Frequency and Clinicopathological Features of Distant Metastasis of Bladder Cancer: A SEER-Based Study

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Abstract

**Background:** Bladder cancer (BCa) is a common malignancy in the urinary system. But the hematogenous metastatic pattern of it was poorly explored. The aim of this study was to provide a better understanding of the prognosis of the different distant metastatic pattern from stage IV BCa patients and support for making a suitable clinical decision.

**Methods:** The Surveillance, Epidemiology and End Result database (SEER) provided data for this study include BCa from 2010 to 2015. Kaplan–Meier method was used to evaluate the survival prognosis of patients of metastatic BCa. Cox proportional hazards regression model was utilized to analyzed risk factors. All statistical tests were two-sided.

**Results:** At the time of diagnosis, a total of 6808 eligible patients at stage IV were extracted from SEER database. Patients who suffered metastasis to either one of the four sites occupied 25.31% (1723/6808) of BCa. Bone was the most common distant metastatic site of BCa (1225 cases), and brain metastases had the worst prognosis whose mean survival was 6.282 months. The results of univariate survival analysis presented that diagnostic age, race, gender, primary site surgery, tumor size, T stage, N stage, primary tumor site, histology, marital status and metastatic number were independent prognostic factors affecting overall survival (OS) (P<0.05). On multivariable Cox regression, squamous cell carcinoma was an independent risk factor affecting the overall survival (P<0.05). The nomogram model was constructed to show the 1-, 3- and 5-year survival rates of patients.

**Conclusion:** In analysis of single metastatic sites, patients with brain metastasis had the worst overall survival and lung metastasis had the best outcomes than other three distant metastases. Knowledge of these differences in metastatic patterns is helpful for clinicians to make better pre-treatment evaluation and clinical decisions.

**Background**

Bladder cancer (BCa), the most common malignancy in the urinary system and causes 18,000 deaths per year and its new cases are almost 80,000 annually, is the fourth most common cancer in the United States for males [1]. The high incidence and mortality of the BCa are associated with the existence of difference between sociodemographics and socioeconomic [2–4]. These factors intertwined together lead to the complexity of BCa.

According to the depth of invasion of the bladder wall, there are two types of histopathological stage, non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). NMIBC is composed of Ta, carcinoma in situ (CIS) and stage T1, and this type occupied 70% in the patients of BCa [5]. Approximately, 15% NMIBC has the potential to progress to MIBC and metastatic BCa after treatments [6]. Actually, 10–15% patients with BCa confirmed distant metastases at the first diagnosis, and the 5-year survival for them was only 8.1% [7, 8].

The Surveillance, Epidemiology and End Results (SEER) data included the metastatic information of bone, brain, liver, and lung since 2010. The patients diagnosed with BCa in stage IV between 2010 and 2015 were included in our study to explore the metastatic pattern. Generally, lung and bone were considered as the most frequent metastatic patterns [9]. In the patients of MIBC, approximately half of them would develop to lung metastasis[10]. As for bone metastasis, it has been reported in about 40% of patients with advanced BCa[11]. The limited sample size led to the insufficient incidence rate of metastasis to distant metastatic sites, and some reports about distant metastasis were only case reports.

Our study aims to provide a better understanding of the prognosis of the different distant metastatic pattern of BCa and support for making a suitable clinical decision at the time of diagnosis.

The American joint committee on cancer (AJCC) cancer staging atlas, 2nd edition staging for BCa defined the classification of TNM, T4b N0 M0, Any T N1-3 M0 and Any T Any N M1 were included in the stage IV.

**Methods**

**Database**

The SEER database is considered as the largest publicly available cancer database in the United States and funded by the National Cancer Institute. The cancer incidence and survival as well as demographic information from population-based cancer registries, including 34.6 percent of the people lives in the United States was collected in SEER programs. The data we implemented was from the 18 population-based cancer registries in SEER database. The metastatic related condition was started to release since 2010, but metastatic sites were restricted to bone, brain, liver and lung.

**Patient population**

The bladder cancers were chosen for survival analysis. The other inclusion criteria were as follows: (1) the diagnosis was microscopically confirmed with active follow-up and known age; (2) the diagnosed years were from 2010 to 2015 and the stage (AJCC 7th ) all were IV stage; (3) the tumor behavior must be malignant. A total of 7484 patients were selected. As we excluded cases with no follow-up (survival time code of 0 months) and unknown age, we got 6808 patients at last.

**Outcome variables**

Variables included age at diagnosis, gender, years of diagnosis, race, tumor size, marital status, insurance status, tumor location, TNM classification system (AJCC, 7th edition, 2010), metastatic sites, overall survival and primary site surgery status were coded in SEER database.

The stratification of age at diagnosis was "<40", "40–70" and "≥70" according to the peak age of the bladder cancer incidence [12].
Following International Classification of Diseases for Oncology (ICD-O-3) codes, we divided the tumor location into 8 types: “Trigone”, “Dome”, “Wall of bladder”, “Bladder neck”, “Ureteric orifice”, “Urachus”, “Overlapping lesion” and “Bladder, NOS”. Among these types, the type “wall of bladder” consisted of “Lateral wall of bladder”, “Anterior wall of bladder” and “Posterior wall of bladder”.

For the race, we reclassified patients into four groups: “White”, “Black”, “Other” and “Unknown”.

We gather the individuals in the “Any Medicaid”, “Insured”, and “Insured/No specifics” groups as “Insured groups” for insurance status. As result, there was for two groups: “Insured” and “Uninsured”.

Because of the confused definition of “Unmarried or domestic partner”, this item was removed when we include marital status. “Unmarried” groups contained single, widowed, and separated/divorced.

According to the ICD-O-3, we selected the highest number of types of histology, and grouped as “Non-Papillary Transitional cell carcinoma”, “Papillary transitional cell carcinoma”, “Squamous cell carcinoma” and “Small cell carcinoma”.

Primary tumor surgery was divided into “Surgical” group and “Non-surgical” group. Surgical group included “Local tumor destruction”, “Local tumor excision”, “Partial cystectomy”, “Simple/total/complete cystectomy”, “Complete cystectomy with reconstruction”, “Pelvic exenteration”, “Cystectomy” and “Surgery, NOS”. Non-surgical group performed only autopsy without surgery of primary site.

Distant metastatic sites were composed of bone, brain, liver and lung. Meanwhile, survival status, follow-up time and causes of death were also drawn from the SEER database.

Statistical analysis

Mean and interquartile range (IQR) were generated for diagnostic age. Pearson's chi-square tests were utilized to compare the distribution of clinical pathological and demographic characteristics. Kaplan–Meier method was used in univariate analysis of the above variables and calculation of the survival curves of overall survival (OS). The evaluation of the survival between different groups was implemented in the log-rank test. The variables in multivariate analysis must be consistent with P-value < 0.05 of OS in the log-rank test. Multivariate Cox proportional hazards regression models were carried out to assess the independent risk factors of bladder cancer.

All above statistical analyses were performed by using the SPSS 20.0 software package (IBM Corporation, Armonk, NY, USA). All statistical tests were set at two-sided, and P < 0.05 was examined statistically significant.

Results

Patient characteristics and metastasis pattern

A total of 6808 patients with distant metastasis were extracted from the SEER database, including 4878 males (71.65%) and 1930 females (28.35%). The median age of this population was 70 years old. At the time of diagnosis, 1225 patients suffered from bone metastasis and 1123 patients suffered from lung metastasis. These two sites were the most common sites in single metastasis. Table 1 showed the demographics and metastasis pattern features of BCa patients.
| Feature                  | Bone (%) | Brain (%) | Liver (%) | Lung (%) |
|--------------------------|----------|-----------|-----------|----------|
| Age at diagnosis         |          |           |           |          |
| Yes                      | 69.0 ± 11.2 | 67.3 ± 12.1 | 70.3 ± 11.2 | 70.5 ± 11.6 |
| No                       | 68.9 ± 11.3 | 69.0 ± 11.3 | 68.8 ± 11.3 | 68.6 ± 11.2 |
| p                        | 0.936     | 0.185     | <0.001    | <0.0      |
| Race                     |          |           |           |          |
| White                    | 1042(17.9) | 86(1.5)   | 606(10.4) | 948(16.3) |
| Black                    | 123(19.3)  | 8(1.3)    | 74(11.6)  | 129(20.2) |
| Other                    | 60(18.0)   | 5(1.5)    | 37(11.1)  | 46(13.8)  |
| Unknown                  | 0(0.0)    | 0(0.0)    | 1(10.0)   | 0(0.0)    |
| Gender                   |          |           |           |          |
| Male                     | 939(19.2)  | 74(1.5)   | 519(10.6) | 787(16.1) |
| Female                   | 286(14.8)  | 25(1.3)   | 199(10.3) | 336(17.4) |
| Primary tumor sites       | <0.001    | 0.044     | <0.001    | 0.0      |
| Trigone                  | 57(16.0)   | 4(1.1)    | 42(11.8)  | 50(14.0)  |
| Dome                     | 29(11.7)   | 7(2.8)    | 23(9.3)   | 33(13.4)  |
| Wall of bladder          | 223(16.2)  | 17(1.2)   | 140(10.1) | 210(15.2) |
| Bladder neck             | 56(23.8)   | 5(2.1)    | 24(10.2)  | 33(14.0)  |
| Ureretic orifice         | 16(16.7)   | 0(0.0)    | 13(13.5)  | 19(19.8)  |
| Urachus                  | 4(9.8)     | 1(2.4)    | 8(19.5)   | 6(14.6)   |
| Overlapping              | 203(16.4)  | 8(0.6)    | 84(6.8)   | 185(14.9) |
| Bladder, NOS             | 637(19.8)  | 57(1.8)   | 384(12.0) | 587(18.3) |
| Histology                | <0.001     | 0.002     | <0.001    | 0.0      |
| Transitional cell carcinoma | 721(18.2) | 57(1.4)   | 367(9.3)  | 612(15.5) |
| Papillary transitional cell carcinoma | 273(16.2) | 20(1.2)   | 130(7.7)  | 302(17.9) |
| Squamous cell carcinoma  | 33(10.3)   | 0(0.0)    | 24(7.5)   | 52(16.2)  |
| Small cell carcinoma     | 70(26.7)   | 9(3.4)    | 93(35.5)  | 35(13.4)  |
| T stage                  | <0.001     | <0.001    | <0.001    | <0.0      |
| T1                       | 184(27.8)  | 12(1.8)   | 102(15.4) | 183(27.6) |
| T2                       | 512(23.1)  | 43(1.9)   | 253(11.4) | 430(19.4) |
| T3                       | 91(6.2)    | 5(0.3)    | 47(3.2)   | 87(5.9)   |
| T4                       | 229(12.4)  | 14(0.8)   | 148(8.0)  | 214(11.6) |
| Tx                       | 199(34.4)  | 25(4.3)   | 160(27.7) | 196(33.9) |
| Tumor Size               | <0.001     | 0.002     | <0.001    | <0.0      |
| < 5 cm                   | 221(11.6)  | 17(0.9)   | 135(7.1)  | 199(10.5) |

Table 1: Clinical features and metastasis sites for bladder cancer

| p | a | b | c | d |
The mean age of patients with bone metastasis was 69 years old, but there was no significant between patients with and without bone metastasis. Males presented a higher percentage of bone metastasis than females. Urachus had the lowest percentage in the primary tumor sites. Squamous cell carcinoma possessed lower bone metastatic percentage than any other type. Notably, tumor in T3 stage had the lowest bone metastatic rate, as well in N1 stage. Unmarried patients appeared to tend to a higher bone metastasis percentage. Obviously, patients with bone metastasis were more liable to operation. Insurance status and race showed no statistical significance in the metastasis of bone.

The same as the bone metastasis, patients with T3 stage or N1 stage had the lowest percentage of brain metastasis in T stage and N stage, respectively. Patients undergoing surgery had a lower brain metastatic rate, as we expected. It is worth mentioning that no brain metastasis was observed in the ureteric orifice and squamous cell carcinoma. No significant difference was concluded in the age of diagnosis, gender, race, and insurance and marital status.

As for liver metastasis, the mean age of patients with metastasis was 1.5 years older than those without. Interestingly, patients with the primary tumor in urachus had the highest percentage of liver metastasis. Just like the bone and brain metastasis, T3 stage and N1 stage still occupied the lowest percentage of liver metastasis. The patients in surgery without liver metastasis had higher percentage than those with liver metastasis. Race, gender, insurance status and marital status were not significantly different between patients with and without liver metastasis.

Features for patients with lung metastasis were comparable to those with bone metastasis, including unmarried predominant and T3 and N1 with the lowest percentage. Patients with lung metastases were older than those without. The difference from other metastases is that the metastatic rate in black patients was much higher than others, \( p = 0.015 \). The ureteric orifice was the primary site that accounts for the highest percentage of lung metastasis. Whatever the metastasis site was, patients underwent primary tumor surgery had a lower percentage than those not.

### Distribution of patients with distant metastases

| Bone (%) | Brain (%) | Liver (%) | Lung (%) |
|----------|-----------|-----------|----------|
| 5 cm-10 cm | 267(14.1) | 24(1.3)   | 163(8.6) | 294(15.6) |
| > 10 cm   | 35(12.5)  | 1(0.4)    | 31(11.1) | 59(21.1)  |
| Unknown   | 692(25.6) | 57(2.1)   | 381(14.1)| 558(20.6) |

| N stage   | Bone (%) | Brain (%) | Liver (%) | Lung (%) |
|-----------|----------|-----------|-----------|----------|
| N0        | 669(33.3)| 1338(66.7)| 59(2.9)   | 1948(97.1)| 365(18.2) | 1642(81.8)| 608(30.3) | 1399(69.7) |
| N1        | 102(6.2) | 1554(93.8)| 4(0.2)    | 1652(99.8)| 74(4.5)  | 1582(95.5)| 118(7.1)  | 1538(92.9) |
| N2        | 222(10.5)| 1885(89.5)| 13(0.6)   | 2094(99.4)| 129(6.1) | 1978(93.9)| 181(8.6)  | 1926(91.4) |
| N3        | 63(11.9) | 466(88.1)| 5(0.9)    | 524(99.1) | 36(6.8)  | 493(93.2) | 44(8.3)   | 485(91.7)  |
| Nx        | 169(33.2)| 340(66.8)| 18(3.5)   | 491(96.5) | 114(22.4)| 395(77.6)| 172(33.8) | 337(66.2)  |

| Insurance status | Bone (%) | Brain (%) | Liver (%) | Lung (%) |
|------------------|----------|-----------|-----------|----------|
| Insured          | 1169(18.1)| 5304(81.9)| 97(1.5)   | 6376(98.5)| 690(10.7) | 5783(89.3)| 1076(16.6)| 5397(83.4) |
| Uninsured        | 38(17.8) | 176(82.2)| 2(0.9)    | 212(99.1) | 21(9.8)  | 193(90.2) | 30(14.0)  | 184(86.0)  |
| Unknown           | 18(14.9) | 103(85.1)| 0(0.0)    | 121(100.0)| 7(5.8)   | 114(94.2) | 17(14.0)  | 104(86.0)  |

| Marital status | Bone (%) | Brain (%) | Liver (%) | Lung (%) |
|----------------|----------|-----------|-----------|----------|
| Married        | 607(16.9)| 2988(83.1)| 52(1.4)   | 3543(98.6)| 364(10.1) | 3231(89.9)| 547(15.2) | 3048(84.8) |
| Unmarried      | 559(19.2)| 2348(80.8)| 44(1.5)   | 2863(98.5)| 322(11.1)| 2585(88.9)| 529(18.2) | 2378(81.8) |
| Unknown        | 53(18.5) | 234(81.5)| 3(1.0)    | 284(99.0) | 29(10.1) | 258(89.9) | 45(15.7)  | 242(84.3)  |

| Primary tumor surgery | Bone (%) | Brain (%) | Liver (%) | Lung (%) |
|-----------------------|----------|-----------|-----------|----------|
| Yes                   | 923(15.9)| 4896(84.1)| 68(1.2)   | 5751(98.8)| 500(8.6)  | 5319(91.4)| 845(14.5) | 4974(85.5) |
| N0                    | 302(30.5)| 687(69.5)| 31(3.1)   | 958(96.9) | 218(22.0)| 771(78.0)| 278(28.1) | 711(71.9)  |

NOS, not otherwise specified.

\(^a\)The comparison between patients with and without bone metastasis.

\(^b\)The comparison between patients with and without brain metastasis.

\(^c\)The comparison between patients with and without liver metastasis.

\(^d\)The comparison between patients with and without lung metastasis
As is illustrated in Fig. 1, the distribution and divergences of the metastatic site were obvious. Bone was the most common metastasis (752 cases), followed by lung (627 cases), liver (313 cases) and brain (31 cases). Most patients (1723 cases) were single site metastasis, followed by two sites (523 cases), three sites (120 cases), and four sites (9 cases). Patients with bone and lung metastases were the most in two sites metastases, and bone and liver and lung were the most common metastatic types in three sites.

**Pathological feature of distant metastases**

The 4 most common pathological types were selected from the SEER database for representing the relationship between the pathology and metastatic sites. As shown in Fig. 2, the percentage of exclusive bone was higher to bones and others in types of transitional cell carcinoma, papillary transitional cell carcinoma and squamous cell carcinoma. The same phenomenon recurred in the lung metastasis. As for liver metastasis, exclusive metastasis surpassed liver and other metastases no matter the histological type. The percentage of exclusive brain metastasis and brain and others were equal in small cell carcinoma.

**Univariate survival analysis of distant metastases**

As is showed in Table 2, all four metastatic sites presented statistically significant (P < 0.001) using univariate survival. On Kaplan-Meier analysis, the differences between patients with and without distant metastasis were statistically significant on OS (Fig. 3). Patients with lung metastasis possessed the longest mean survival time (MST) and brain metastasis experienced the lowest MST. Meanwhile, diagnostic age, race, gender, primary site surgery, tumor size, T stage, N stage, primary tumor site, histology, marital status and metastatic number were prognostic factors affecting OS (P < 0.001). Interestingly, patients with T3 stage had better OS than T1 stage (T1: 17.458 months; T3: 24.895 months; P < 0.001). As we expected, the smaller the tumor size, the longer the survival months (P < 0.001). It makes sense that the tumor from the ureteric orifice had the worst OS and from urachus possess the best OS. There is no doubt that papillary transitional cell carcinoma has the best survival outcomes and squamous cell carcinoma has the worst. And it can be interpreted that the married patients exhibited OS advantage comparing with those unmarried (married: 20.309 months; unmarried: 16.638 months; P < 0.001). However, there was an insignificant difference between patients with insured and uninsured patients (insured: 18.582 months; uninsured: 16.897 months; p = 0.413)
| Variable                      | Incidence proportion of distant metastases N = 6808 (n %) | Mean survival time of OS, months | 95% CI              | P(OS) |
|-------------------------------|----------------------------------------------------------|----------------------------------|---------------------|-------|
| Age at diagnosis, years       |                                                          |                                  |                     | < 0.001 |
| < 40                          | 61                                                       | 23.610                           | 16.528–30.692       |       |
| > 40, and < 70                | 3274                                                     | 21.804                           | 20.896–22.713       |       |
| > 70                          | 3473                                                     | 15.289                           | 14.559–16.018       |       |
| Race                          |                                                          |                                  |                     | < 0.001 |
| White                         | 5826                                                     | 18.813                           | 18.177–19.450       |       |
| Black                         | 638                                                      | 14.838                           | 13.246–16.429       |       |
| Others                        | 334                                                      | 19.395                           | 16.609–22.181       |       |
| Unknown                       | 10                                                       | 44.481                           | 23.957–65.005       |       |
| Gender                        |                                                          |                                  |                     | 0.001 |
| Male                          | 4878                                                     | 18.963                           | 18.266–19.660       |       |
| Female                        | 1930                                                     | 17.357                           | 16.292–18.422       |       |
| Primary tumor surgery         |                                                          |                                  |                     | < 0.001 |
| Yes                           | 5819                                                     | 19.673                           | 19.028–20.317       |       |
| No                            | 989                                                      | 11.268                           | 10.088–12.448       |       |
| T                             |                                                          |                                  |                     | < 0.001 |
| T1                            | 663                                                      | 17.458                           | 15.585–19.331       |       |
| T2                            | 2213                                                     | 19.314                           | 18.240–20.388       |       |
| T3                            | 1469                                                     | 24.895                           | 23.500–26.289       |       |
| T4                            | 1848                                                     | 15.484                           | 14.506–16.463       |       |
| Unknown                       | 578                                                      | 10.100                           | 8.920–11.280        |       |
| Tumor Size                    |                                                          |                                  |                     | < 0.001 |
| < 5 cm                        | 1899                                                     | 24.825                           | 23.576–26.074       |       |
| 5 cm-10 cm                    | 1890                                                     | 17.370                           | 16.307–18.432       |       |
| > 10 cm                       | 280                                                      | 13.511                           | 11.142–15.880       |       |
| Unknown                       | 2703                                                     | 15.389                           | 14.553–16.224       |       |
| N                             |                                                          |                                  |                     | < 0.001 |
| N0                            | 2007                                                     | 12.347                           | 11.504–13.189       |       |
| N1                            | 1656                                                     | 26.714                           | 25.311–28.117       |       |
| N2                            | 2107                                                     | 19.906                           | 18.859–20.954       |       |
| N3                            | 529                                                      | 17.944                           | 15.968–19.921       |       |
| Unknown                       | 509                                                      | 10.141                           | 8.791–11.492        |       |
| Primary tumor sites           |                                                          |                                  |                     | < 0.001 |
| Trigone                       | 357                                                      | 20.343                           | 17.754–22.933       |       |
| Dome                          | 247                                                      | 23.586                           | 20.258–26.914       |       |
| Wall of bladder               | 1380                                                     | 19.658                           | 18.308–21.008       |       |
| Bladder neck                  | 235                                                      | 18.376                           | 15.313–21.440       |       |
| Ureteric orifice              | 96                                                       | 16.543                           | 12.364–20.723       |       |
| Urachus                       | 41                                                       | 23.027                           | 14.852–31.202       |       |
| Variable                        | Incidence proportion of distant metastases N = 6808 (n %) | Mean survival time of OS, months | 95% CI            | P(OS) |
|--------------------------------|---------------------------------------------------------|---------------------------------|-------------------|-------|
| Overlapping                    | 1239                                                    | 18.596                          | 17.260–19.931     |       |
| Bladder, NOS                   | 3213                                                    | 17.285                          | 16.460–18.110     |       |
| Histology                      | < 0.001                                                 |                                 |                   | 0.413 |
| Transitional cell carcinoma    | 3951                                                    | 17.987                          | 17.239–18.734     |       |
| Papillary transitional cell carcinoma | 1689                                                | 22.138                          | 20.847–23.429     |       |
| Squamous cell carcinoma        | 321                                                     | 10.859                          | 8.944–12.773      |       |
| Small cell carcinoma           | 262                                                     | 15.346                          | 12.672–18.021     |       |
| Insurance status               |                                                        |                                 |                   | < 0.001|
| Insured                        | 6473                                                    | 18.582                          | 17.981–19.183     |       |
| Uninsured                      | 214                                                     | 16.897                          | 13.993–19.802     |       |
| Unknown                        | 121                                                     | 16.863                          | 12.865–20.861     |       |
| Marital status                 |                                                        |                                 |                   | < 0.001|
| Married                        | 3595                                                    | 20.309                          | 19.465–21.154     |       |
| Unmarried                      | 2907                                                    | 16.638                          | 15.802–17.475     |       |
| Unknown                        | 287                                                     | 15.216                          | 12.720–17.713     |       |
| Metastasis sites               |                                                        |                                 |                   | < 0.001|
| Bone                           | 1225                                                    | 8.929                           | 8.258–9.600       | < 0.001|
| Brain                          | 99                                                      | 6.282                           | 4.773–7.791       | < 0.001|
| Liver                          | 718                                                     | 7.422                           | 6.622–8.222       | < 0.001|
| Lung                           | 1123                                                    | 10.015                          | 9.102–10.927      | < 0.001|
| Metastases                     |                                                        |                                 |                   | < 0.001|
| One site                       | 1722                                                    | 10.916                          | 10.191–11.641     |       |
| Two sites                      | 523                                                     | 7.160                           | 6.386–7.933       |       |
| Three sites                    | 120                                                     | 4.470                           | 3.686–5.253       |       |
| Four sites                     | 9                                                       | 3.111                           | 0.614–5.608       |       |

OS: Overall survival; CI: 95% confidence interval; NOS: Not otherwise specified.

**Multivariable Cox regression analysis of distant metastases**

The variables exhibiting the influence on survival (P < 0.05) in univariated analysis were included in Multivariable Cox regression analysis. On multivariable Cox regression (Table 3), squamous cell carcinoma of histology was an independent risk factor (HR = 1.689, CI = 1.050–2.718, P = 0.031). Moreover, primary site surgery and tumor size were independent risk factors affecting OS. Of tumor size, patients with tumor size > 10 cm had worse OS (HR = 1.714, CI = 1.180–2.490, P < 0.05) than patients with other size.
Table 3  
Multivariate analysis for BC patients with distant metastasis

|                | Hazard ratio | 95% CI      | P Value |
|----------------|--------------|-------------|---------|
| **Age**        |              |             |         |
| <40            | Reference    |             |         |
| 40–70          | 1.943        | 0.465–8.120 | 0.363   |
| > 70           | 2.767        | 0.661–11.576| 0.163   |
| **Gender**     |              |             |         |
| Male           | Reference    |             |         |
| Female         | 0.940        | 0.762–1.161 | 0.567   |
| **Race**       |              |             |         |
| White          | Reference    |             |         |
| Black          | 0.942        | 0.702–1.264 | 0.690   |
| Others         | 0.882        | 0.517–1.506 | 0.646   |
| **Primary tumor surgery** | | | |
| Yes            | Reference    |             |         |
| No             | 1.585        | 1.215–2.067 | 0.001   |
| **T**          |              |             |         |
| T1             | Reference    |             |         |
| T2             | 1.189        | 0.913–1.549 | 0.199   |
| T3             | 1.095        | 0.771–1.554 | 0.613   |
| T4             | 1.300        | 0.936–1.804 | 0.117   |
| **Tumor Size** |              |             |         |
| < 5 cm         | Reference    |             |         |
| 5 cm-10 cm     | 1.232        | 1.014–1.497 | 0.036   |
| > 10 cm        | 1.714        | 1.180–2.490 | 0.005   |
| **N**          |              |             |         |
| N0             | Reference    |             |         |
| N1             | 1.056        | 0.780–1.429 | 0.725   |
| N2             | 0.929        | 0.725–1.191 | 0.562   |
| N3             | 1.111        | 0.731–1.689 | 0.622   |
| **Primary tumor sites** | | | |
| Trigone        | Reference    |             |         |
| Dome           | 1.252        | 0.688–2.280 | 0.462   |
| Wall of bladder| 1.186        | 0.760–1.851 | 0.452   |
| Bladder neck   | 1.110        | 0.558–2.207 | 0.766   |
| Ureteric orifice| 1.104       | 0.525–2.323 | 0.795   |
| Urachus        | 0.496        | 0.057–4.324 | 0.526   |
| Overlapping    | 0.930        | 0.589–1.469 | 0.756   |
| Bladder, NOS   | 0.969        | 0.628–1.494 | 0.885   |
| **Histology**  |              |             |         |
| Transitional cell carcinoma | Reference | | |
| Papillary transitional cell carcinoma | 0.775 | 0.631–0.951 | 0.014   |
| Squamous cell carcinoma | 1.689 | 1.050–2.718 | 0.031   |
### Construction of nomogram model for distant metastasis of bladder cancer

The construction of the nomogram model was based on the results of multivariable Cox regression and clinical feasibility (Fig. 4). We selected age, primary surgery, tumor size, T/N stage, histology and metastatic sites as influence factors integrating into nomogram model. Every factor has its own corresponding score for the prediction of the survival possibility. For instance, patients with surgery scores 0 points, those without scores 44 points. The total point for all factors is 450. Adding up corresponding scores, it is accessible for us predicted 1-year survival rate, 3-year survival rate and 5-year survival rate, individually.

| Metastasis sites | Hazard ratio | 95% CI       | P Value |
|------------------|--------------|--------------|---------|
| Bone             | 0.766        | 0.500-1.171  | 0.218   |
| Marital status   |              |              |         |
| Married          | Reference    |              |         |
| Unmarried        | 0.960        | 0.725-2.597  | 0.736   |
| Liver            | 0.815        | 0.613-1.420  | 0.606   |
| Lung             | 0.736        | 0.581-1.113  | 0.345   |

CI: confidence interval; NOS: Not otherwise specified

### Discussion

BCa is the most common cancer in the urinary system followed the prostate cancer in males[1]. According to a population-based retrospective study, the mortality rate fluctuated slightly after the diagnosis of metastatic BCa without amelioration over the past few years [8]. From 1993 to 2000, the 5-year relative survival of AJCC stage IV BCa was only 17.4% based on the National Cancer DataBase [13]. Consequently, it is necessary to analyze the relationship between different metastatic pattern and overall survival in AJCC stage IV BCa patients.

In our study, we found that: (1) bone and lung were the most common metastatic sites; (2) male patients outnumber females in stage IV; (3) squamous cell carcinoma was the poorest prognostic histological types; (4) T3 had better survival outcomes than any T stage; (5) on multivariate analysis, the primary tumor surgery, tumor size and histology were independent prognostic factors impacting the patients with distant metastasis.

The results of our study were aligned with previous research, bone and lung were the most common site of distant metastasis for BCa [9]. As for bone metastasis, the coexistence of both osteolytic and osteoblastic lesions can be observed [14]. If the bone metastatic lesions do not be treated properly, some skeletal-related events (SREs) would be occurred, which can make people debilitative [15, 16]. Those events include pathologic fractures, spinal cord compression, radiation therapy to bone, surgery to bone, and hypercalcemia of malignancy [17]. Kinnane et al. also concluded that the great mass of patients with bone metastasis would suffer one SRE at least without bone-targeted therapies [18]. From these above, bone-targeted treatments are inevitable in case of the occurrence of SREs. For lung, there are numerous studies revealed the association between lung metastasis and survival. Interestingly, no survival advantages were presented in metastasectomy [9]. Meanwhile, Luzzi et al. discovered that diameter of the metastatic lesions < 3 cm was an independent prognostic factor that possessed higher 5-year survival in lung metastasis [19].

On multivariate analysis, primary tumor site was an independent prognostic factor of OS (P < 0.05), with patients who suffered from tumor in ureteric orifice obtaining the shortest overall survival. This conclusion is consistent with the outcomes of Eric et al, which discovered that the patients with primary tumors involving the ureteral orifice had 12.9% recurrence rate of upper urinary tract. [20]. This phenomenon might be caused by the loss of the anti-reflux mechanism after resected the orifice, and thus the tumor cells seeded to the upper urinary tract [21]. However, Mano et al reported their outcomes in 65 patients, which revealed only one patient was diagnosed with recurrent tumor in the upper urinary tract after transurethral resection of bladder tumor from ureteral orifice, and their conclusion suggested that ureteral orifice resection was not very relevant with an increased risk of tumor recurrence in the upper urinary tract [22]. These outcomes disagree with the results of Eric et al. and us, which might be caused by the small number of patients.

Consistent with the results of other studies, primary surgery was a benefit for the survival of patients with locally advanced disease [23]. Nevertheless, only surgery does not curative enough for locally advanced and metastatic BCa patients [24]. As a chemosensitive tumor, adjuvant therapy as chemotherapy always be proceeded within the perioperative period. Herr et al. reported 80 underwent radical cystectomy after chemotherapy, 24 of the 80 cases (30%) presented no active cancer [25]. Currently, open radical cystectomy (ORC) plus pelvic lymphadenectomy is the gold standard for high-grade invasive BCa and benefits local cancer control [26]. Meanwhile, laparoscopic radical cystectomy (LRC) is an alternative treatment for those patients, which can reduce morbidity in the perioperative period [27]. Robot-assisted radical cystectomy (RARC) has many considerable advantages, but there are some studies revealed that LRC and RARC have no obvious advantages on ORC in controlling postoperative complications [28, 29].

Notably, urachus is the rarest site of BCa in our study, which is consistent with what we now know from early literature [30, 31]. Adenocarcinomas is the most common pathological type of urachus malignancy [32]. In some earlier reports, because of the lack of effective treatment protocol, the 5-year survival rate of
locally advanced urachus cancers was 43% [31]. With the progress in surgical techniques and adjuvant therapies in recent years, the 5-year survival rate has risen to 50% [33, 34]. Even so, urachal cancer exhibited a better prognosis than other types of bladder cancer whatever the order of initiation of tumor formation [35, 36].

To our knowledge, this is the first study focusing on the hematogenous metastatic pattern of BCa patients based on SEER database. Inevitably, there are obvious limitations due to the limited information of SEER database and the retrospective nature of this kind of study. First of all, the metastatic data to above 4 sites were provided since 2010 and follow-up time is not very long. Secondly, comparing to those patients with synchronous metastasis, metachronous metastasis may possess larger quantity. Besides, information on other metastatic sites is bland, such as upper urinary tract and adrenal gland. Moreover, laboratory parameters including alkali phosphatase, alanine transaminase could not acquire from SEER for assessing the influence of metastatic sites.

**Conclusion**

In conclusion, patients with brain metastasis have the worst OS in single metastases. In contrast, lung metastasis possess the better survival outcome than the other three distant metastasis. To our knowledge, BCa patients with AJCC stage IV is under a poor prognosis and need a proper pre-treatment evaluation urgently. Knowledge of these differences in metastatic patterns is helpful for clinicians to make better pre-treatment evaluation and clinical decisions.

**Abbreviations**

BCa: bladder cancer; SEER: Surveillance, Epidemiology, and End Results; OS: Overall survival; NMIBC: non-muscle-invasive bladder cancer; MIBC: muscle-invasive bladder cancer; CIS: carcinoma in situ; AJCC: The American Joint Committee on Cancer; ICD-O-3: International Classification of Diseases for Oncology; IQR: interquartile range; MST: mean survival time; HR: hazard ratio; CI: confidence interval; SREs: skeletal-related events; ORC: open radical cystectomy; LRC: laparoscopic radical cystectomy ; RARC: Robot-assisted radical cystectomy.

**Declarations**

**Ethics approval and consent to participate**

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. We signed the 'Surveillance, Epidemiology, and End Results Program Data Use Agreement' in accordance with the requirement of using SEER database. Approval was waived by the local ethics committee, as SEER data is publicly available and de-identified.

**Consent for publication**

All authors listed approved the publication of the manuscript.

**Availability of data and material**

The datasets analyzed during the current study are publicly available for use in accordance with a limited use agreement for SEER research data: Surveillance, Epidemiology, and End Results (SEER) Program (https://seer.cancer.gov) SEER*Stat Database.

**Competing interests**

The authors declare that they have no conflict of interest.

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**Authors’ contributions**

HBW and DHZ designed the study. JM, JXC and YXZ contributed to data acquisition and statistical analysis and prepared the manuscript. JM, XPC, WZ and QZ drafted the manuscript. All authors revised this manuscript critically. HBW, FL, ZJM and DHZ supervised the study. All authors read and approved the final manuscript.

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**Code availability**

SEER*stat 8.3.6 software was used to extract the data.

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Figures

![Figure 1](image)

Venn diagram of the distribution of distant metastatic sites of bladder cancer. There were four types of metastatic sites in 6808 patients.
Figure 2

The distribution of metastases in a single versus multiple concomitant sites, stratified by pathology categories: bone (A), brain (B), liver (C), and lung (D).
Figure 3

Kaplan-Meier curves and Log-Rank test for OS according to the site of metastasis: (A) OS between patients with and without bone metastasis, P < 0.001 (B) OS between patients with and without brain metastasis, P < 0.001 (C) OS between patients with and without liver metastasis, P < 0.001 (D) OS between patients with and without lung metastasis, P < 0.001.
Figure 4

Nomogram for predicting the 1-year, 3-year and 5-year overall survival in patients with primary bladder cancer.