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Incidence and Patterns of Second Primary Malignancies in Genitourinary Cancer Survivors: A 20-Year Single-Center Experience

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ABSTRACT

Objective: Genitourinary (GU) cancers represent a major global cancer burden. With improved survival, second primary malignancies (SPMs) have become an important challenge in survivorship care. However, data specific to GU cancer survivors are limited.

Material and Methods: We conducted a retrospective cohort study of patients with GU cancers diagnosed at Gazi University between 2004 and 2024. Patients with prior malignancies were excluded. Demographic and clinical data were retrieved from medical records. SPMs were defined as synchronous (≤6 months) or metachronous (>6 months).

Results: Among 1,628 patients, 57 developed an SPM, yielding an overall incidence of 3.5%. Incidence rates by subgroup were as follows: prostate cancer, 5.1% (28/548); bladder cancer, 2.7% (12/445); renal cell carcinoma (RCC), 2.9% (11/385); and testicular cancer, 2.4% (6/250). Overall, 26.3% of SPMs were synchronous and 73.7% were metachronous. The most common SPMs were lung cancers (22.8%) and secondary GU cancers (22.8%), followed by gastrointestinal cancers (15.8%) and skin cancers (14.0%). Subgroup analysis showed distinct patterns: in prostate cancer survivors, lung cancers (25.0%) and bladder cancers (17.8%) were most frequent; in bladder cancer survivors, gastrointestinal cancers (33.3%) and lung cancers (25.0%) predominated; in RCC patients, lung cancers were most common (27.3%); and in testicular cancer survivors, secondary urogenital tumors predominated (50.0%). The median interval to SPM diagnosis was 25.9 months, with the longest latency observed in testicular cancer survivors (76.4 months).

Conclusion: The incidence of SPMs in GU cancers was lower than that reported in population-based studies, but the distribution patterns were consistent, with lung and urogenital tumors predominating. These results emphasize the need for tailored, long-term surveillance in GU cancer survivors.

Keywords: Cancer diagnosis and treatments; genitourinary; kidney tumors; prostate cancer

INTRODUCTION

Genitourinary cancers constitute a heterogeneous group of malignancies with a significant global impact, and data from the most recent Global Burden of Disease Study demonstrate that these malignancies represent an increasing proportion of the global cancer burden.[1,2] Over the past two decades, advancements in therapeutic strategies have contributed to a decline in mortality rates for prostate, bladder, and kidney cancers, whereas mortality for testicular cancer has remained relatively stable.[3] As survival outcomes improve, survivorship care has become increasingly important, particularly in addressing not only long-term physical and psychosocial sequelae, but also the heightened risk of developing second primary malignancies (SPMs) in this patient population.

The development of SPMs represents a serious and growing concern, particularly in patients with genitourinary (GU) cancers who may be exposed to various carcinogenic therapies, such as radiotherapy (RT), chemotherapy, and

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hormone treatments.[4-6] These secondary cancers can significantly impact morbidity, mortality, and healthcare burden, yet they remain understudied in this patient population.

Although previous studies have explored SPMs in cancer survivors more broadly,[7,8] data specific to GU malignancies are limited. Better understanding of the incidence patterns and timing of SPM development in this group is needed to inform tailored survivorship care strategies. In this study, we investigate the incidence and distribution of SPMs among patients with prostate, bladder, kidney, and testicular cancers.

MATERIAL AND METHODS

Study Design and Patient Population

This study is a single-center, retrospective cohort analysis of patients diagnosed with GU cancers who presented to the Department of Medical Oncology at Gazi University School of Medicine between 2004 and 2024. Initial patient identification was conducted using ICD-10 diagnostic codes corresponding to GU malignancies, specifically: C61.0-C61.9 (prostate cancer), C62.0-C62.9 (testicular cancer), C64.0-C64.9 (kidney cancer), and C67.0-C67.9 (bladder cancer). For the purposes of this study, cancers classified as C65.0-C65.9 (renal pelvis) and C66.0-C66.9 (ureter) were grouped with bladder cancer (C67.0-C67.9) due to their anatomical proximity and similar clinical management. Within this cohort, patients who developed a SPM after the initial diagnosis of a GU cancer were identified. All primary and secondary malignancies were subsequently confirmed by histopathological examination, and diagnoses were validated using pathology reports to ensure that SPMs represented independent primary tumors rather than recurrences or metastases. Patients with a history of primary malignancy before diagnosis of GU cancer were excluded from the analysis to ensure that the GU tumor was the index cancer. This study was conducted in accordance with the Declaration of Helsinki, and ethical approval was obtained from the Ethics Committee of Gazi University (research code: 2025-1570, date: 22.09.2025).

Data Collection and Endpoints

Data collection was performed retrospectively through a review of electronic medical records and patients' files. Demographic variables, including age at diagnosis and gender, were extracted from patients' medical records. Detailed clinical information was collected, encompassing the histological types of both the primary GU cancer and any subsequent SPMs. Treatment modalities received for the primary tumor, such as surgery, chemotherapy, RT, and hormonal therapy, were recorded. Tumor staging data at the time of diagnosis were obtained for both the primary and secondary malignancies. The stage of the primary tumor when the secondary malignancy was diagnosed was also documented to assess disease status during follow-up. The interval between the initial diagnosis of the primary GU cancer and the diagnosis of the SPM was calculated to evaluate temporal patterns in the development of secondary malignancies. Cancers detected within six months of the initial primary tumor are classified as synchronous, while those that appear more than six months after the first primary tumor are considered metachronous.[9] The primary endpoint of the study was the incidence and classification of SPMs. The secondary endpoint was defined as the time interval between the diagnoses of the primary and secondary malignancies.

Statistical Analysis

Statistical analyses were performed with IBM SPSS software version 25.0 (S.P.S.S. Inc., Chicago, IL, U.S.A.). Categorical variables are presented as counts and percentages. Means and standard deviations for normally distributed variables, and medians and interquartile ranges (25th-75th percentiles) for non-normally distributed variables were reported. Normality was evaluated using the Kolmogorov-Smirnov test. The incidence of SPMs was calculated as the proportion of patients who developed an SPM following the diagnosis of a primary GU cancer. Subgroup analyses were performed based on the type of primary GU cancer (prostate, kidney, bladder, testicular) and the type of SPM. The incidence of SPMs and of their subtypes was calculated for the overall cohort and for each primary cancer type. The median follow-up time was calculated using the reverse Kaplan-Meier method. The time interval between the diagnosis of the primary GU cancer and the SPM was calculated in months.

RESULTS

Study Population, Follow-up and Frequency of SPMs

A total of 1,628 patients with primary GU cancers were included. The most common primary malignancies were prostate cancer (33.7%), bladder cancer (27.3%), renal cell carcinoma (RCC) (23.6%), and testicular cancer (15.4%). During follow-up, 57 patients developed an SPM, yielding an overall incidence of 3.5%. The highest SPM rate was observed in prostate cancer (n=28, 5.1%), followed by RCC (n=11, 2.9%), bladder cancer (n=12, 2.7%), and testicular cancer (n=6, 2.4%). Overall, 26.3% of SPMs were synchronous and 73.7% were metachronous, with synchronous SPM rates of 28.6% for prostate cancer, 16.7% for bladder cancer, 36.4% for RCC, and 16.7% testicular cancer.

The median follow-up for the overall cohort was 140.8 months [95% confidence interval (CI): 101.7-179.9]. Median follow-up for each primary tumor type was as follows: 186.9

months (95% CI: 84.3-289.6) for prostate cancer, 140.8 months (95% CI: 77.1-204.5) for testicular cancer, 135.4 months (95% CI: 102.7-168.1) for RCC, and 51.6 months (95% CI: 44.8-58.5) for bladder cancer.

Among prostate cancer patients, eight synchronous SPMs were identified: lung cancer (n=3); gastrointestinal cancer (n=2; both colon); urogenital cancer (n=2; low-grade bladder cancer and RCC); and head and neck cancer (n=1; larynx). In bladder cancer patients, the two synchronous tumors were a gastrointestinal stromal tumor (GIST) and testicular cancer. In patients with RCC, the four synchronous tumors were colon, ovarian, pancreatic neuroendocrine, and prostate cancers. Among testicular cancer patients, only one case of a synchronous tumor was observed: thyroid cancer.

Patient Characteristics of Cases with Second Primary Malignancies

Subsequent analyses were restricted to the 57 patients who developed an SPM. All patients were male, except three female patients with RCC. The median age at primary tumor diagnosis was 66.1 years for prostate cancer, 69.1 years for bladder cancer, 58.8 years for RCC, and 34.7 years for testicular cancer. Median ages at SPM diagnosis were 72.9, 70.1, 61.6, and 42.3 years, respectively. At the time of primary diagnosis, metastatic disease was present in 44.4% of prostate cancer patients, 8.3% of bladder cancer patients, 18.2% of RCC patients, and 16.6% of testicular cancer patients. At the time of SPM diagnosis, metastases were observed in 35.7% of prostate cancer patients (n=10), 45.5% of bladder cancer patients (n=5), and 9.0% of RCC patients (n=1), whereas no metastatic SPM was detected in testicular cancer patients.

Among prostate cancer patients with metastatic SPM, the most frequent sites were the colon (n=2), the lung (n=2), and cancers of unknown primary (n=2), followed by bladder cancer, medullary thyroid carcinoma, GIST, and lymphoma (n=1 each). Metastatic SPMs in bladder cancer included lung cancer (n=2), gastric cancer (n=2), and pancreatic cancer (n=1). The only metastatic SPM observed in patients with RCC was pancreatic cancer. At the time of SPM diagnosis, the primary tumor remained metastatic in 35.7% of patients with prostate cancer, 25.0% of patients with bladder cancer, and 27.3% of patients with RCC; all patients with testicular cancer were in remission. Baseline demographic and clinical characteristics are summarized in Table 1.

Distribution of SPMs According to Primary GU Cancer

The most frequent SPM types observed among the 57 patients were lung cancer (n=13, 22.8%) and GU cancers other than the primary index tumor (n=13, 22.8%). These were followed by gastrointestinal cancers (n=9, 15.8%) and skin cancers (n=8, 14.0%). Less common SPM types included endocrine cancers (n=4, 7.0%), hematological malignancies (n=2, 3.5%), gynecological cancers (n=1, 1.8%), head and neck cancers (n=2, 3.5%), cancers of unknown primary (n=2, 3.5%), and GISTs (n=3, 5.3%).

The distribution of SPM types varied according to the primary GU cancer. The most frequent subsequent cancers among patients with prostate cancer were lung cancer (n=7) and secondary GU cancers (n=7). In bladder cancer survivors, gastrointestinal cancers (n=4) and skin and lung cancers (n=3 each) were predominant. Among RCC patients, lung cancer (n=3) was the most common. Testicular cancer survivors most frequently developed urogenital malignancies (n=3) The overall distribution is illustrated in Figure 1, while the specific SPM subtypes for each primary tumor type are detailed in Figure 2.

Among prostate cancer patients who developed bladder cancer (n=5), all cases were low-grade urothelial carcinomas, and four patients had a history of primary RT for prostate cancer.Among prostate cancer patients who developed lung cancer (n=7), all cases were non-small-cell lung carcinoma; 5 patients (71.4%) had a history of smoking.

Interval Between Primary and Second Primary Malignancies

The median interval between the diagnosis of the primary GU cancer and the development of SPM was 25.9 months [interquartile range (IQR): 5.4-86.8] for the overall cohort of 57 patients. When stratified by primary cancer type, the median intervals were 25 months (IQR: 3.5-102.3) for prostate cancer, 21.1 months (IQR: 12.5-38.1) for bladder cancer, 19.3 months (IQR: 4-71.8) for RCC, and 76.4 months (IQR: 40.6-173) for testicular cancer. In the overall cohort, the shortest median intervals to SPM development were observed for gynecological (5.4 months), endocrine (7.5 months), and gastrointestinal (11.5 months) cancers.

DISCUSSION

In this study, we evaluated the timing and distribution of SPMs in patients with primary GU cancers. Across all groups, the most frequently observed SPMs were lung, urogenital, gastrointestinal, and skin cancers. We found that approximately one-quarter of all SPMs were synchronous, while the majority were metachronous. The shortest median intervals to development of SPMs were observed in secondary gynecological, endocrine, and gastrointestinal malignancies, whereas the longest were observed for SPMs of unknown primary site and for SPMs at certain urogenital sites. These findings align with previous population-based studies reporting substantial variability in SPM latency across tumor types, likely reflecting differences in carcinogenic exposures, tumor biology, and surveillance intensity.

TABLE 1: Clinicopathological features of patients.

Variable	Whole cohort (n=57)	Prostate cancer (n=28)	Bladder cancer (n=12)	Kidney cancer (n=11)	Testicular cancer (n=6)
Age at diagnosis of primary malignancy (years, median; min-max)	64.6 (26.4-89.7)	66.1 (53.6-80.9)	69.1 (32.1-89.7)	58.8 (49.1-70.6)	34.7 (26.2-64)
Age at diagnosis of secondary malignancy (median; min-max)	68.4 (29.6-90.7)	72.9 (54.3-82.9)	70.7 (43.7-90.7)	61.6 (49.6-75.2)	42.3 (29.6-67.7)
Gender					
Female	3 (5.3%)	0 (0%)	0 (0%)	3 (27.3%)	0 (0%)
Male	54 (94.7%)	28 (100%)	12 (100%)	8 (72.7%)	6 (100%)
Smoking history					
None	25 (43.9%)	12 (42.9%)	5 (41.7%)	5 (45.5%)	3 (50%)
Active-smoker	13 (22.8%)	7 (25%)	3 (25%)	1 (9.1%)	2 (33.3%)
Ex-smoker	19 (33.3%)	9 (32.1%)	4 (33.3%)	5 (45.5%)	1 (16.7%)
Histology of the PT					
-Adenocarcinoma	28	28	-	-	-
-High-grade urothelial	7	-	7	-	-
-Low-grade urothelial	3	-	3	-	-
-Squamous cell	2	-	2	-	-
-Clear cell RCC	8	-	-	8	-
-Papillary RCC	2	-	-	2	-
-Chromofobe RCC	1	-	-	1	-
-Seminoma	4	-	-	-	4
-Non-seminoma	2	-	-	-	2
Stage of PT at diagnosis					
Stage 0-2	27 (47.4%)	11 (39.3%)	5 (41.7%)	7 (63.6%)	4 (66.6%)
Stage 3	14 (24.6%)	4 (14.3%)	6 (50%)	2 (18.2%)	2 (33.3%)
Stage 4	16 (28.1%)	13 (46.4%)	1 (8.3%)	2 (18.2%)	-
Stage of SPM at diagnosis					
Stage 0-2	33 (57.9%)	15 (53.6%)	5 (41.7%)	7 (63.6%)	6 (100%)
Stage 3	7 (12.3%)	3 (10.7%)	2 (16.6%)	2 (18.2%)	-
Stage 4	17 (29.8%)	10 (35.7%)	5 (41.7%)	2 (18.2%)	-
Stage of PT at diagnosis of SPM					
Remission	32 (56.1%)	14 (50%)	8 (72.7%)	6 (54.5%)	4 (66.6%)
Under treatment for non-metastaic disease	9 (15.8%)	4 (14.3%)	1 (9.1%)	2 (18.2%)	2 (33.3%)
Metastatic	16 (28.1%)	10 (35.7%)	3 (27.3%)	3 (27.2%)	-
Previous treatment for PT					
Chemotherapy	22	7	8	1	6
ADT	19	19	-	-	-
ARPI	2	2	-	-	-
TKI	5	-	-	5	-
Radiotherapy for primary	11	10	-	1	-
Intravesical treatment	3	-	3	-	-
Immunotherapy	1	-	-	1	-
Survival					
Alive	28 (47.4%)	11 (39.3%)	5 (45.5%)	6 (54.5%)	6 (100%)
Exitus	29 (52.6%)	17 (60.7%)	6 (54.5%)	5 (45.5%)	-

ADT: Androgen-deprivation treatment; ARPI: Androgen receptor pathway inhibitor; PT: Primary tumor; RCC: Renal cell carcinoma; SPM: Second primary tumor; min: Minimum; max: Maximum; TKI: Tyrosine kinase inhibitor.

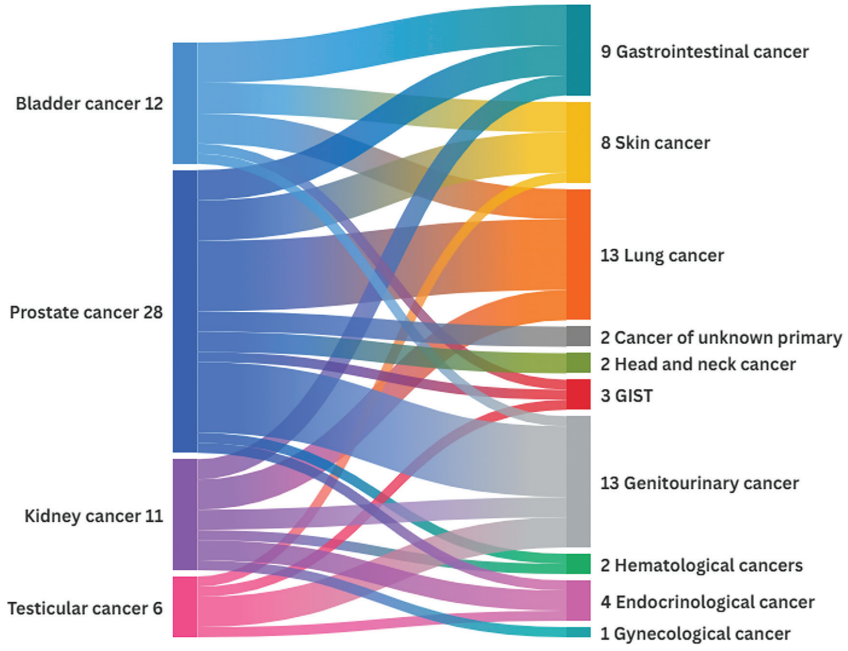

FIGURE 1: General distribution of second primary tumors.

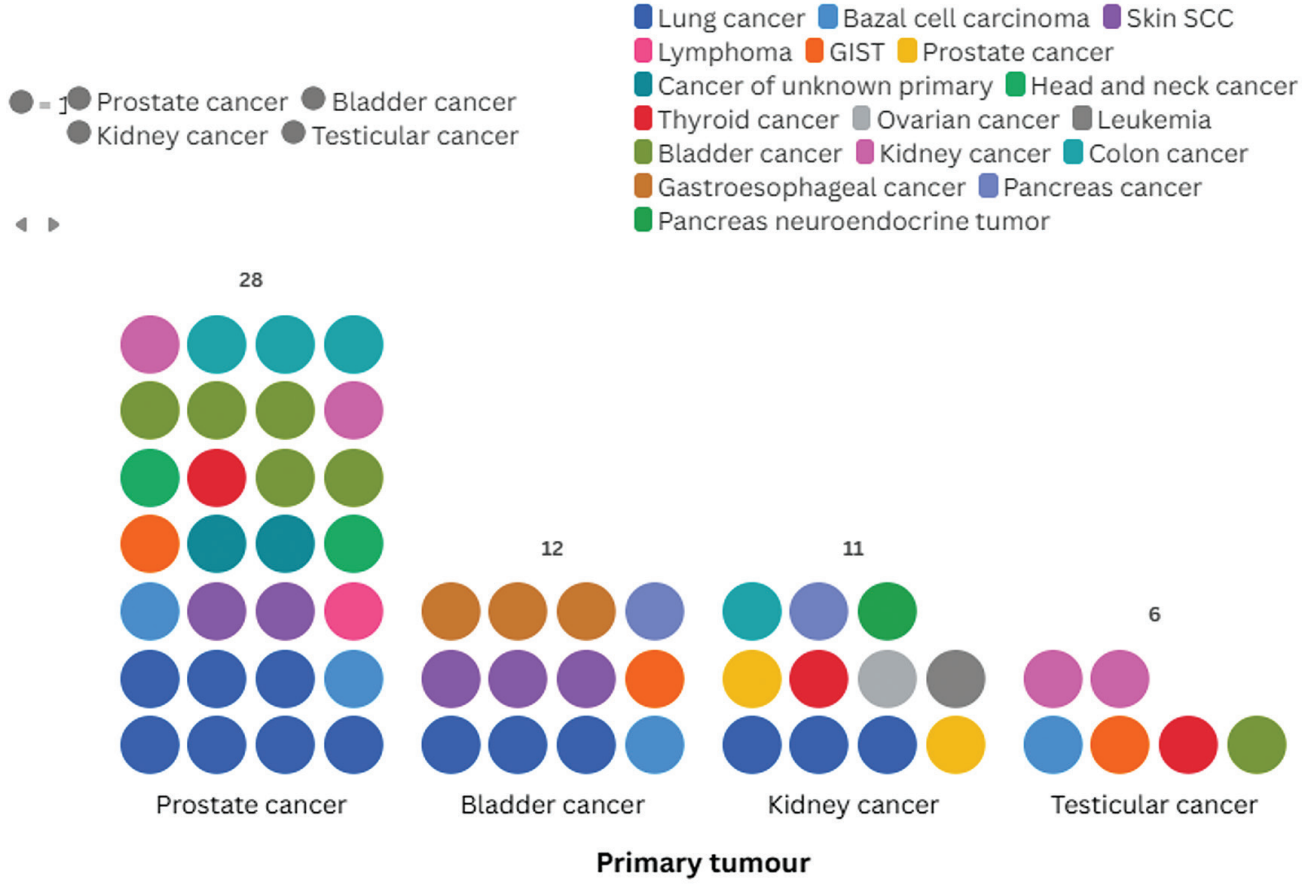

FIGURE 2: Detailed distribution of secondary malignancies in each genitourinary cancer.

Although there are several reports addressing the development of SPMs in individual GU cancers, particularly in the prostate and bladder, data on SPM occurrence across all GU malignancies remain limited. In a study using the Surveillance, Epidemiology, and End Results Program (SEER) database that included 1,041,217 patients with GU cancers, the overall incidence of SPMs was 11%, with a higher incidence observed in endocrine system cancers and urinary system cancers. These findings highlight the need for careful long-term surveillance in patients with GU cancer and suggest that certain subgroups may be at increased risk for developing secondary malignancies.[10] On the other hand, a more recent analysis of the SEER database, including 140,620 patients with GU cancers, reported an SPM incidence of 23.9%, with respiratory and urogenital tumors being the most frequently observed.[11] Interestingly, in our cohort, the incidence of SPMs was 3.5%, which is considerably lower than the rates reported in other studies. This difference may be related to sample size, country-specific patterns, or heterogeneity of SPM incidence among GU cancers. Additionally, the relatively low incidence of SPMs observed in our cohort may be partly explained by methodological and cohort-specific factors. Although the overall median follow-up duration was substantial, its length varied considerably across subgroups, with notably shorter follow-up in certain cancer types, which may have limited detection of late-occurring SPMs. In addition, the retrospective, oncology department-based design of the study may have resulted in incomplete capture of SPMs that were diagnosed and managed outside the medical oncology setting, such as those followed primarily in surgical or other specialty clinics. Patients with early-stage disease who did not require prolonged oncologic follow-up may therefore be underrepresented. Furthermore, SPMs diagnosed at external institutions may not have been consistently recorded in the institutional database. Collectively, these factors may have contributed to an underestimation of the true incidence of SPMs in our cohort. Consistent with the literature, lung and GU cancers were the most common SPMs in our dataset, underscoring the importance of vigilant surveillance for lung and secondary GU malignancies in patients with a primary GU cancer.

In our cohort, prostate cancer constituted the largest proportion of cases, and these patients exhibited a higher incidence of SPMs compared with both the overall cohort and patients with other malignancies. In a SEER-based analysis of 284,738 patients, the incidence of SPMs in prostate cancer was reported as 5.3%,[12] which is comparable to the rate observed in our cohort (5.1%), indicating consistency with previously published data. In the same study, age at prostate cancer diagnosis, histological grade, tumor grade, history of RT, and prior surgery were all associated with the development of SPMs.[12] Although we cannot establish causality in our analysis, since only patients with SPMs were included, it is noteworthy that the overall incidence of SPMs in our cohort was substantially lower than that reported in the literature, whereas the incidence among prostate cancer patients was comparable to previous studies. Although prostate cancer patients represented the subgroup with the highest incidence of SPMs in our cohort, a large US population-based study has reported that prostate cancer survivors have a lower overall risk of developing SPMs compared with the general population, including a reduced risk of lung cancer. In contrast, these studies consistently demonstrated an increased risk of bladder, kidney, soft-tissue, and endocrine malignancies.[13] However, in our cohort, lung and GU cancers were the most frequently observed SPMs, suggesting potential geographic or cohort-specific differences and underscoring the heterogeneity of SPM risk among prostate cancer patients. However, since our study did not include a direct comparison with the general population, no conclusions can be drawn regarding relative risk in this context. In contrast, a Swiss cohort study of 20,000 patients reported that prostate cancer survivors had a lower risk of developing an SPM than the general population during the first four years after diagnosis, but this risk subsequently increased in a stepwise manner. Notably, consistent with our findings, the three most common SPM types in that study were lung, GU, and colorectal cancers. Moreover, treatment modality was shown to influence the type of SPM that developed.[14] These observations suggest that our results are consistent with international data and highlight the potential impact of treatment-related factors on SPM patterns.

One of the most well-documented findings in the literature is an increased risk of SPMs among prostate cancer patients who received RT. Compared with patients who did not undergo RT, those treated with RT have been shown to be at higher risk of developing SPMs, particularly bladder cancer, colorectal cancers (including colon and anus), hematologic malignancies, and lung cancer.[15-17] Numerous studies have demonstrated that prostate cancer patients receiving RT exhibit an increased risk of developing pelvic malignancies, particularly bladder cancer.[15,18,19] Furthermore, a meta-analysis indicated that all RT modalities are associated with an increased risk of secondary bladder cancer; secondary bladder cancers requiring cystectomy have a poorer prognosis than primary bladder cancers.[20] Current evidence suggests that stereotactic body RT may be safer than other RT modalities in this regard.[21] In our cohort, five patients with prostate cancer developed secondary bladder cancer, making secondary bladder cancer the second most frequent SPM after lung

cancer. Four of these five patients had a history of prostate RT. Although some studies have reported that secondary bladder cancers following prostate RT tend to be more aggressive and high-grade,[22] all tumors in our patients were low-grade. These findings underscore the importance of vigilant surveillance for bladder cancer in prostate cancer patients who have received RT.

The development of SPMs in bladder cancer patients is among the most extensively studied topics within GU malignancies. In a SEER-based study involving 238,358 patients with bladder cancer, the incidence of SPMs was 19.7%, which was significantly higher than in the general population. In that study, the most frequent SPMs were hypopharyngeal, esophageal, hepatic, and lung cancers.[23] In another U.S.-based study, the incidence of SPMs among patients who underwent radical cystectomy was 12.3%, with lung and colorectal cancers being the most commonly observed.[24] In a study from Türkiye analyzing data from 2,334 patients in a 38-year cohort, the incidence of SPMs among patients with urothelial carcinoma was 11.1%, with lung cancer the most frequently observed SPM.[25] In our cohort, the incidence of SPMs in bladder cancer patients was lower than in these large population-based studies; this can be explained by a smaller sample size and shorter follow-up duration. However, consistent with the literature, lung cancer emerged as one of the most frequent secondary malignancies. Moreover, similar to the SEER data, gastroesophageal tumors were among the most common SPMs observed in our cohort.

The development of SPMs in RCC patients has been investigated in multiple cohorts, which have reported an increased incidence of SPMs in these patients compared with the general population. In a SEER database study of 43,477 patients with RCC, the incidence of SPMs was 13.6%; the five most common cancer types were brain, pancreas, liver, lung, and prostate.[26] In a population-based study conducted in Taiwan, the incidence of SPMs among patients with RCC was reported as 11.6% in the local cohort, whereas the nationwide incidence was 4.68%. The most common cancer subtypes observed were bladder cancer, liver cancer, colon cancer, lung cancer, and prostate cancer.[27] In a Danish cohort, it was demonstrated that the risk of developing SPMs increased with time after an RCC diagnosis; the incidence rose from 2.8% in the first year to 17.8% in the twentieth year.[28] Furthermore, Rabbani et al.[29] showed that the histological subtype of RCC may influence the development of SPMs, with a particularly increased risk of bladder and prostate cancers observed in patients with papillary RCC. In our cohort, the overall incidence of SPMs was lower than in previous reports. However, consistent with the literature, lung and prostate cancers were among the most frequently observed subtypes. The lower incidence in our study may be attributable to ethnic differences as well as the relatively shorter follow-up period. Moreover, because the majority of our patients had clear-cell RCC, we could not assess the potential impact of histological subtype on the development of SPMs.

In patients with testicular cancer, the risk of developing SPMs is increased due to both the younger age at diagnosis and the use of RT and chemotherapeutic agents such as etoposide, which are associated with a higher likelihood of secondary cancers, especially hematological malignancies.[30,31] In a cohort study of 40,575 patients, the incidence of SPMs among testicular cancer survivors was 5.6%. Notably, malignant mesothelioma showed the greatest relative increase in risk (relative risk: 3.4), while other cancers with elevated risk included esophageal, lung, colon, bladder, pancreatic, and gastric cancers. The overall pattern was similar between the seminoma and non-seminoma groups, although younger patients exhibited a higher risk. In a meta-analysis comprising 88,683 patients, the incidence of SPMs was found to be 5.8; while surgery alone did not increase the risk, RT, chemotherapy, or their combination were associated with an elevated risk. In particular, subdiaphragmatic RT has been identified as a significantly stronger risk factor for the development of SPMs.[32] In our cohort, the incidence of SPMs was 2.4%, which is lower than that reported in the literature. None of the patients had a history of RT; notably, two of the six patients who developed SPMs were diagnosed with RCC. Although this association is not commonly reported in the literature,[33] it was observed in our cohort. Additionally, were no hematological malignancies among patients with testicular cancer. This result might be related to a short follow-up time. The relatively small sample size may have influenced this finding.

Among patients with urogenital cancers in our cohort, the most frequently observed SPMs were lung cancers, other urogenital cancers, gastrointestinal cancers, and skin cancers. Several interrelated mechanisms likely contribute to this pattern. First, shared environmental and lifestyle exposures such as smoking, alcohol consumption, dietary factors, and ultraviolet radiation, all of which are well-known carcinogens, may predispose survivors to multiple malignancies, including lung and GI tumors, due to widespread systemic effects.[34] Second, treatment-related modalities, namely RT and chemotherapy, have been shown to induce DNA damage and epigenetic changes, thereby elevating the risk of SPMs across different organ systems. This is particularly relevant for skin and GI tumors following pelvic or abdominal irradiation.[35] Third, the concept of field cancerization explains how widespread pre-neoplastic changes in epithelial tissues, potentially driven by chronic exposure to carcinogens, can lead to multifocal

tumor development in anatomically adjacent regions (e.g., urogenital and GI tracts).[36,37]

Beyond describing incidence patterns, several findings from our cohort have potential clinical implications. Notably, RCC was observed as an SPM among testicular cancer survivors. Although this association has been infrequently reported in the literature, it may reflect shared genetic susceptibility, treatment-related effects, or increased imaging surveillance in this relatively young patient population. Testicular cancer survivors often undergo long-term radiological follow-up, which may facilitate earlier detection of incidental renal tumors.[38-41] Additionally, systemic therapies and an underlying predisposition to malignancy cannot be excluded. This observation underscores the importance of long-term surveillance of testicular cancer survivors, even in the absence of traditional risk factors or prior exposure to RT. From a clinical perspective, the predominance of lung and secondary GU malignancies as SPMs in our cohort has important implications for survivorship care. These findings suggest that follow-up strategies in GU cancer survivors should extend beyond recurrence surveillance and incorporate risk-adapted screening for common SPMs. In particular, attention to respiratory symptoms, smoking history, and appropriate thoracic imaging may be warranted, especially in patients with known tobacco exposure. Similarly, vigilance for secondary GU tumors is crucial, particularly among prostate cancer survivors with a history of pelvic RT. Collectively, these observations support a more individualized and long-term surveillance approach, tailored to the primary tumor type, treatment exposure, and patient-specific risk factors.

Study Limitations

This study has some limitations. The relatively small sample size and shorter follow-up period may have led to an underestimation of the true incidence of SPMs. Detailed information on lifestyle factors and treatment modalities was limited. Due to the limited number of patients who developed SPM and incomplete data on certain clinical and lifestyle factors, such as smoking history and RT exposure, formal univariate risk factor analyses could not be performed reliably. The single-center nature of this study may limit the generalizability of the findings, and larger multicenter cohorts are needed to more accurately estimate the incidence of SPMs. In addition, the lack of routinely available genetic and molecular data precluded evaluation of inherited susceptibility or treatment-related genomic alterations. Prospective multicenter studies incorporating molecular profiling are warranted.In addition, the potential impact of histological subtypes could not be assessed due to the small sample size. Finally, the retrospective design is subject to inherent biases. On the other hand, this study provides one of the few analyses of SPMs in GU cancers in our population, offering valuable local data that complement international findings. The single-center design ensured consistency in diagnosis and follow-up, reducing heterogeneity in data collection.

CONCLUSION

In conclusion, our findings indicate that the incidence and distribution of SPMs among patients with urogenital cancers in our cohort were generally lower than those reported in the literature. However, lung, prostate, and other urogenital tumors remained the most frequent sites, consistent with previous studies. These results underscore the multifactorial etiology of SPMs, involving environmental exposures, treatment-related effects, and genetic predispositions. Importantly, our data emphasize the need for long-term, tailored surveillance strategies for GU cancer survivors. Prospective studies with larger sample sizes and extended follow-up are warranted to further elucidate risk factors and guide personalized monitoring and preventive interventions.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki, and ethical approval was obtained from the Ethics Committee of Gazi University (research code: 2025-1570, date: 22.09.2025).

Informed Consent: Retrospective cohort study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.E., H.A., O.S., G.S., F.G., U.C., A.Ü., O.Y., A.Ö., N.Ö., Concept: T İ.E., F.G., N.Ö., Design: İ.E., Data Collection or Processing: İ.E., H.A., U.C., A.Ü., O.Y., A.Ö., N.Ö., Analysis or Interpretation: İ.E., H.A., O.S., G.S., F.G., Literature Search: İ.E., Writing: İ.E., O.S., N.Ö.

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