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Original Contribution

Secondary tumors of the bladder: A survival outcome study

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ABSTRACT

The urinary bladder may be involved by a variety of secondary tumors that originate from other organs. Bladder secondary tumors are rare and may be mistaken as bladder primary tumors because of their overlapping morphologic features. To avoid the diagnostic pitfalls, we analyzed the clinicopathologic features of bladder secondary tumors in a large cohort of patients. Our patient cohort consisted of 45 females and 38 males with a mean age of 58.7 ± 15.4 years (range 10–87 years). The tumors involved the bladder via direct extension from adjacent organs (n = 42) and distant metastasis (n = 41). In females, the majority of secondary tumors originated from the gynecologic tract (n = 25), and other common origins included the colon/rectum (n = 5) and breast (n = 4). In males, the most common origin was the prostate (n = 18), followed by the colon/rectum (n = 4) and kidney (n = 3). 75.9% of the secondary tumors were adenocarcinoma (n = 63), and other common tumor types included sarcoma (n = 6), squamous cell carcinoma (n = 5), melanoma (n = 4), and neuroendocrine carcinoma (n = 3). 67.5% of patients (n = 56) died of the disease with a median overall survival of 23 months from the time of secondary involvement of the bladder. Patients with secondary tumors via direct extension had a median survival time of 20 months, which was not significantly different from that for patients with secondary involvement via distant metastasis (24 months) (p = 0.83). Median survival in cases with prostate primary was 20 months as compared to 23 months for all other tumor types (p = 0.68). The majority of secondary tumors are composed of adenocarcinoma, which highlights the importance of differentiating primary from secondary involvement in bladder adenocarcinoma. Regardless of the origin, bladder secondary tumors are associated with a poor prognosis.

1. Introduction

Secondary malignancies of the bladder are much less frequent as compared to primary tumors; however, they usually represent terminal stages of the disease. A number of secondary tumors can involve the bladder via metastasis or direct extension. Distinguishing primary from secondary bladder tumors can be challenging due to considerable overlap in morphologic features as well immunohistochemical profile [1-3]. This distinction is, however, crucially important due to significant management differences and prognostic outcome. The purpose of this study is to investigate the frequency of different secondary tumors of the bladder and their survival outcome. A detailed discussion of pathologic features, differential diagnosis, and clinical relevance is also included.

2. Materials and methods

After the study was approved by Institutional Review Board we searched our pathology database from January 2001 to December 2019 for secondary tumors involving the bladder. In total, 83 cases were identified. Data such as age, gender, tumor type, date of initial diagnosis, date of bladder involvement and date of death/last follow up were collected. Diagnosis of secondary involvement of bladder was confirmed using the clinical history, radiologic features, immunohistochemical support and absence of conventional urothelial carcinoma or carcinoma in situ.

Patients' demographics and clinical characteristics were summarized using descriptive statistics. Overall survival (OS) was defined as the time interval between date bladder involvement and date of death, and was censored at the last follow-up date for patients who were alive. Survival curves were estimated using the Kaplan-Meier method.

3. Results

Among 83 patients, 45 (54.2%) were female and 38 (45.8%) were male. Mean age was 58.7 ± 15.4 years. The seventh decade was most

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Table 1
Distribution of different secondary tumors of the bladder in male and female patients.

Primary site	Males	Females	Total
Prostate	18	–	18
Ovary	–	12	12
Colon and rectum	4	5	9
Uterus	–	7	7
Cervix	–	6	6
Esophagus and stomach	2	3	5
Bone and soft tissue	3	1	4
Kidney	3	1	4
Skin	3	1	4
Breast	0	4	4
Appendix	1	2	3
Small bowel	1	1	2
Lung and pleura	1	1	2
Thyroid	1	0	1
Gall bladder	0	1	1
Anal canal	1	0	1

common age of presentation (30 patients). The tumors involved the bladder via direct extension from adjacent organs (n = 42) or distant metastasis (n = 41). 25 (30.1%) patients had primary tumor in the gynecologic tract and 21 (25.3%) in the gastrointestinal tract. Direct extension from prostatic adenocarcinoma accounted for 18 (21.7%) cases. In females, the majority of secondary tumors originated from the gynecologic tract (n = 25), and other common origins included the colon/rectum (n = 5) and breast (n = 4) (Table 1, Fig. 1). In males, the most common origin was the prostate (n = 18), followed by the colon/rectum (n = 4) and kidney (n = 3) (Table 1, Fig. 2). 75.9% of the secondary tumors were adenocarcinoma (n = 63), and other common tumor types included sarcoma (n = 6), squamous cell carcinoma (n = 5), melanoma (n = 4), and neuroendocrine carcinoma (n = 3). Additionally, the study cohort included one case each of pleural mesothelioma and malignant mixed Mullerian tumor (sarcomatoid carcinoma). The 6 cases of sarcoma included, two cases of desmoplastic small round cell tumor and one case each of fibrosarcoma, leiomyosarcoma, osterosarcoma and gastrointestinal stromal tumor. Fig. 3 demonstrates some examples of secondary tumors in our cohort. 67.5% of patients (n = 56) died of the disease. Median overall survival from the time of bladder involvement was 23 months (95% CI 14–31.9 months). Median survival for female patients was 25 months as compared to 20 months in male patients (p = 0.14). Median survival in cases with prostate primary was 20 months as compared to 23 months for all other tumor types (p = 0.68) (Fig. 4). Median survival for bladder involvement by direct extension was 20 months as compared to 24 months in cases of metastatic disease (p = 0.83) (Fig. 5).

4. Discussion

Secondary tumors of the bladder are uncommon and account for approximately 2–3% of all bladder tumors [3]. Generally, they represent advanced stage and late complication of primary malignancy. Form a pathologic standpoint they present a diagnostic challenge. The differential diagnosis is broad, depending on each different histologic primary.

Two previous studies showed that primary colonic adenocarcinoma was the most common secondary tumor involving the bladder [1,2]. In our cohort a quarter of cases (n = 21) came from the gastrointestinal tract; however, most common primary tumor in our cohort was prostatic adenocarcinoma (n = 18, 21.7%). In study by Bates et al. [1] prostate was the second most common primary after colon. Overall 63 (75.9%) patients in our cohort and 54% patients in study by Bates et al. [1] had secondary involvement of bladder by some kind of adenocarcinoma. Irrespective of the primary site of origin, an adenocarcinoma involving a urinary bladder elicits a wide differential diagnosis including; primary adenocarcinoma of the urinary bladder, urachal adenocarcinoma, urothelial carcinoma with glandular differentiation, clear cell adenocarcinoma, prostatic adenocarcinoma, and metastatic adenocarcinoma from other primary sites.

Presence of conventional urothelial carcinoma or urothelial carcinoma in situ component helps distinguishing urothelial carcinoma with glandular differentiation. Clear cell adenocarcinoma typically arises in the urethra and shows female predominance [4]. Morphologically, they show mixed tubulocystic, papillary, and solid patterns. Tumor cells are flat to cuboidal with clear to eosinophilic cytoplasm and frequently exhibit hobnail pattern. These tumors are frequently immunoreactive to P504S (AMACR) and PAX-8 [4,5]. For gynecologic tract primaries, PAX8 is an extremely valuable stain. Although these morphologic features and immunohistochemical profile help distinguishing clear cell adenocarcinoma from other differential diagnoses listed above, clear cell adenocarcinoma arising from the bladder/urethra is histologically and immunohistochemically indistinguishable from its counterpart arising from the female genital tract. Therefore clinical and radiologic

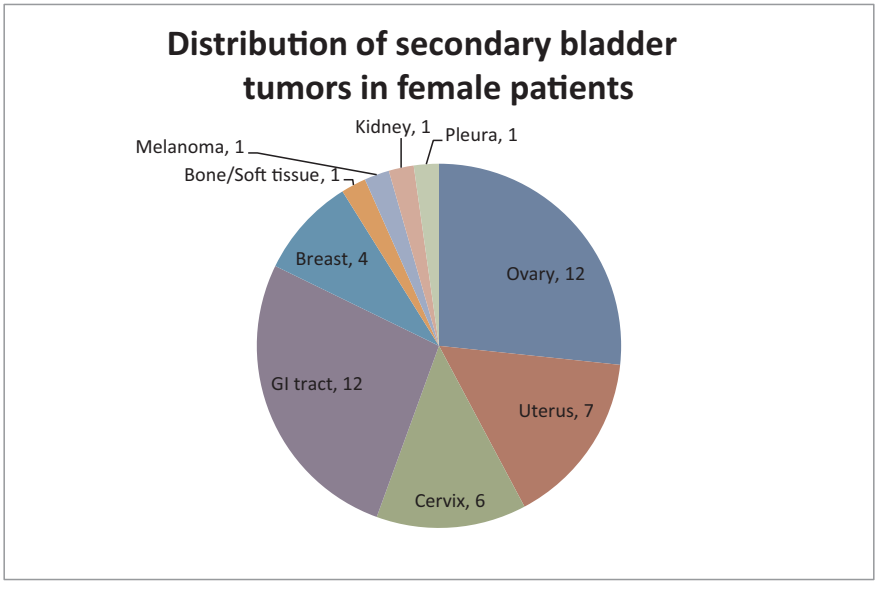

Fig. 1. Distribution of secondary bladder tumors in female patients.

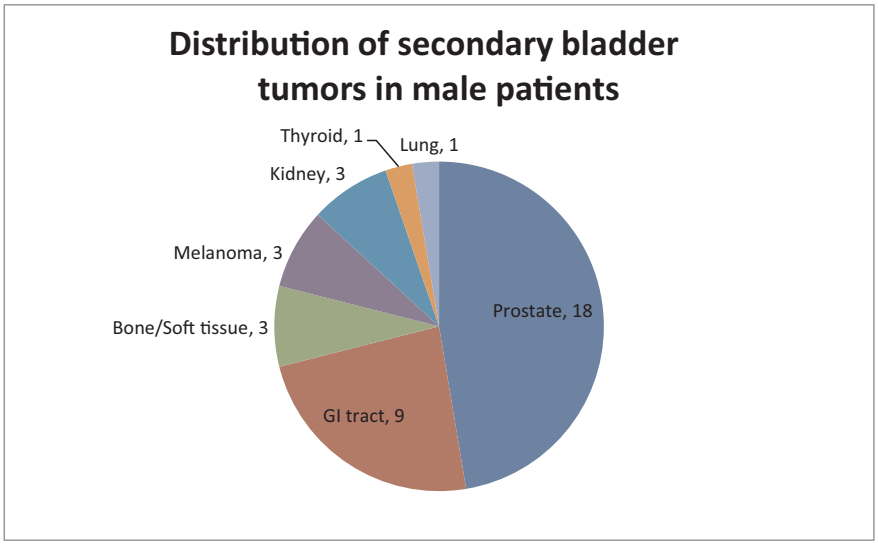

Fig. 2. Distribution of secondary bladder tumors in male patients.

correlation is recommended to determine the site of origin of this tumor. Urachal adenocarcinoma is exceedingly rare and usually arises in the urachus or the urachal remnant [6,7]. The urachal remnant is most commonly found at the bladder dome, but it can occur anywhere along the bladder midline [8]. Urachal adenocarcinoma affects relatively younger patients (median age 51 age) and predominantly affects male patients (male:female; 2:1) [6,7]. Urachal adenocarcinoma is morphologically indistinguishable from non-urachal primary bladder adenocarcinoma and adenocarcinoma of colorectal origin. Additionally the immunohistochemical profile of these tumors shows considerable overlap. Nonetheless, the distinction is important as urachal adenocarcinoma patients have extremely favorable outcome to partial cystectomy with en bloc resection of the urachus and umbilicus [9]. Johnson et al. [10] proposed criteria for correctly classifying a tumor as urachal adenocarcinoma. These include: (1) tumor in the dome or any midline of the bladder, (2) sharp demarcation between the tumor and the surface epithelium, and (3) absence of primary adenocarcinoma in other organ systems. Secondarily involvement of the bladder by prostatic adenocarcinoma can be confirmed by using a variety of immunohistochemical markers including NKX3.1, PSA, PAP, prostein, AR and ERG. Secondary involvement by colorectal and gynecologic tract primaries on the other hand is not possible based on morphologic and immunohistochemical profile alone. Thorough work up is needed for ruling out adenocarcinoma of these sites before designating the tumor as bladder primary. For adenocarcinomas coming from other uncommon primary sites such as breast or kidney, appropriate history, morphology and immunohistochemical profile clinches the right diagnosis. In case of metastatic lobular breast carcinoma, an important differential diagnosis is the plasmacytoid variant of urothelial carcinoma. Both of these entities have similar morphologic features. The diagnostic difficulty is compounded by the fact that estrogen receptor positivity has been found in high grade urothelial carcinomas [11]. Additionally GATA3 and E-cadherin immunohistochemical stains cannot distinguish the two entities [12,13]. However, some studies suggest that mammoglobin and gross cystic disease fluid protein can be utilized in differentiating the two entities [14,15].

Squamous cell carcinoma of the cervix and anal canal can secondarily involve bladder. We had 5 of such cases. The differential diagnosis in this scenario is urothelial carcinoma with squamous differentiation and primary squamous cell carcinoma of the bladder. Based on histologic features alone, this distinction can be extremely challenging [16]. Presence of in situ or conventional urothelial carcinoma component favors urothelial primary; however, in rare instances, cervical cancer can colonize or show pagetoid spread in the urothelium, mimicking urothelial carcinoma in situ [16]. Immunohistochemical expression of p16 has been noted in cervical squamous cell carcinoma as well as urothelial carcinoma and is therefore not useful in discriminating the two entities [17,18]. HPV expression by in-situ hybridization, however, favors a cervical primary [19]. Clinical history and radiologic correlation are more important than any other finding and usually lead to appropriate categorization of the tumor.

Neuroendocrine carcinoma involving the urinary bladder is another diagnostic dilemma. The differential diagnosis in this scenario is urothelial carcinoma with neuroendocrine differentiation, secondary involvement by high grade prostatic adenocarcinoma that has transformed into small cell carcinoma and metastatic neuroendocrine carcinoma. Differentiating these entities can be extremely challenging as immunohistochemical stains are of little help. Prostatic adenocarcinoma transformed into small cell carcinoma usually losses the expression of markers of prostatic origin including PSA, PAP, AR, prostein and NKX3.1. If residual prostate acinar adenocarcinoma is present with small cell carcinoma, it is diagnostic for prostate primary. However, in the absence of the conventional acinar adenocarcinoma component, the only reliable way to distinguish these entities is clinical history and clinical and imaging correlation including cystoscopic findings.

Melanoma is the great mimicker and can metastasize to any tissue or organ including the bladder. It can be misdiagnosed as high grade urothelial carcinoma. However, with due diligence this pitfall can be easily avoided by using appropriate immunohistochemical stains [11].

There have been limited studies on the survival outcome of patients with secondary tumors of the bladder. In the current study, we analyzed the overall survival time of patients from the time of bladder involvement, which showed a median overall survival of 23 months (95% CI 14–31.9 months). Metastatic involvement of the bladder is expected to have poorer outcome as compared to the secondary involvement of the bladder by direct spread. However, our data did not find any significant difference in the outcome of these two groups. A possible explanation of this finding may be that, that all patients were at advanced, terminal stages of their primary disease. Additionally we did not find any significant survival difference among prostate primary versus all other tumor types. This suggests that the secondary involvement of the bladder by any tumor portends a dismal prognosis irrespective of the primary site or route of involvement.

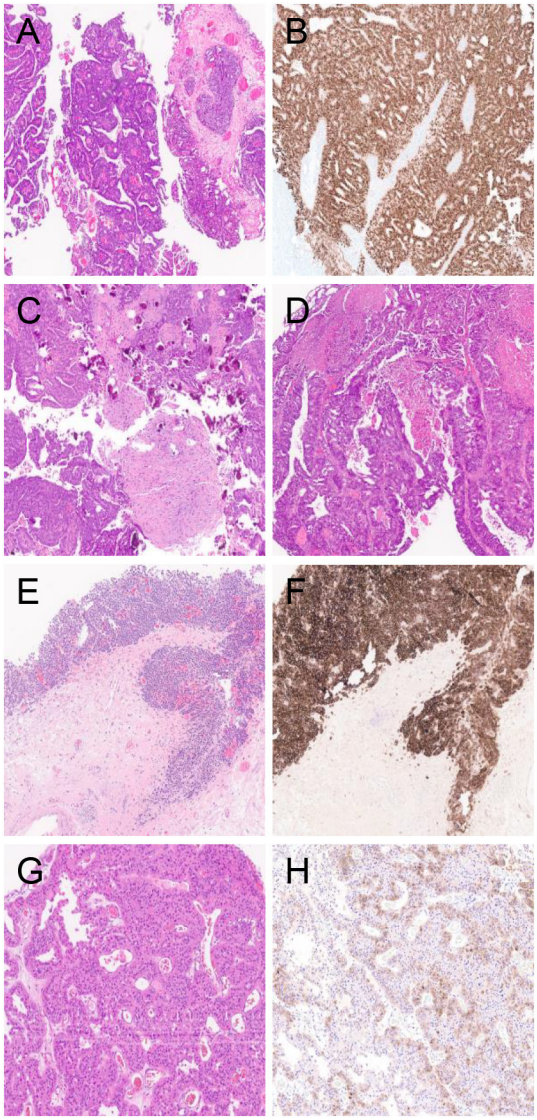

Fig. 3. Secondary tumors involving the urinary bladder. Prostatic adenocarcinoma (A) with positive staining for NKX3.1 (B); high grade serous carcinoma (C); colonic adenocarcinoma (D); melanoma (E) with positive staining for PANMEL (F); and Hürthle cell carcinoma (G) with positive staining for thyroglobulin (H).

5. Conclusion

Tumors from a variety of organs may secondarily involve the urinary bladder by direct extension or metastasis. Most common secondary bladder tumors are adenocarcinomas, which pose a differential diagnostic challenge from primary bladder adenocarcinoma. Correctly identifying secondary tumors of the bladder requires a clinicopathologic approach, which integrates all available data including clinical history, radiologic findings, morphologic features and immunohistochemical profile. Regardless of the origin, bladder secondary tumors are associated with a poor prognosis.

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Declaration of competing interest

All authors have no conflict of interest.

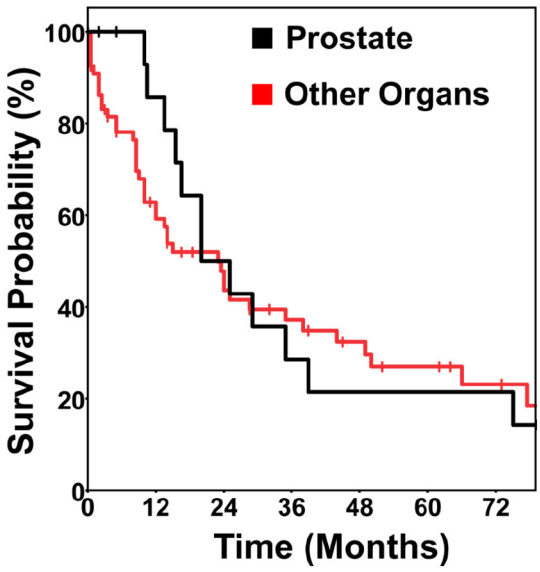

Fig. 4. Survival comparison between prostatic adenocarcinoma involving bladder and all other tumors involving the bladder.

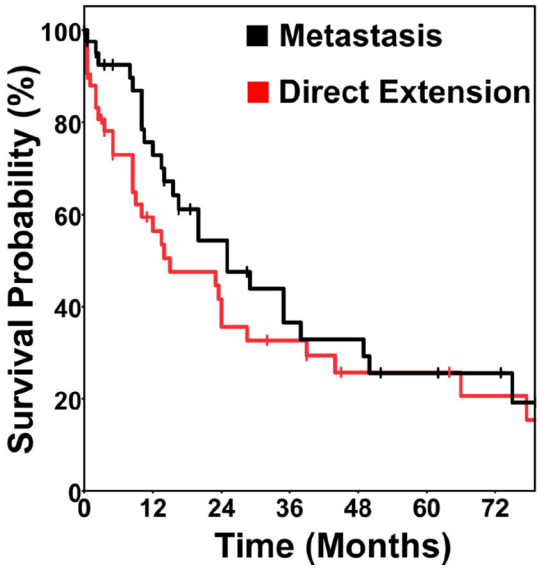

Fig. 5. Survival comparison between tumors involving bladder by direct extension and by metastasis.

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All authors have contributed significantly, and are in agreement with the content of the manuscript.

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