Incidence and Survival Trends of Bladder Rhabdomyosarcoma: A SEER-based Analysis of 125 Cases

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Abstract
Background To elucidate the bladder rhabdomyosarcoma clinicopathological characteristics and reveal the prognostic factors.

Methods We screened data from SEER database (1975-2016) stratified by age group, evaluated the differences between groups with Chi-square and Fisher’s test, conducted the Kaplan-Meier survival analysis and plotted the survival curve. The significant factors were brought into Cox regression analysis and calculated the HR(95%CI).

Results About half of the patients who develop bladder RMS will be younger than 2 years of age. Embryonal RMS account for 76% of all histopathology types. Age at diagnosis more than 16-y (HR=6.595,95%CI:3.62-12.01, p=7.04e-10), NOT embryonal rhabdomyosarcoma (HR=3.61, 95%CI:1.99-6.549, p =4.1e-06), without radiotherapy combined or surgery alone (HR=4.382, 95%CI:1.99-6.549, p =2.4e-05) and not performed the surgery (HR=2.982,95%CI:1.263-7.039, p =0.0126) were negatively correlated with 5-year survival time, while race( p =0.341), whether performed the lymphadenectomy( p =0.722) showed no influence on survival time. Cox regression results show that age, histology, SEER stage, treatment combined or alone influence the clinical outcomes.

Conclusions We demonstrated the demographic and characteristic of bladder rhabdomyosarcoma, identified and excluded the prognostic factors for the 5-year overall survival and clinical outcomes.

Background
Rhabdomyosarcoma(RMS) is one of the most common soft tissue tumor in children[1]. About 15%-20% RMS arise from the genitourinary tract: bladder, prostate and urethra[2]. Most genitourinary rhabdomyosarcoma cases occured in children under 5 years old[3]. There are two major histologic subtypes of RMS: embryonal RMS(ERMS) and alveolar RMS(ARMS). The majority of ERMS cases have an early onset and are always associated with better prognosis than ARMS[4]. As the incidence of bladder rhabdomyosarcoma is relative rare, most of the previous studies are single center case report or small samples cohort and mainly focused on the surgical treatment[5-9], except for the research conducted by the former Intergroup Rhabdomyosarcoma Study (IRS) Group and its successor
Children’s Oncology Group (COG) STS Committee [10-12]. Surveillance, Epidemiology, and End Results (SEER) program of NCI is the largest open access public source of population-based clinical information of cancers in the United States since 1973[13]. The SEER database have obvious advantages in the study of rare diseases as it have collected 5013 cases of all kinds of RMS so far, represent about 28% of the U.S. population[14].

The primary aim of the present study was to describe the clinicopathological characteristics of bladder RMS by age group in SEER program. Meanwhile, we tried to explore prognostic factors which are of great value for clinical decision making.

Methods
We downloaded a cohort of rhabdomyosarcoma patients’ clinicopathological information from SEER*Stat’s client-server mode(8.3.6 version, 1975–2016, April 15th ,2019 released). All the bladder RMS cases were selected based on the Site recode ICD-O-3/WHO 2008 standard. Age at diagnosis, year of diagnosis, race, gender, histology(ICD-O-3 Hist/behav), SEER historic stage A (1973–2015), regional nodes examined (1988+), regional nodes positive (1988+), survival months, vital status and the treatment (reason no cancer-directed surgery), Radiation sequence with surgery and chemotherapy recode information were extracted. As only 41 cases had CS tumor size (2004–2015) records, we didn’t take it into account directly. Furthermore we staged the cases according to the TNM stage system.

Patients were divided into eight groups according the age (0–2, 2–16, 16–60, > 60) and year of diagnosis(1975–1984, 1985–1994, 1995–2004, 2005–2016) respectively (Fig. 1). Chi-square or Fisher’s exact test were performed to test the basic distribution, Kaplan-Meier Survival Analyses were carried out to estimate survival rates and survival curves were plotted. Cox regression analyses were conducted to assess the prognostic factors and their hazard ratios, such as age, year of diagnosis, histology, SEER stage, TNM stage, whether performed radiotherapy and surgery and whether received chemotherapy. All statistical analyses were performed in the R software environment (version 3.4.0; http://r-project.org/), p < 0.05 was set as statistics significance.

Results
One hundred and twenty-five cases were identified according the criteria, include eighty-one male and forty-four female patients. The mean follow-up time of the cohort was 9.23 (0–38.16) years. Fourty-six patients died of their disease. White race accounted for the majority (99 cases, 79.2%), followed by Black (20 cases, 16%) and Others (6 cases, 4.8%). Most of these cases (95 cases, 76%) were diagnosed as embryonal rhabdomyosarcoma (ERMS), ERMS was more prevalent among pediatric patients (under 16 years) compared to adult patients (91.01% vs 38.89%, p < 0.001). Information of the SEER historic stage was available for 113 cases. TNM stage was evaluated based on the SEER stage, region node situation and tumor size. We found that the ratio of advanced stage (regional and distant stage or stage 3 and 4) cases in children and adult were similar (67.5 vs 76.47% and 39.24% vs 39.39%).

The ratio of lymphadenectomy in this cohort was 17.6% and showed no significant differences between the pediatric with the adult patients, so as the lymph node positive ratio. 44 patients received radiotherapy before (4) or after (40) surgery, 48 patients had surgery only and 33 patients didn’t treated by surgery. Pediatric patients had higher percentage of radiotherapy treatment than adult patients (40.45% vs 22.22%). Moreover, the proportion of children who have not undergone surgery was also higher than adult (32.58% vs 11.11%). This phenomenon was consist with that the chemotherapy percentage in children was also higher than adult (96.63% vs 41.67%). All these clinicopathological characteristics stratified by age were showed in Table 1.
Table 1
Demographic, clinicopathological and treatment characteristics of bladder RMS stratified by age group

|                      | neonates/infants | children   | adults     | elder     | p-value |
|----------------------|------------------|------------|------------|-----------|---------|
|                      | 0–2 years        | 3–16 years | 17–60 years| > 60 years|         |
| Gender               |                  |            |            |           |         |
| Male                 | 30               | 27         | 10         | 14        | 0.7229  |
| Female               | 19               | 13         | 7          | 5         |         |
| Race                 |                  |            |            |           |         |
| White                | 38               | 29         | 15         | 17        | 0.311   |
| Black                | 9                | 7          | 2          | 0         |         |
| Other                | 2                | 4          | 0          | 2         |         |
| Year of diagnosis    |                  |            |            |           | 0.04953 |
| 1975–1984            | 7                | 3          | 4          | 4         |         |
| 1985–1994            | 6                | 10         | 0          | 3         |         |
| 1995–2004            | 13               | 13         | 1          | 2         |         |
| 2005–2016            | 24               | 14         | 12         | 10        |         |
| Histology            |                  |            |            |           | 6.614e-10|
| Embryonal            | 46               | 35         | 10         | 4         |         |
| Other                | 3                | 5          | 7          | 15        |         |
| SEER Stage           |                  |            |            |           | 0.1738  |
| Localized            | 18               | 8          | 3          | 4         |         |
| Regional             | 21               | 11         | 7          | 9         |         |
| Distant              | 7                | 15         | 6          | 4         |         |
| Blank                | 3                | 6          | 1          | 2         |         |
| TNM Stage            |                  |            |            |           | 0.1709  |
| Stage 2              | 32               | 16         | 10         | 10        |         |
| Stage 3              | 7                | 3          | 0          | 3         |         |
| Stage 4              | 7                | 14         | 6          | 4         |         |
| Unknown              | 3                | 6          | 1          | 2         |         |
| Lymphadenectomy      |                  |            |            |           | 0.5038  |
| Yes                  | 8                | 7          | 5          | 2         |         |
| No                   | 41               | 33         | 12         | 17        |         |
| Lymphnode positive   |                  |            |            |           | 0.177   |
| Yes                  | 1                | 1          | 2          | 0         |         |
| No                   | 48               | 39         | 15         | 19        |         |
| Radiotherapy&Surgery|                  |            |            |           | 0.002159|
| Radiotherapy before Surgery | 1 | 3 | 0 | 0 |         |
| Radiotherapy after Surgery | 18 | 14 | 6 | 2 |         |
| Direct Surgery       | 13               | 11         | 8          | 16        |         |
| No Surgery           | 17               | 12         | 3          | 1         |         |
| Chemotherapy         |                  |            |            |           | 1.604e-14|
| Yes                  | 47               | 39         | 12         | 3         |         |
| No                   | 2                | 1          | 5          | 16        |         |

The overall 5-year survival of total bladder rhabdomyosarcoma was 36.8%. Kaplan-Meier survival analysis results showed that gender, race, whether performed lymph node dissection and the positive rate of lymph node, SEER stage and TNM stage showed no significant differences in the 5-year overall survival rate. Factors associated with worse OS were elder age at diagnosis, not embryonal RMS, higher clinical stage and not performed radiotherapy or chemotherapy. Kaplan-Meier survival curve were plotted based on these findings (Fig. 2–6). Table 2 summarized the number, 5-year OS and p value for these factors. All these statistics significant factors were included to handle the cox
regression analysis. The hazard ratio and 95% confidential interval (CI) were calculated and listed in Table 3.

| Table 2 |
|---------------------------------|
| 5 year overall survival rates of different groups bladder RMS |

|             | Number | 5-year OS(%) | p-value |
|-------------|--------|--------------|---------|
| Gender      |        |              |         |
| Male        | 81     | 51(62.96%)   | 0.508   |
| Female      | 44     | 28(63.64%)   |         |
| Age         |        |              |         |
| 0–2         | 49     | 41(83.67%)   |         |
| 3–16        | 40     | 29(72.5%)    |         |
| 17–60       | 17     | 7(41.18%)    |         |
| > 60        | 19     | 2(10.53%)    |         |
| Race        |        |              |         |
| White       | 99     | 60(60.6%)    | 0.341   |
| Black       | 18     | 13(72.22%)   |         |
| Other       | 8      | 6(75%)       |         |
| Year of diagnosis |     |              | 3.22e-15 |
| 1975–1984   | 18     | 6(33.33%)    |         |
| 1985–1994   | 19     | 12(63.16%)   |         |
| 1995–2004   | 28     | 19(67.86%)   |         |
| 2005–2016   | 60     | 42(70%)      |         |
| Histology   |        |              | 4.01e-06 |
| Embryonal   | 95     | 68(71.58%)   |         |
| Other       | 30     | 11(36.67%)   |         |
| SEER Stage  |        |              | 0.0618  |
| Localized   | 33     | 26(74.29%)   |         |
| Regional    | 48     | 28(58.33%)   |         |
| Distant     | 32     | 15(46.88%)   |         |
| Blank       | 12     | 10(83.33%)   |         |
| TNM Stage   |        |              | 0.156   |
| Stage 2     | 68     | 44(67.71%)   |         |
| Stage 3     | 13     | 10(76.92%)   |         |
| Stage 4     | 31     | 15(48.39%)   |         |
| Unknown     | 12     | 10(83.33%)   |         |
| Lymphadenectomy |     |              | 0.722  |
| Yes         | 22     | 14(63.64%)   |         |
| No          | 103    | 65(63.11%)   |         |
| Lymphnode positive | | 0.292  |
| Yes         | 4      | 2(50%)       |         |
| No          | 121    | 77(63.64%)   |         |
| Radiotheray&Surgery |     |              | 0.000227 |
| Radiotherapy before Surgery | 4 | 3(75%) |
| Radiotherapy after Surgery | 40 | 28(70%) |
| Direct Surgery | 48 | 21(43.75%) |
| No Surgery  | 33     | 27(81.82%)   |         |
| Chemotherapy|        |              | 1.7e-11  |
| Yes         | 101    | 75(74.26%)   |         |
| No          | 24     | 4(16.67%)    |         |
| Factor                        | HR(95%CI)               | p-value     |
|------------------------------|-------------------------|-------------|
| **Age**                      |                         |             |
| 0–2                          | Ref                     |             |
| 3–16                         | 1.763(0.7069–4.397)     | 0.22393     |
| 17–60                        | 5.063(1.9714–13.001)    | 0.00075     |
| > 60                         | 15.553(6.5420–36.975)   | 5.27e-10    |
| **Histology**                |                         |             |
| Embryonal                    | Ref                     |             |
| Other                        | 3.61(1.99–6.549)        | 2.4e-05     |
| **SEER Stage**               |                         |             |
| Localized                    | 0.8172(0.1690–3.951)    | 0.802       |
| Regional                     | 1.7476(0.4071–7.503)    | 0.453       |
| **Distant**                  |                         |             |
| Blank                        | Ref                     |             |
| **TNM Stage**                |                         |             |
| Stage2                       | 1.383(0.3258–5.873)     | 0.660       |
| Stage3                       | 1.135(0.1875–6.867)     | 0.890       |
| Stage4                       | 2.573(0.5918–11.19)     | 0.208       |
| **Radiotherapy&Surgery**     |                         |             |
| Radiotherapy before Surgery  | 0.9854(0.1178–8.242)    | 0.9891      |
| Radiotherapy after Surgery   | 1.7783(0.6668–4.743)    | 0.2500      |
| Direct Surgery               | 4.3823(1.8045–10.643)   | 0.0011      |
| No Surgery                   | Ref                     |             |
| **Chemotherapy**             |                         |             |
| No                           | Ref                     |             |
| Yes                          | 5.714(3.159–10.33)      | 8.15e-09    |

**Discussion**

SEER program of NCI has been used to analyze a variety of malignancies. Bladder rhabdomyosarcoma, as a rare malignant genitourinary neoplasm, is relatively lack of precious large-scale epidemiological study. In our research, we compared the epidemiology characteristics in each age group and explored the prognostic factors affecting the 5-year OS by utilizing an open access population-based public database.

As expected, most of the cases occur in 0–2 age group (49 cases) and about two-thirds of cases were diagnosed in children younger than 10 years old as Perez et al had reported[15]. But unlike the former study results said that ERMS had a bimodal peak in early adolescence[16], there were only 11 cases between 11–24 years old in our research. We divided patients as pediatric and adult in principle and further divide pediatric group into infant (0–2 years) and children (3–16 years) according the WHO classification. The adult group was made up of adult (17–60 years) and the elder (> 60 years).

Cox regression results showed that age was a significant risk factor, the hazard ratio for elder group can be 15.553 to infant group.

The total ratio of male and female is about 2:1. It remains relatively stable in different age groups,
which is not consistent with former research (about 75% arise in male) as they focused on the whole genitourinary RMS and the prostate RMS increased the proportion of male patients[17]. We confirmed that the gender was not associated with different survival time and was not a risk factor. As all SEER data were collected in the United States, this study was lack of global representation of race proportions. The number of cases increased significantly over every ten years, however when we considered the whole SEER database, the percentage of bladder RMS was quite stable (3.37%, 3.36%, 2.17%, 2.21%).

Embryonal RMS is the most common pathological type in pediatric bladder RMS and ERMS always indicates a better prognostic than non-embryonal RMS. This well-known phenomenon has been reported many times and was also validated in our study, only the percentage of ERMS (71.58%) is lower than former studies (about 90%)[17].

Summary stage system is used by SEER program based on the theory of cancer growth: localized, regional and distant. We converted the Summary Stage into TNM system according the regional nodes examination results, tumor size and metastasis situation. Both of the stage systems were brought into analysis. The stage distribution among age groups demonstrated no differences. As staging increases, patient survival rates gradually decline.

Regarding the surgical treatment of bladder RMS, lymph node dissection (LND) plays an critical role as the bladder is a rich blood supply organ. Due to lack of the majority of the regional nodes examination results, survival analysis and cox regression results can be affected and cannot achieve satisfactory goal. Meanwhile, the LND template and positive lymph node location have not been included in SEER data, that make it difficult to analysis the association of LND with prognostic.

Currently, radiotherapy, multi-agent chemotherapy and surgery are all important invention choices, the problem is the treatment timing and sequences of these therapy for suitable subgroup patients[18]. In this research, radiotherapy improved the prognostic significantly no matter before surgery or after surgery than surgery alone, so as the chemotherapy. Although we cannot get the chemotherapy regimens and radiotherapy dose data, we believe the core function of radiotherapy and chemotherapy in RMS treatment are beyond doubt.
In 2000, the Intergroup Rhabdomyosarcoma Study Group (IRSG) and other 3 groups came together to merge COG. During IRSG studies and COG period, they have published 6 protocols for RMS[12, 19–23]. The 5-year overall survival rates had increased from 55% in IRS-I to 71% in IRS-IV, this trend was also noticed in our research: from 33% (1975–1984) to 70% (2005–2016). This can be attributed to the improvement of technology development in this years.

In former other studies, M. Fisch et al[24] evaluated different treatment modalities include conservative surgery, radical surgery and irradiation therapy in 22 urogenital tract rhabdomyosarcoma and they recommended radical operative intervention with multiple biopsies after chemotherapy to for the long-term benefit. In their updated study[8], they still confirmed the previous conclusion. Sherbiny et al reported a one single-centre experience of 30 cases low urinary tract tumor and 11 cases of them is bladder rhabdomyosarcoma. They stratify patients into two risk-groups according their response to the chemotherapy and for the low risk group patients, their bladders could be salvaged. Kathleen Kieranc and Margarett Shnorhavorian [9]systematically summarized the epidemiology and treatment status of bladder/prostate rhabdomyosarcoma.

As far as we know, this is the largest samples retrospective study based on the data of SEER program for bladder RMS under the conditions of relatively comprehensive information and the long follow-up time. The limitations of this study are mainly the inherent defects of the SEER program: it is impossible to compare different chemotherapy regimens, to discuss the influence of positive surgical margins, to know the related immunohistochemistry results, to examine the fusion genes (PAX3/7-FOX1) exist. All of these elements can promote the accuracy judgement of treatment and prognosis research. Moreover, as urologists, while concerning about the tumor control, we also focused on the urination control situation for the patient quality of life. Therefore, we look forward further studies to provide more clinical evidences for us to explore and treat bladder RMS better.

Conclusions
In conclusion, most of the bladder RMS cases occured in pediatric group, whereas the incident trends stayed stable. The majority of pediatric bladder RMS was ERMS and ERMS always had better survival outcomes when compared with other histology type. Radiotherapy and chemotherapy have the equal
importance as complete surgery for the treatment decision.

Abbreviations
SEER
the surveillance, epidemiology, and end results
RMS
rhabdomyosarcoma
ARMS
alveolar rhabdomyosarcoma
ERMS
embryonal rhabdomyosarcoma
IRSG
Intergroup Rhabdomyosarcoma Study Group
LND
lymph node dissection
OS
overall survival

Declarations

**Ethics approval and consent to participate**

We received permission to access the research data file in the SEER program from the National Cancer Institute, US (reference number 13562-Nov2018). Approval was waived by the local ethics committee, as SEER data is publicly available and de-identified.

**Consent to publish**

No individually identifiable data are presented.

**Availability of data and materials**

We received permission to access the research data file in the SEER program from the National Cancer Institute, US (reference number 13562-Nov2018).

Competing interests
The authors declare that they have no competing interests

Authors' Contributions

Conceptualization: HZ and ZF
Data curation: PL, HZ and HC
Formal analysis: PL, TG and WZ
Funding acquisition: HZ
Methodology: HC and YZ
Project administration: PL and LM
Software: PL, HC and XZ
Supervision: HZ
Validation: TT
Visualization: PL and HZ
Writing – original draft: PL and H
Writing – review & editing: HZ

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Figures
Figure 1

Case number in different age groups
Figure 2

Kaplan-Meier survival curve for different age groups.
Figure 3

Kaplan-Meier survival curve for different year of diagnosis.
Figure 4

Kaplan-Meier survival curve for ERMS or not.
Figure 5

Kaplan-Meier survival curve for radiotherapy or surgery treatment.
Figure 6

Kaplan-Meier survival curve for chemotherapy or not.