z1 and Z2 patients. Radical cystectomy was infrequently performed for clinical stage II (19.6%) and stage III (25.2%) bladder cancer patients. CZ patients had significantly shorter overall and cancer-specific survival durations compared with Z1 and Z2 patients. Older age, female sex, higher tumor grade or stage, and higher arsenic levels were associated with both poorer overall and cancer-specific survival in a multivariate analysis with a Cox proportional model.
Conclusion: In Taiwan, patients with arsenic-related bladder cancer may have poorer tumor characteristics and decreased overall and cancer-specific survival rates.

1. Introduction

Arsenic, the 20th most abundant element in the earth's crust, is a naturally occurring metalloid.[1,2] Weathering of rocks results in arsenic trioxide, which enters drinking water via dissolution in rain, rivers, or groundwater.[3] Among the sources of arsenic, contaminated groundwater has the highest concentration, and individuals who rely on groundwater as a primary water supply are at risk for inadvertent chronic arsenic exposure. West Bengal, Bangladesh, and Taiwan (primarily the southwest coast) are the most affected regions worldwide for risk of arsenic exposure.[4] Many epidemiological studies have shown that arsenic exposure is associated with bladder cancer, skin cancer, various internal cancers, vascular disease, diabetes mellitus, and other chronic diseases.[5,6] In addition, a dose–response relationship was observed between chronic arsenic exposure from artesian well water ingestion and the incidence of bladder cancer in several earlier, worldwide studies.[7–12] Chen et al[13] had reported that individuals with high arsenic exposure (> 100 μg/L) were at a ≥ 5-fold risk of bladder cancer than those without evident exposure.

To date, only a few studies investigating the clinicopathological characteristics, management, and long-term clinical outcomes of arsenic-related bladder cancer have been published. Chen et al[8] revealed that arsenic-related bladder cancer patients had a shorter overall and cancer-specific survival duration than the

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patients living in nonarsenic endemic areas. However, this series was derived from only three hospitals and might be limited by selection bias.

To determine the true nature of arsenic-related bladder cancers, our study investigated the differences in clinicopathological characteristics and survival outcomes in bladder cancer patients living in areas of Taiwan with differing degrees of arsenicpollution by analyzing a nationwide database.

2. Materials and methods

2.1. Patient population

From 2008 to 2011, 7699 patients were newly diagnosed with bladder cancer, as bladder urothelial carcinoma, in Taiwan. Patients with a history of bladder cancer were excluded. Data were obtained from the Taiwan Cancer Registry Database, which is maintained by the Department of Health, Executive Yuan, Taiwan, and included collected data for newly diagnosed cancer patients in every hospital with more than a 50-bed capacity in Taiwan. Each patient had 95 columns of demographic and clinical information, including age, sex, residency, clinical stage, pathological stage, tumor differentiation, treatment, and outcomes. Tumor grade and stage were categorized according to the World Health Organization/International Society of Urological Pathology System and the American Joint Committee on Cancer/Union for International Cancer Control system.

2.2. Definition of arsenic exposure area

Blackfoot disease, urothelial carcinoma, and some internal cancers are endemic to several areas of Taiwan, where the arsenic level in well water is high at 350–1100 ng/mL. We defined these areas as the core zone (CZ), including the following four towns: Beimen and Syuejia in Tainan City and Budai and Yijhu in Chia-Yi County. According to reports of arsenic exposure in Taiwan from Chen et al,[8] zone 1 (Z1) refers to areas surrounding the CZ, where the arsenic level in well water is $\geq$ 350 ng/mL, but not considered an endemic area for blackfoot disease. Zone 2 (Z2) refers to the remaining areas in Taiwan, where the arsenic level in well water is < 350 ng/mL. Patients were categorized as residing in the CZ, Z1, or Z2 according to residency codes, which indicate the towns where the patients were born.

2.3. Outcome measurement

Patient information in the national cancer registry was linked to death registry databases of the Bureau of Health Promotion, Department of Health, Executive Yuan, Taiwan. The extracted data included death and date of death through 2013. The median duration of follow-up was defined as the median of the interval between the date of bladder cancer diagnosis and death or censoring. Overall mortality and bladder cancer mortality refer to the interval between the date of bladder cancer diagnosis and death due to all causes or to bladder cancer, respectively.

2.4. Statistical methods

The Kaplan–Meier method was used to analyze survival outcomes. The log-rank test was used to compare survival outcomes between the CZ, Z1, and Z2 groups. The Kruskal–Wallis rank test was used to compare medians between patient groups. Contingency tables were constructed for comparisons using the Chi-square test. All statistical tests were two-tailed, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient demographics

From 2008 to 2011, 119 (1.5%) patients in the CZ, 1145 (14.9%) patients in Z1, and 6435 (83.6%) in Z2 were diagnosed with bladder urothelial carcinoma. The median age at diagnosis was 71 years in the CZ, 70 years in Z1, and 71 years in Z2. Although median ages among the three groups were not different, a higher proportion of patients aged 60–79 years was seen in the CZ (70.6%) compared to Z1 (52.8%) and Z2 (53.2%). Only 15 patients (12.6%) in the CZ were older than 80 years, compared with 19.7% in Z1 and 21.6% in Z2.

In this nationwide cohort, the male/female ratio was 2.5. This male predominance was generally observed throughout Taiwan, regardless of the level of arsenic exposure. However, the male/female ratio in the CZ was significantly lower than that in Z1 and Z2 ($p = 0.014$). Smoking history was obtained for the last year and was available for 2055 patients in this cohort (26.7%). A total of 732 (35.6%) patients revealed current or ever-smoking histories. Fewer patients in the CZ had a history of smoking (29%) than in Z1 (34.8%) or Z2 (35.9%; $p = 0.69$). In the CZ, 60.5% of patients were diagnosed and managed at regional hospitals, and the remaining patients were at medical centers. In contrast, 64.5% of Z2 patients were diagnosed and treated in medical centers (Table 1).

Table 1
Clinicopathological characteristics of bladder cancer patients in Taiwan.

Area	Core Zone	Zone 1	Zone 2	*p*
Cases, *n*	119 (1.5%)	6435 (83.6%)	119 (1.5%)	
Age at diagnosis (y)				
Median age	71	70	71	
Range	45–87	14–96	3–99	
< 40	0	18 (1.6)	112 (1.7)	
40–49	3 (2.5)	73 (6.4)	405 (6.3)	
50–59	17 (14.3)	225 (19.7)	1102 (17.1)	
60–69	33 (27.7)	251 (21.9)	1421 (22.1)	
70–79	51 (42.9)	353 (30.8)	2003 (31.1)	
≥ 80	15 (12.6)	225 (19.7)	1392 (21.6)	
Sex				
Men	77 (64.7)	785 (68.6)	4640 (72.1)	
Women	42 (35.3)	360 (31.4)	1795 (27.9)	
Men/women ratio	1.83	2.18	2.58	0.014
Smoking status				
Nonsmoker	22 (1.7)	184 (13.9)	1117 (84.4)	0.69
Smoker	9 (1.2)	98 (13.4)	625 (85.4)	
Hospital				
Medical center	47 (39.5)	599 (52.3)	4160 (64.6)	
Area hospital	72 (60.5)	546 (47.7)	2275 (35.4)	
Ratio	0.65	1.10	1.83	
Clinical stage				<0.001
Stage 0	17 (15.7)	223 (24.9)	1410 (26.8)	
Stage I	34 (31.5)	331 (37.0)	2175 (41.3)	
Stage II	34 (31.5)	165 (18.5)	864 (16.4)	
Stage III	12 (11.1)	83 (9.3)	389 (7.4)	
Stage IV	11 (10.2)	92 (10.3)	423 (8.0)	
Unclear	11	251	1174	
Pathological stage				<0.001
Stage 0	5 (9.1)	199 (29.3)	849 (33.4)	
Stage 1	20 (36.4)	339 (49.9)	900 (35.4)	
Stage 2	16 (29.1)	61 (9.0)	367 (14.4)	
Stage 3	8 (14.5)	34 (5.0)	200 (7.9)	
Stage 4	6 (10.9)	47 (6.9)	224 (8.8)	
Unclear	64	465	3895	
Differentiation				<0.001
Low grade	18 (19.1)	282 (30.1)	1976 (37.0)	
High grade	76 (80.9)	656 (69.9)	3361 (63.0)	
Ratio (low/high)	0.24	0.43	0.59	

Data are presented as *n* (%).

3.2. Clinicopathological characteristics

Fewer patients in the CZ had clinically nonmuscle invasive bladder cancer (stages 0 and I) compared with those in Z1 or Z2 (47.2%, 62.0%, and 68.1%, respectively; $p < 0.001$ for between-group comparison). In addition, a higher level of arsenic exposure was significantly associated with a lower proportion of nonmuscle invasive bladder cancer ($p < 0.001$ for trend). Locally advanced (stages II and III) bladder cancer tumors were more frequently observed among patients from the CZ compared with patients from Z1 or Z2 (42.6%, 27.7%, and 23.8%, respectively; $p < 0.001$ for between-group comparison). Similar presentations in pathological stages were noted among the three groups (CZ, 43.6%; Z1, 14%; and Z2, 22.3%, $p < 0.001$ for between-group comparison). The proportion of high-grade differentiated tumors was higher in the CZ group than in the Z1 and Z2 groups (80.9%, 69.9%, and 63.0%, respectively; $p < 0.001$ for between-group comparison). In addition, Z1 patients had more high-grade differentiated tumors than Z2 patients ($p < 0.001$).

3.3. Management

For nonmuscle invasive bladder cancer, transurethral resection was done in almost all patients (96.8% with stage 0 and 93.5% with stage I), and there was no significant difference in treatment between the groups (Table 2)–>. Radical cystectomy was infrequently performed in patients with clinical stage II (19.6%) and stage III (25.2%) disease. More CZ patients with clinical stage II and III bladder cancer underwent radical cystectomy than in Z1 or Z2 groups, although statistical significance was not reached (clinical stage II, $p = 0.316$ for between-group comparison; clinical stage III, $p = 0.658$ for between-group comparison). Radiation to the urinary bladder was used for 289 (18.7%) patients with clinical stage II and stage III bladder cancer. For clinical stage III bladder cancer, more patients in the CZ group received radiotherapy than in the Z1 and Z2 groups, but the difference did not reach statistical significance ($p = 0.408$). CZ patients with clinical stage IV disease received systemic chemotherapy more frequently than did those in Z1 and Z2, but again statistical significance was not achieved ($p = 0.708$).

Table 2
Management of bladder cancer patients in Taiwan.

Area	Core zone	Zone 1	Zone 2
Cases, *n*	119 (1.5)	1145 (14.9)	6435 (83.6)
Stage I			
TURBT	33 (97.1)	316 (95.5)	2026 (93.1)
No treatment	0	4 (1.2)	48 (2.2)
Partial cystectomy	0	0	18 (0.8)
Radical cystectomy	1 (2.9)	10 (3.0)	63 (2.9)
Radiation	0	1 (0.3)	11 (0.5)
Simple cystectomy	0	0	6 (0.3)
Unclear surgery	0	0	3 (0.1)
Stage II			
TURBT	16 (47.1)	95 (57.6)	493 (57.1)
No treatment	1 (2.9)	1 (0.6)	29 (3.4)
Partial cystectomy	1 (2.9)	8 (4.8)	36 (4.2)
Radical cystectomy	11 (32.4)	30 (18.2)	167 (19.3)
Radiation	3 (8.8)	30 (18.2)	132 (15.3)
Simple cystectomy	2 (5.9)	1 (0.6)	6 (0.7)
Unclear surgery	0	0	1 (0.1)
Stage III			
TURBT	1 (8.3)	33 (39.8)	159 (40.9)
No treatment	0	2 (2.4)	15 (3.9)
Partial cystectomy	2 (16.7)	8 (9.6)	16 (4.1)
Radical cystectomy	5 (41.7)	20 (24.1)	97 (24.9)
Radiation	4 (33.3)	20 (24.1)	100 (25.7)
Simple cystectomy	0	0	2 (0.5)
Stage IV			
Systemic chemotherapy	7 (63.6)	43 (46.7)	184 (43.5)
TURBT	2 (18.2)	19 (20.7)	140 (33.1)
No treatment	1 (9.1)	9 (9.8)	48 (11.3)
Partial cystectomy	0	1 (1.1)	3 (0.7)
Radical cystectomy	1 (9.1)	20 (21.7)	45 (10.6)
Simple cystectomy	0	0	1 (0.2)
Unclear surgery	0	0	2 (0.5)

Data are presented as *n* (%).
TURBT = transurethral resection of bladder tumors.

3.4. Survival outcomes

A total of 2070 (26.9%) patients in our cohort died during a median follow-up of 26.9 months. More CZ patients (38.7%) died than did patients in Z1 (28.1%, $p = 0.214$) and Z2 (26.4%, $p = 0.004$). CZ patients had a significantly shorter overall survival duration compared with patients in Z1 and Z2 (log-rank test, $p = 0.008$ and $p = 0.001$, respectively; Fig. 1A). In our cohort, 1118 (14.5%) patients died from bladder cancer by the end of 2013. More patients (26.9%) in the CZ died from bladder cancer than did patients in Z1 (15.3%, $p = 0.002$) or Z2 (14.2%, $p < 0.001$). CZ patients had significantly worse cancer-specific survival outcomes compared with Z1 and Z2 patients (log-rank test, $p < 0.001$ and $p < 0.001$, respectively; Fig. 2). However, there were no differences in overall survival or in cancer-specific survival between Z1 and Z2 patients.

Based on the Cox proportional hazard model for overall survival, old age, female sex, high tumor grade and stage, and high arsenic levels were associated with a reduced overall survival duration (Table 3). Although more CZ patients received treatment in regional hospitals than Z1 and Z2 patients, there were no significant differences in overall survival outcomes between regional hospitals and medical centers. A multivariable analysis for overall survival revealed that Z1 and Z2 patients had borderline benefits ($p = 0.047$

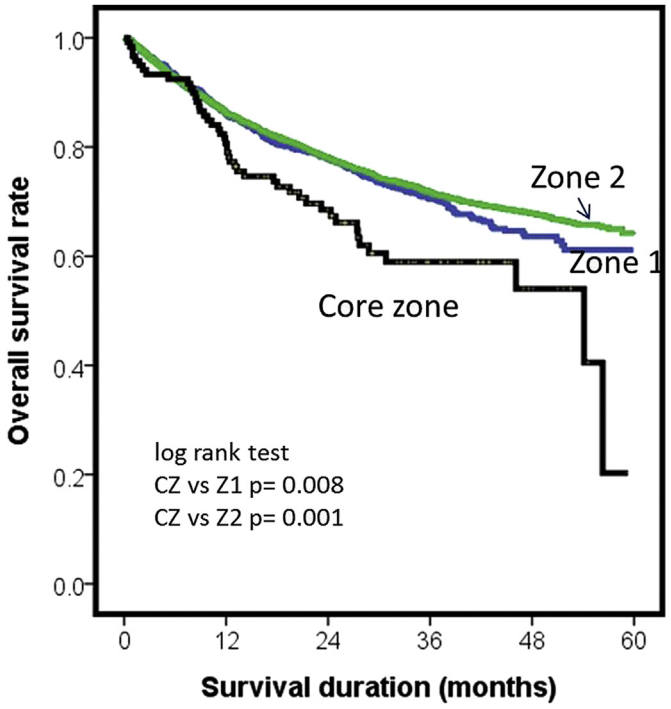

Fig. 1. Overall survival of bladder cancer patients stratified by levels of arsenic contamination. Core zone (CZ; arsenic endemic area with a well water arsenic level of 350–1100 ng/mL), zone 1 (Z1; a well water arsenic level of ≥ 350 ng/mL but not a blackfoot disease endemic area), and zone 2 (Z2; a well water arsenic level of < 350 ng/mL).

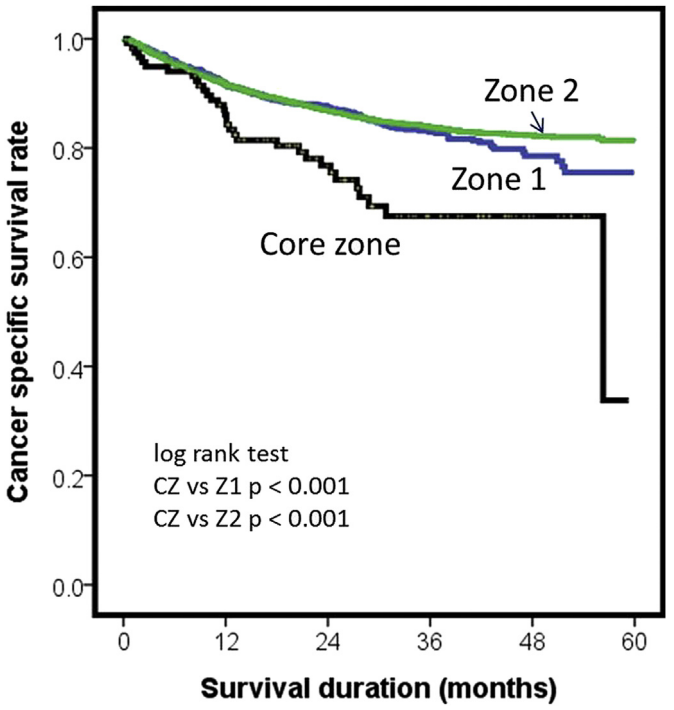

Fig. 2. Cancer-specific survival of bladder cancer patients stratified by the levels of arsenic contamination. Core zone (CZ; arsenic endemic area with a well water arsenic level of 350–1100 ng/mL), zone 1 (Z1; a well water arsenic level of ≥ 350 ng/mL but not a blackfoot disease endemic area), and zone 2 (Z2; a well water arsenic level of < 350 ng/mL).

and $p = 0.051$, respectively) compared to CZ patients. Age, sex, tumor grade and stage, and arsenic levels remained prognostic for cancer-specific survival; in the multivariable analysis, CZ patients had poorer survival outcomes than the others.

4. Discussion

In our study, patients with bladder cancer in the CZ were primarily between the ages of 60 years and 79 years; had a higher proportion of females; had higher tumor grade differentiation; and higher clinical and pathological stages than did the patients in the other areas of Taiwan. Chen et al[8] had noted that more unfavorable bladder cancer stage distribution and survival outcomes were seen in patients with a higher level of arsenic exposure in a limited cohort. Our study, using a nationwide database of bladder cancer patients, between 2008 and 2011, found similar results. For both overall survival and cancer-specific survival, CZ patients had poorer outcomes compared with patients in Z1 and Z2, where the arsenic levels in well water were lower. Other than arsenic exposure, possible reasons that patients in the CZ tended to have higher stage and grade bladder cancer and poorer clinical outcomes may have included: (1) fewer patients were treated in medical centers and (2) the higher proportion of elderly patients in the CZ group.

Cigarette smoking is a well-documented cause of bladder cancer, with about 50% of all bladder cancers attributable to smoking.[14] In our study, patients in the CZ had less smoking history compared with those patients in Z1 and Z2. However, more advanced stage and higher grade of bladder cancers were noted in CZ patients than in Z1 and Z2 patients. Chen et al[8] had reported that smoking was not an independent prognostic factor for survival in patients with arsenic-related bladder cancer. In fact, the carcinogenic effects of cigarette smoking seem to be weaker than those of arsenic,[7] and our results support this finding. Furthermore, a synergistic relationship may exist between arsenic and smoking in regard to bladder cancer. Ferreccio et al[15] had identified dose–response patterns for arsenic in smokers and nonsmokers living in areas of high arsenic concentrations. Further studies should be conducted to evaluate the effects of nicotine dose and bladder cancer tumor grade in arsenic-exposed populations.

As for treatment options, more clinical stage II patients in the CZ underwent radical cystectomy and more clinical stage IV patients received systemic chemotherapy compared with those in other areas. This indicates that a proportionally higher number of individuals in the CZ received standard therapy than individuals in other areas. This may be related to the awareness of cancer risk in arsenic endemic areas, and that patients were willing to receive standard treatment for bladder cancer. Taiwan's government has paid much attention to health issues in areas with blackfoot disease, and epidemiological cohort studies have provided free screening programs for residents in arsenic endemic areas for many years.[7,16] This may explain why residents in the CZ had a higher awareness of health risks and were willing to accept medical advice as compared with residents of other areas.

A high incidence of upper urinary tract urothelial carcinoma (UTUC) in arsenic-endemic areas in southwestern Taiwan has been documented,[17,18] and the characteristics of UTUC in the endemic areas of Blackfoot disease include: (1) male/female ratio of 1:2; (2) a younger age of onset (55–60 years); and (3) ureteral tumors twice as common as the renal pelvis site.[18] The male/female ratio in UTUC is contrary to the bladder urothelial carcinoma results in our study. In addition to bladder urothelial carcinoma, arsenic exposure combined with cigarette smoking contributes to a higher risk of UTUC.[17] However, this previous study was limited by a hospital-based, case–control design. It is necessary to conduct a nationwide study investigating the relationship between arsenic exposure, cigarette smoking, Chinese herb use, and urothelical carcinoma, and further understand the susceptibility of different sites of urothelium to potential environmental carcinogens.

4.1. Limitations

Our study has several limitations. First, we used a census register for stratifying patients into three zones; however, the census register does not always reflect the actual place of residency. Therefore, the exact number of patients in each zone may not be clearly identified. Second, despite the fact that we had treatment guidelines for bladder cancer in place, the efforts made by individual physicians to persuade patients to undergo surveillance or radical surgery may have differed. Moreover, the database did not reveal the use of post-transurethral bladder tumor resection instillation therapy, and it did not collect data on the number of patients with clinical stage II or stage III disease who received systemic chemotherapy either. The survival outcomes might therefore be biased accordingly. Third, only 119 CZ patients were enrolled, which is relatively smaller than the number of patients enrolled from Z1 or Z2. This may have masked minor differences in clinical outcomes. Fourth, our study was a retrospective study, in which data accuracy may be inferior to that of a prospective study. Fifth, the study period was relatively short. Extending the study period in future trials will help make the findings more robust.

5. Conclusion

Bladder cancer patients who live in a high arsenic endemic area (the CZ) had higher clinical and pathological stage cancers and had poorer overall and cancer-specific survival rates than patients living in other areas of Taiwan.

Table 3
Univariate and multivariate analyses of overall and cancer-specific deaths in bladder cancer patients.

Factors	Cases, *n*	Overall death						
		Deaths, *n*	Univariate			Multivariate		
			HR	CI	*p*	HR	CI	*p*
Age	7699	2070	1.05	1.05–1.06	< 0.001	1.05	1.05–1.06	< 0.001
Arsenic levels								
Core zone	119	46	Ref.			Ref.		
Zone 1	1145	322	0.66	0.49–0.91	0.01	0.73	0.54–1.00	0.047
Zone 2	6435	1702	0.62	0.46–0.83	0.001	0.75	0.56–1.00	0.051
Sex								
Male	5502	1422	Ref.			Ref.		
Female	2197	648	1.1	1.05–1.15	< 0.001	1.08	1.03–1.13	0.001
Hospital levels								
Regional	2893	760	Ref.			Ref.		
Medical center	4806	1310	1	0.95–1.05	0.948	1.03	0.98–1.07	0.283
Grade								
Low	2276	328	Ref.			Ref.		
High	4093	1300	1.39	1.31–1.48	< 0.001	1.2	1.13–1.28	< 0.001
Stage								
0	1650	208	Ref.			Ref.		
I	2540	454	1.41	1.19–1.66	< 0.001	1.21	1.02–1.43	0.026
II	1063	363	3.05	2.57–3.62	< 0.001	2.32	1.95–2.77	< 0.001
III	484	233	4.8	3.98–5.79	< 0.001	3.6	2.97–4.36	< 0.001
IV	526	423	12.9	10.9–15.2	< 0.001	9.89	8.31–11.72	< 0.001
Factors	Cases, *n*	Cancer-specific death						
		Cancer-specific deaths, *n*	Univariate			Multivariate		
			HR	CI	*p*	HR	CI	*p*
Age	7699	1118	1.05	1.04–1.05	< 0.001	1.04	1.04–1.05	< 0.001
Arsenic levels								
Core zone	119	32	Ref.			Ref.		
Zone 1	1145	175	0.53	0.36–0.77	0.001	0.6	0.41–0.88	0.008
Zone 2	6435	911	0.48	0.34–0.69	< 0.001	0.64	0.45–0.92	0.015
Sex								
Male	5502	751	Ref.			Ref.		
Female	2197	367	1.13	1.06–1.21	< 0.001	1.1	1.04–1.17	0.002
Hospital levels								
Regional	2893	399	Ref.			Ref.		
Medical center	4806	719	1.03	0.97–1.09	0.406	1.06	1.00–1.13	0.061
Grade								
Low	2276	105	Ref.			Ref.		
High	4093	760	1.69	1.55–1.85	< 0.001	1.39	1.26–1.52	< 0.001
Stage								
0	1650	62	Ref.			Ref.		
I	2540	170	1.78	1.33–2.37	< 0.001	1.43	1.07–1.92	0.017
II	1063	214	6	4.53–7.97	< 0.001	4.15	3.11–5.54	< 0.001
III	484	156	10.69	7.96–14.35	< 0.001	7.17	5.31–9.68	< 0.001
IV	526	319	31.87	24.26–41.88	< 0.001	21.94	16.60–28.99	< 0.001

CI = confidence interval; cStage = clinical stage; HR = hazard ratio.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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