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ORIGINAL PAPER

Primary Bladder Sarcoma: A multi-institutional experience from the Rare Cancer Network

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Summary

Purpose or Objective: *Primary sarcoma of the urinary bladder (SUB) is a rare but aggressive form of bladder cancer (BCa). Available evidence on SUB is limited to case reports and small series. The aim of the present multi-institutional study was to assess the clinical features, treatments, and outcomes of patients with SUB.*

Materials and methods: *Using a standardized database, 7 institutions retrospectively collected the demographics, risk factors, clinical presentation, treatment modalities and follow-up data on patients with SUB between January 1994 and September 2021. The main inclusion criteria included BCa with soft tissue tumor histology and sarcomatoid differentiation.*

Results: *Fifty-three patients (38 men and 15 women) were identified. Median follow-up was 18 months (range 1-263 months). Median age at presentation was 69 years (range 16-89 years). Twenty-six percent of patients had a prior history of pelvic radiotherapy (RT), and 37% were previous smokers. The main presenting symptoms at diagnosis were hematuria (52%), pelvic pain (27%), and both hematuria and pelvic pain (10%). American Joint Committee on Cancer (AJCC) 8 th edition stage II, III and IV at diagnosis were 21%, 63% and 16%, respectively. Treatment modalities included surgery alone (45%), surgery plus neo- or adjuvant-chemotherapy (17%), surgery plus neo- or adjuvant-RT (11%), RT with concurrent chemotherapy (4%), neo-adjuvant chemotherapy plus surgery plus adjuvant RT (2%) and palliative treatment (21%). Rates of local and distant recurrences were 49% and 37%, respectively. Five-year overall survival and progression-free survival (PFS) were 66.5% and 37.6%, respectively. No statistically significant differences in PFS between the treatment modalities were observed.*

Conclusions: *Primary SUB is a heterogeneous disease group, commonly presenting at advanced stages and exhibiting aggressive disease evolution. In contrast to urothelial carcinoma, the primary pattern of recurrence of SUB is local, suggesting the need for multimodal approaches. Continuous international collaborative efforts seem warranted to provide guidance on how to best tailor treatments based on SUB-specific indices.*

KEY WORDS: *Primary sarcoma of the urinary bladder (SUB); Bladder cancer.*

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INTRODUCTION

Although uncommon, primary *sarcoma of the urinary bladder* (SUB) is an aggressive type of *bladder cancer* (BCa), accounting for less than 1% of all BCa. The most common risk factors for the development of this disease is smoking and previous exposure to *radiotherapy* (RT) and cyclophosphamide (1, 2).

Based on mesenchymal and epithelial components, SUB can be classified as *Sarcomatoid carcinoma* (SC) and *Carcinosarcoma* (CS), both considered *malignant biphasic tumors* (MBT) by the *World Health Organization* having malignant epithelial and mesenchymal elements (3). More recently researchers have cast doubts on the significance of distinguishing between these two entities in both bladder and other solid malignancy as they consider these two histological subtypes as separate moments between epithelial (*Sarcomatoid carcinoma*) and mesenchymal differentiation (*Carcinosarcoma*) (4). Usually, the epithelial element contains high-grade transitional-cell carcinoma with some epidermoid and/or glandular differentiation, while the heterologous element contains chondrosarcoma, malignant fibrous histiocytoma, osteosarcoma, leiomyosarcoma, fibrosarcoma, or rhabdomyosarcoma. Both SC and CS cases are most common among older men, manifesting as fast-growing, advanced-stage polypoid tumors (1-4). When the mesenchymal element lacks epithelial components, SUB can be considered a true heterologous sarcoma (TS).

Usually, treatment of SUB has been deduced from the management of *urothelial carcinoma* (UC) of the bladder. Muscle-invasive UC of the bladder often results in distant metastasis after radical cystectomy, and therefore, neo-adjuvant or adjuvant chemotherapy has been recommended as a part of a multimodal approach (5, 6).

However, because of to the rarity of SUB and the absence of randomized controlled trial in this setting, definitive conclusions about the optimal treatment option cannot be made. Poor outcomes have been reported in patients with SUB, whatever the treatment used. Even after adjust-

ing for tumor stage, overall survival (OS) rates for SUB vs high-grade, pure UC are 54% *vs* 77% at 1 year and 37% *vs* 47% at 5 years, respectively (4, 7).
Published data on SUB only consist of case reports and limited case series. Not much is understood of SUB biology and behavior and its rarity does not permit to design specific treatment guidelines. Thus, we intend to summarize the current multi-institutional knowledge of SUB and present an overview of the epidemiology, clinical features, and management of this uncommon type of BCa that can help clinicians to better tailor clinical decisions on this rare disease.

Methods

Data on SUB from January 1994 to September 2021 from 7 institutions were retrospectively collected. *International Review Board* (IRB) approval based on each country/institution was obtained for retrospective review of data.
We only collected data from localized primary bladder tumors with soft tissue tumor histology, including SC, CS and TS. The data obtained included age, gender, country and institution, symptoms at the time of diagnosis, risk factors (smoking and RT exposure), tumor size, tumor location, margins and nodal status. Sarcoma subtype, grade and specific immuno-histochemical markers of these tumors were noted. Staging at the time of pathological diagnosis was based on the TNM (tumor, lymph node, metastasis) classification for genitourinary tumors.
Treatment modalities analyzed included cystectomy (radical, partial, other), RT (definitive, adjuvant, neo-adjuvant or palliative) and chemotherapy (neo-adjuvant, adjuvant, radio-sensitizer or palliative).
Overall survival (OS), *cancer-specific survival* (CSS), *disease-free survival* (DFS), *distant metastases* (DM) and *local control* (LC) were calculated from diagnosis to the date of any specific event or the date of last follow-up in case an event did not occur.
Probabilities for OS, CSS and DFS were determined by Kaplan-Meier estimates. *Local recurrence* (LR) and DM were estimated using cumulative incidence function considering death as a competing risk. Selective comparisons of survival curves were calculated by the log-rank test. Multivariate models were not used because of the small number of patients and events. For statistical analyses the software program STATA (*version 13; College Station, Texas, USA*) was used.

Results

Fifty-three patients were evaluated, 38 men (72%) and 15 women (28%), who had a median age at presentation of 69 years (range 16-89 years). Twenty-six percent of patients had a prior history of pelvic RT; contrary to patients with transitional cell carcinoma, only 37% of patients had a history of tobacco use. Symptoms at diagnosis were mainly hematuria (52%), pelvic pain (27%), and both hematuria and pelvic pain (10%).
Median tumor size was 4.5 cm (range 1.5-9.5 cm). Extravesical spread (T3/T4) was the most common presentation of the primary tumor in 59% of cases. Nodal metastases were identified in 35% of patients. AJCC 8th edition stage II, III and IV at diagnosis were 21%, 63% and 16%, respectively. The majority of tumors presented with high grade histology (88%). Distribution of TS and MBT were 43% and 57%, respectively. Leiomyosarcoma was the most common histology in the TS group (63%), followed by angiosarcoma (13%), pleomorphic undifferentiated sarcoma (10%), rhabdomyosarcoma (7%), chondrosarcoma of soft tissue (3%) and leiomyoma (3%). Table 1 presents patient and tumor characteristics.
Seventy-three percent of patients underwent radical or partial cystectomy. Specifically, treatment modalities included surgery alone (45%), surgery preceded or followed by either chemotherapy (17%) or radiotherapy (11%), definitive radiotherapy with concurrent chemotherapy (4%), neo-adjuvant chemotherapy plus surgery plus adjuvant radiotherapy (2%) and palliative treatment (21%). Treatment modalities are outlined in Table 2.

Table 1.
Patient and tumor characteristics.

Patients characteristics	N (%)
Age mean	69
Gender	
Male	38 (72)
Female	15 (28)
Prior history of RT	14 (26)
Tobacco exposure	20 (37)
Symptoms	
Hematuria	28 (52)
Pelvic pain	14 (27)
Both	5 (10)
Other	6 (11)
Tumor size (median)	4.5 cm (1.5 -9.5)
T stage	
T1/T2	22 (41)
T3/T4	31 (59)
Nodal metastases	19 (35)
AJCC	
II	11 (21)
III	33 (63)
IV	9 (16)
Malignant Biphasic Tumors (MBT)	23 (43)
True Sarcoma (TS)	31 (57)
Leiomyosarcoma	19 (61)
Angiosarcoma	7 (22)
Pleomorphic undifferentiated sarcoma	2 (7)
Rhabdomyosarcoma	2 (7)
Chondrosarcoma	1 (3)

Table 2.
Treatment modalities.

Treatment modalities	N (%)
Surgery alone	24 (45)
Surgery plus neo-adjuvant or adjuvant chemotherapy	9 (17)
Surgery plus neo-adjuvant or adjuvant radiotherapy	6 (11)
Definitive radiotherapy with concurrent chemotherapy	2 (4)
Neo-adjuvant chemotherapy plus surgery plus adjuvant radiotherapy	1 (2)
Palliative	11 (21)

Figure 1.
OS 5-year rate 66.5% (53.3-83)

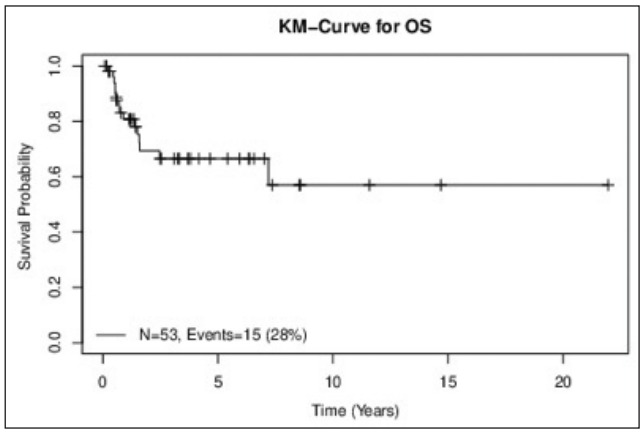


Figure 2.
PFS 5-year rate: 37.6% (25.8-54.7).

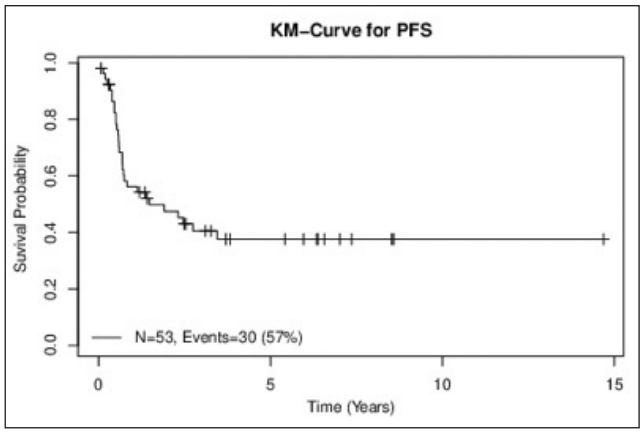


Figure 3.
LR 5-year rate: 49% (34-64).

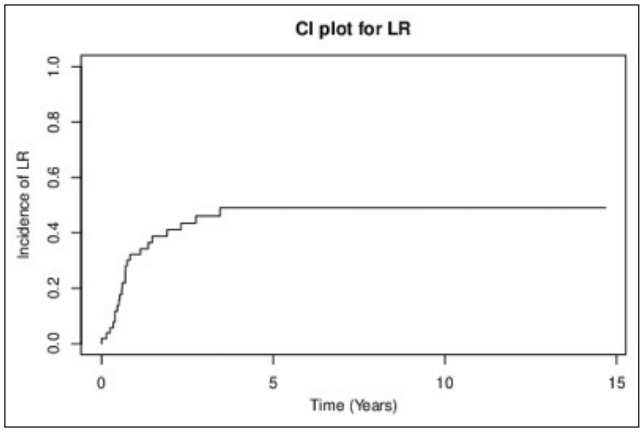
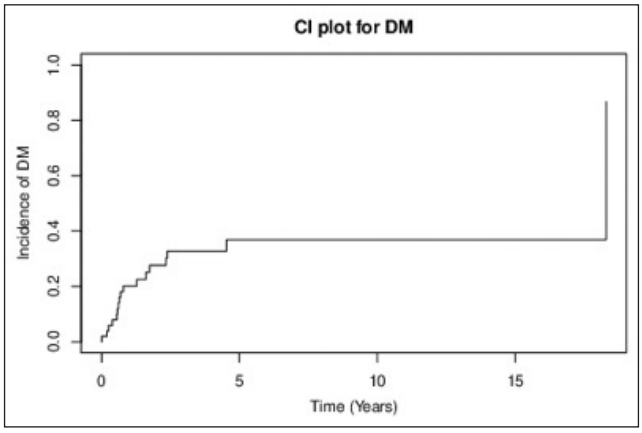


Figure 4.
DM 5-year rate: 36.9% (21.4-52.4).



Median follow-up was 18 months (range 1-263 months). *Local recurrence* (LR) occurred in 49% of patients and *distant metastases* (DM) were present in 37%. Five-year OS and PFS were 66.5% and 37.6%, respectively. Kaplan-Meier curves for OS and PFS and the cumulative incidence for LR and DM are shown in Figures 1, 2, 3 and 4 respectively.

When outcomes in subgroups were examined, a more advanced tumor stage (T2 *vs* T3/T4) correlated to shorter PFS (median PFS for T2-category was not reached and for T3/T4 was 8.4 months; p = 0.059). Prior history of pelvic radiotherapy also related to lower PFS (7 *vs* 31 months, p = 0.0018) and OS (9 *vs* 43 months, p = 0.0007). We found no statistically significant differences in PFS between treatment modalities or between the presence *vs* absence of epithelial components (TS and MBT).

Discussion

Although the occurrence of rare cancers in the general public is a serious health issue as a whole, acquiring statistically-reliable clinical trial data is difficult due to the low number of patients with an individual rare cancer type within specific areas (8).

Since most available literature on rare cancers is published as single-institution case reports, it is arduous to draw prognostic implications from these data; furthermore the impact of local practices on treatment outcomes is amplified when dealing with rare diseases. Patients with rare neoplasm show significantly poorer results than patients with more common malignancies; mean 5-year survival for the former is up to 20% lower than for the latter (9). This is the case with primary SUB, a disease comprising less than 1% of all BCa, which poses a challenge in the treatment of this uncommon histological variant.

Poor outcomes have been reported in patients with SUB, whatever the treatment used. The five-year *overall survival* (OS) rate of the present cohort is 66.5%, which exceeds the findings of previous studies where survival rates at five years were consistently below 50% (4, 10, 11). This difference in outcomes can be attributed, at least partially, to two key factors within the study. Firstly, this cohort predominantly consisted of a younger population, with a median age at presentation of 69 years, which is lower than other reports (4). Younger patients have generally been associated with better treatment tolerance, higher overall fitness levels, and potentially more favorable disease characteristics, all of which could contribute to improved survival rates. Secondly, the analysis encompassed both malignant biphasic tumors (CS and SC) and true heterologous sarcomas (TS). By including both types of tumors, we accounted for the inherent biological diver-

sity, variable clinical behavior of both entities and perhaps different outcomes.

Twenty-six percent of the patients of the cohort have a previous history of pelvic *radiation therapy* (RT), observing inferior outcomes in this subgroup compared to those without prior RT (median OS of 9 *vs.* 43 months, p = 0.0007). Is well known that Radiation-induced sarcomas pose treatment challenges as they arise in areas with complications from previous treatments, making surgical removal difficult. Retrospective analyses have shown poor prognosis in these patients compared to sporadic soft-tissue sarcomas, with 5-year OS rates ranging between 32% and 45% (12) which are in line with the findings of this study.

Continuing with subgroup analyses, patients with extravesical spread (T3/T4) exhibit notable decreases in progression-free survival (PFS) compare to those with less advanced tumors (median PFS for T2-category was not reached and for T3/T4 was 8.4 months). The reduced PFS observed in this particular subgroup of patients (T3/T4) can be attributed to the higher likelihood of developing distant metastases, but also because of the complex relationship between advanced tumor stage and critical anatomical structures, resulting in a potentially decreased effectiveness of local treatment. Data from pelvic sarcomas exemplify this last phenomenon, with successful attainment of a microscopically margin-negative resection (R0) surgery achieved only in 70% of cases (13).

Contrary to UC, where distant recurrence is the primary pattern, this study reveals that rates of local and distant recurrences observed were 49% and 37%, respectively. These findings hold significant implications, particularly considering that approximately 60% of patients in this cohort exhibit extra-vesical spread (T3/T4). The high rates of local failures observed emphasize the critical need for optimizing local therapies, particularly within the latter sub-group.

Typically, the treatment approach for SUB has been extrapolated from the management of UC of the bladder, where cystectomy and chemotherapy are considered fundamental in a multimodality approach (5, 6).

Retroperitoneal sarcomas (RPS) exhibit a behavioral pattern that aligns more closely with the presents findings, showing a higher incidence of local recurrence, which remains the primary cause of mortality (14). Within this context, local recurrence and metastatic disease occur in approximately 50-60% and 20% of cases, respectively (15), mirroring the failure pattern observed in this study. The importance of local control drives management of RPS, with surgery been the mainstay of curative intent therapy (16). Complete gross resection (R0 or R1) has been associated with improved disease-free survival (17). However, even with a histologically negative margin (R0), local recurrence can still occur (18). Considering the high incidence of local recurrences following surgery, neoadjuvant radiotherapy has emerged as an attractive yet controversial option for RPS (19, 20).

Despite the retrospective nature of this study, and therefore hampered by its intrinsic biases, the high local failure rates seen in this cohort prompts the hypothesis that neoadjuvant radiotherapy as part of a multi-disciplinary approach for SUB may play an important role in reducing loco-regional failure rate and improving, at least to some extent, the survival of this patients, especially in higher tumor stages (T3/T4) where R0 surgery with wide margins is more difficult to obtain and were poorer outcomes we have observed.

Although the existing evidence is limited, our retrospective data can provide valuable insights into this uncommon neoplasm, enabling clinicians to make more informed clinical decisions tailored to this rare disease.

Conclusions

Primary SUB is a heterogeneous disease group, commonly presenting at advanced stages and exhibiting aggressive disease evolution. In contrast to UC, the primary pattern of recurrence of SUB is local, suggesting the need for multimodal approaches. Continuous international collaborative efforts seem warranted to provide guidance on how to best tailor treatments based on SUB-specific indices.

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