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Synchronous or Metachronous Prostate Adenocarcinoma and Bladder Cancer Coexistence: A Retrospective Cohort Study

Senkron veya Metakron Prostat Adenokarsinomu ve Mesane Kanseri Birlikteliği: Retrospektif Kohort Çalışması

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ABSTRACT Objective: Advances in modern medicine have improved the detection of synchronous and metachronous cancers. Among male genitourinary malignancies, prostate adenocarcinoma (PCa) and bladder cancers can rarely coexist. **Material and Methods:** This retrospective study included male patients diagnosed with PCa and bladder cancers between 2012 and 2019 at Zonguldak Bülent Ecevit University. Patients with synchronous or metachronous cancers and complete clinical data were included, while those with direct tumor infiltration or missing records were excluded. **Results:** Among 1,173 PCa and 591 bladder cancer cases, 15 synchronous or metachronous cases were identified. The median ages at the time of diagnosis for PCa and bladder cancer patients were 69 and 70 years, respectively. Bladder cancer was diagnosed in 7 patients during PCa follow-up, while PCa was detected in 2 patients during bladder cancer follow-up. Synchronous cancers occurred in 6 patients. Bladder cancers were high-grade or advanced, while PCa encompassed most pathological groups. A significant association was found between the age at bladder cancer diagnosis and the PCa risk group (p=0.046). Patients had a median smoking history of 40 pack-years, with only one non-smoker. Metachronous PCa developed within 2 years of bladder cancer, while metachronous bladder tumors appeared 1-7 years after PCa, with a median of 6 years. **Conclusion:** The coexistence of prostate adenocarcinoma and bladder cancers in our cohort highlights the need for vigilant screening for secondary malignancies in affected patients. These findings suggest a potential link between high-grade bladder tumors and prostate cancer risk, warranting further research into shared carcinogenic pathways.

Keywords: Bladder cancer; metachronous neoplasms; prostate cancer; synchronous neoplasms; urogenital cancers

ÖZET Amaç: Modern tıptaki ilerlemeler, senkron ve metakron kanserlerin daha fazla tespit edilmesine olanak sağlamıştır. Erkek ürogenital sisteminin en yaygın maligniteleri arasında prostat adenokarsinomu (PKA) ve mesane kanserleri yer alır. Bu maligniteler nadir olmakla birlikte, senkron veya metakron şekilde birlikte var olabilirler. **Gereç ve Yöntemler:** Bu retrospektif çalışma, 2012-2019 yılları arasında Zonguldak Bülent Ecevit Üniversitesi'nde PKA ve mesane kanseri tanısı almış erkek hastaları içermektedir. Senkron veya metakron kanserleri ve tam klinik verileri olan hastalar dâhil edilmiştir, doğrudan tümör infiltrasyonu veya eksik kaydı bulunan hastalar hariç tutulmuştur. **Bulgular:** 1.173 PKA ve 591 mesane kanseri vakası arasında, 15 senkron veya metakron vaka tespit edilmiştir. PKA ve mesane kanseri hastalarının tanı anında ortanca yaşları sırasıyla 69 ve 70 yıldır. Mesane kanseri, PKA takibi sırasında 7 hastada teşhis edilmişken; mesane kanseri takibi sırasında ise 2 hastada PKA tespit edilmiştir. 6 hastada senkron PKA ve mesane kanseri gözlemlenmiştir. Mesane tümörlerinin tamamı yüksek dereceli veya ileri evreydi, PKA vakaları ise Uluslararası Ürolojik Patoloji Derneği [International Society of Urological Pathology (ISUP)] Grade 4 hariç tüm patolojik grupları kapsıyordu. Mesane tümörü tanısı yaşı ile senkron/metakron PKA risk grubu arasında anlamlı bir ilişki bulunmuştur (p=0,046). Hastaların ortalama sigara içme geçmişi 40 paket-yıldır, sadece bir hasta sigara içmediğini belirtmiştir. Metakron PKA, mesane kanserinden sonraki ilk 2 yıl içinde tespit edilmiştir. Buna karşılık, PKA sonrası metakron mesane kanserleri 1-7 yıl içinde, ortalama 6 yıl sonra tespit edilmiştir. **Sonuç:** Kohortumuzda prostat adenokarsinomu ve mesane kanserlerinin birlikte görülmesi, etkilenen hastalarda ikincil maligniteler için dikkatli taramanın önemini vurgulamaktadır. Bu bulgular, yüksek dereceli mesane tümörleri ile prostat kanseri riski arasında potansiyel bir bağlantıyı işaret etmekte olup, ortak kanserojen yolların araştırılmasını gerektirmektedir.

Anahtar Kelimeler: Mesane kanseri; metakron neoplazmlar; prostat kanseri; senkron neoplazmlar; ürogenital kanserler

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Prostate adenocarcinoma (PCa) and bladder cancers are among the most prevalent malignancies affecting the male genitourinary system, yet their coexistence as synchronous or metachronous malignancies is exceedingly rare. PCa is the second most frequently diagnosed cancer and the 5th leading cause of cancer-related deaths among men worldwide, with an estimated 1.4 million new cases annually.[1] The majority of PCa cases are diagnosed in older men, and risk factors include genetic predisposition, hormonal influences, and lifestyle factors such as smoking, obesity and dietary habits.[2-6]

Bladder cancer is the 7th most frequent malignancy among men globally and the tenth among both sexes. The global age-standardized incidence rate is estimated at 9.5 cases per 100,000 men annually.[7] Urothelial carcinoma constitutes over 90% of bladder cancers, and risk factors include smoking, genetic factors, occupational exposure to carcinogens, and chronic urinary tract irritation.[8-10]

The coexistence of PCa and bladder cancers presents unique diagnostic and therapeutic challenges. While synchronous cases refer to the simultaneous detection of both malignancies, metachronous cases involve the sequential occurrence of one malignancy following the diagnosis of the other. These cases are hypothesized to share common carcinogenic pathways, including chronic inflammation, smoking-related DNA damage, and possibly therapeutic interventions such as radiation therapy.[11]

Although limited in prevalence, synchronous and metachronous PCa and bladder cancers highlight the importance of comprehensive follow-up and early detection strategies in patients diagnosed with either malignancy. This study aims to explore the clinical and pathological features of synchronous and metachronous PCa and bladder cancers in a single-center cohort, providing insights into their risk factors, time intervals, and potential associations.

MATERIAL AND METHODS

This retrospective, single-center cohort study was conducted at the Zonguldak Bülent Ecevit University Faculty of Medicine and included male patients diagnosed with PCa and bladder cancers between 2012 and 2019. Ethical approval for the study was obtained from the Institutional Review Board of Zonguldak Bülent Ecevit University (No: 2020/21-27).

Male patients with synchronous or metachronous PCa and bladder cancers were included if their clinical and follow-up data were complete. Cases with direct infiltration of prostate and bladder cancers into each other or missing medical records were excluded.

Data were collected from the hospital's electronic medical records system. Demographic characteristics such as age at diagnosis, smoking history (pack-years), and comorbidities were recorded. Prostate cancer data included prostate-specific antigen levels, Gleason scores, International Society of Urological Pathology (ISUP) grade groups, prostate volumes, treatment modalities (surgery, radiation therapy, hormone therapy), and metastasis status at diagnosis and follow-up. Bladder cancer data included tumour pathology (e.g., grade, stage, histological type), tumour size and location, surgical treatment, and follow-up information. The time intervals between the diagnoses of PCa and bladder cancers were also documented, as well as any concurrent treatments or interventions.

The statistical analysis was performed using SPSS software (version 27.0.1.0, IBM, Armonk, NY, USA). Descriptive statistics were used to summarize continuous variables, including median, range, and mean, and categorical variables, including frequencies and percentages. The normality of continuous variables was assessed using the Shapiro-Wilk test. For normally distributed variables, parametric tests were used, while non-parametric tests were applied to non-normally distributed data. Spearman's rank correlation coefficient was used to examine the relationship between continuous variables, such as the age of bladder cancer diagnosis and the risk group of synchronous or metachronous PCa. Comparisons across multiple groups were performed using the Kruskal-Wallis test. A p value of less than 0.05 was considered statistically significant.

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. In-

formed consent was obtained from all patients. All patient data were anonymized, and identifying information was kept confidential.

RESULTS

A total of 1,749 male patients with PCa or bladder cancers were included in the analysis, comprising 1,173 PCa cases and 591 bladder cancer cases. Among these, 15 cases were identified as having synchronous or metachronous PCa and bladder cancers, and the detailed findings focus exclusively on these cases (Table 1, Table 2).

Demographics:

- PCa: Median age 69 years (minimum: 57-maximum: 85 years)
- Bladder cancers: Median age 70 years (minimum: 55-maximum: 85 years)

Synchronous and Metachronous Cases:

- Bladder cancers identified in 7 patients during PCa follow-up (0.60% of PCa patients).
- PCa identified in 2 patients during bladder tumor follow-up (0.34% of bladder tumor patients).
- Synchronous PCa and bladder cancers identified in 6 patients (0.34% of all patients).

Pathology:

- Prostate cancer diagnoses were established via transrectal prostate biopsy in 13 patients, transurethral resection of the prostate in 1 patient, and cystoprostatectomy specimens performed due to bladder tumor in 1 patient. The ISUP grades were determined based on the final pathology from radical prostatectomy in those who underwent radical surgery.
- In bladder tumor patients, all initial pathological diagnoses were obtained through transurethral resection of the bladder. The stage and grade of the tumors were subsequently determined from the final pathology of radical cystectomy specimens in cases treated surgically.
- Bladder tumors: All cases were high-grade (e.g., T1G3, T2G3) or advanced (e.g., sarcomatoid carcinoma, squamous cell carcinoma).

TABLE 1: The clinical and pathological data of the patients metachronous prostate adenocarcinoma and bladder cancer

	At the time of prostate cancer (PCa) diagnosis						At the time of bladder cancer diagnosis			
Patient	Age (median=66)	PSA (ng/mL) (median=11)	Prosyaye Volume (cc) (median=35)	PCa Risk Group	ISUP Grade	Pathology (Gleason score)	Interval Between Cancers (years) (median=4)	Age (median=68)	Pathology	Smoking history (pack-years) (median=40)
1	61	6.72	25	Low-risk	1	3+3	7	68	T1G2	20
2	66	23	20	High-risk	2	3+4	6	72	T1G3	30
3	72	8.86	20	Intermediate-risk	2	3+4	4	76	T1G3	50
4	60	5.27	24	Low-risk	1	3+3	7	67	T2G3 (Sarcomatoid Cacinoma)	40
5	78	43.53	60	High-risk	2	3+4	7	85	T2G3	15
6	80	154	60	High-risk	5	5+5	1	81	T2G3	40
7	64	11	35	Intermediate-risk	2	3+4	4	68	T1G2	30
8	69	12.09	50	Intermediate-risk	2	3+4	1	68	T1G3	75
9	57	6.46	55	Low-risk	1	3+3	2	55	T1G3	80

PCa: Prostate adenocarcinoma; PSA: Prostate-specific antigen; ISUP: International Society of Urological Pathology

TABLE 2: The clinical and pathological data of the patients synchronous prostate adenocarcinoma and bladder cancer

At the time of synchronous diagnosis of prostate cancer (PCa) and bladder cancer								
Patient	Age (median=72)	PSA (ng/mL) (median=19.4)	Prostate Volume (cc) (median=42)	PCa Risk Group	ISUP Grade	Pathology of PCa (Gleason score)	Pathology of Bladder Cancer	Smoking history (pack-years) (median=35)
1	78	11.4	42	High-risk	5	5+5	T1G2	40
2	85	50	60	High-risk	5	4+5	T1G3	0
3	62	15.8	109	Intermadiate-risk	3	4+3	T2G3	30
4	74	30.96	42	High-risk	2	3+4	T2G3	20
5	70	23	25	High-risk	2	3+4	T2G3	40
6	69	4.5	40	Low-risk	1	3+3	T3G3 (Squamous Cell Carcinoma)	45

PCa: Prostate adenocarcinoma; PSA: Prostate-specific antigen; ISUP: International Society of Urological Pathology

■ PCa: Patients included ISUP Grade 1, 2, 3, and 5; no cases with ISUP Grade 4 were observed.

A statistically significant relationship was observed between the age of bladder cancer diagnosis and the risk group of synchronous/metachronous PCa, with higher ISUP grades being more likely as age increases (p=0.046) (Table 3).

Smoking History:

■ Median pack-years: 40.

■ Only one patient had no smoking history.

Metachronous Tumor Timeline:

■ Metachronous PCa: Diagnosed within 2 years after bladder tumors.

■ Metachronous bladder cancers: Diagnosed 1-7 years after PCa (median 6 years).

DISCUSSION

The coexistence of prostate adenocarcinoma (PCa) and bladder cancers, either synchronously or metachronously, represents a rare but clinically significant scenario in uro-oncology. This study highlights the need for vigilant follow-up in patients with either malignancy, especially those with shared risk factors such as smoking and advanced age.[8,12]

The incidence of bladder cancer in patients with prostate cancer (n=9,780) was 1.5%, while in our study, the incidence in patients with prostate cancer (n=1,173) was 1.3%, a value consistent with similar studies, despite the presence of a wide range of publications in the literature.[13] The median age of patients with synchronous or metachronous PCa and bladder cancers was approximately 70 years, aligning with existing literature that indicates increased cancer risk with advancing age.[14] Notably, a significant linear relationship was observed between the age at bladder cancer diagnosis and the risk group of synchronous or metachronous PCa (p=0.046), suggesting that older age at bladder cancer diagnosis may be associated with higher-risk PCa.

TABLE 3: Relationship between age at bladder cancer diagnosis and risk groups of synchronous or metachronous prostate cancer

ISUP Grade	Number of Patients	Mean Age	SD	Median Age	Minimum Age	Maximum Age
1	4	64.75	6.55	67.50	55	69
2	7	73.29	5.96	72.00	68	85
3	1	62.00	-	62.00	62	62
5	3	81.33	3.51	81.00	78	85
Total	15	71.87	8.23	70.00	55	85

ISUP: International Society of Urological Pathology; SD: Standard deviation

Smoking is a well-established risk factor for bladder cancer due to its role in inducing DNA damage via carcinogenic metabolites.[15] Similarly, the pro-inflammatory and hormonal effects of smoking may contribute to the pathogenesis of PCa.[16] Studies have demonstrated that smoking increases the aggressiveness of bladder cancer and is associated with a higher likelihood of developing multiple genitourinary malignancies.[17] In our cohort, patients had a median smoking history of 40 pack-years, with only one patient reporting no smoking history. This finding underscores the role of tobacco exposure in the pathogenesis of both malignancies and supports existing evidence linking smoking to increased cancer risk.

The observation that bladder tumors in our cohort were predominantly high-grade or advanced aligns with prior studies showing an association between aggressive bladder cancer pathology and synchronous malignancies.[18] Similarly, the diverse pathological spectrum of PCa in our series underscores the heterogeneity of the disease, suggesting that its coexistence with bladder cancer is not limited to specific ISUP grade groups.

Notably, metachronous tumors were identified within distinct timelines: PCa following bladder cancer within 2 years, and bladder cancer following PCa within an average of 5 years. This finding is consistent with previous reports suggesting that the inflammatory milieu and therapeutic interventions for the primary malignancy, such as radiation therapy, may predispose patients to secondary malignancies.[19] A recent study demonstrated an increased risk of secondary malignancies in the bladder and rectum after prostate cancer treatment, particularly with radiation therapy, emphasizing the need for long-term monitoring.[20,21]

Despite the rarity of synchronous and metachronous PCa and bladder cancers, these cases highlight the importance of adopting a multidisciplinary approach to management. The causes and mechanisms underlying the development of multiple primary tumors remain incompletely understood. The widespread implementation of diagnostic methods and rigorous follow-up strategies, the persistence of genetic and behavioral risk factors contributing to the initial cancer, and the effects of chemotherapy or radiotherapy are considered the primary factors leading to the emergence of secondary primary cancers in cancer patients.[22] The development of 2 primary malignancies is influenced by a variety of factors, including theories related to carcinogenesis. These factors encompass immune deficiency, inherited defects in tumor suppressor genes, persistent exposure to environmental carcinogens, genetic instability, field cancerization, increased use of systemic chemotherapy and radiotherapy, hormonal manipulation, genetic or targeted therapies, tissue transplantation, prolonged survival, aging, smoking, dietary habits, and other contributing elements.[23-25]

Our study emphasizes the critical role of smoking cessation in reducing the risk of multiple malignancies. Integrating smoking cessation interventions into standard patient counseling and management protocols is essential for this high-risk population. However, the study has several limitations that should be acknowledged. Its single-center design may restrict the generalizability of the findings to other populations or healthcare settings. The retrospective nature of the study introduces potential biases, such as incomplete or inconsistent medical records, which could influence the accuracy of the results. Additionally, the relatively small number of patients with synchronous or metachronous prostate adenocarcinoma and bladder cancers limits the statistical power and robustness of the findings. The follow-up period may not have been sufficient to identify all metachronous cases, particularly those occurring beyond the study timeframe. Furthermore, the study lacked molecular or genetic analyses that could provide deeper insights into shared carcinogenic mechanisms. Although smoking history was reported, detailed data on smoking cessation, duration, and intensity were not thoroughly analyzed, potentially affecting the observed associations. The influence of treatment modalities, such as radiation therapy and hormonal manipulation, on secondary cancer development also warrants further exploration. Finally, unassessed confounding factors, including environmental exposures and lifestyle variables, may have impacted the findings. Addressing these limitations in future studies with larger cohorts, longer follow-up periods, and comprehensive data collection will be crucial for validating and extending the current insights.

In conclusion, the coexistence of PCa and bladder cancers necessitates heightened clinical vigilance and a multidisciplinary approach to optimize outcomes. Future studies with larger cohorts and longer follow-up periods are needed to elucidate the underlying mechanisms of synchronous and metachronous tumorigenesis and to develop evidence-based strategies for surveillance and management.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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