Prognosis of primary or metachronous prostate cancer in multiple primary genitourinary cancers; a single center experience with long-term results

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ABSTRACT

Objective: This study aims to analyze the challenges, approaches and long-term results of primary or metachronous prostate cancer (PCa) in cases with multiple primary genitourinary cancers.

Methodology: A total of 17 patients were included in the study. Patients with multiple primary genitourinary cancers were divided into two groups according to the diagnosis of primary or metachronous PCa as group 1 and group 2.

Results: The median age of patients was similar in both groups. The median smoking status (pack-years) was higher in group 2 than group 1. The median prostate-specific antigen (PSA) level was higher in group 1 than group 2. The median follow-up time from primary to the metachronous tumour was higher in group 1 than group 2. The rate of recurrence in PCa was higher in group 1 than group 2. No statistically significant difference was observed in terms of patients’ age, smoking status, PSA levels at diagnosis of PCa and biochemical recurrence or metastasis between the two groups (p > 0.05).

Conclusion: Primary PCa cases may progress more aggressively than metachronous PCa cases. Biochemical recurrence and metastasis may be less threatening in metachronous PCa cases than primary cases. Therefore, aggressive treatment can be avoided for metachronous PCa cases.

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Introduction

Multiple primary neoplasms (MPN) was first described by Billroth in 1889 and it was developed with different definitions over time. Definition of MPN is at least two primary neoplasms diagnosed in the same patient and incidence range between 0.7% and 1.23% [1–3]. MPN is divided into metachronous or synchronous tumours. If the secondary tumour occurs within 6 months from the diagnosis of the primary tumour, it is defined as synchronous, and if seen after 6 months, it is defined as a metachronous tumour [4]. Metachronous tumours often develop after treatments such as radiotherapy (RT) or systemic chemotherapy (CTX). Smoking status, senility, comorbidities, immunological and genetic problems are some of the other reasons.

Multiple primary genitourinary cancers as metachronous tumours are not very common in urological cancers. Among the urological cancers, the upper urinary tract of epithelium originated tumours and vesical tumours are best known for metachronous tumours [5]. Frequency of these tumours is quite low if we exclude RT and CTX related metachronous tumours.

Prostate cancer (PCa) is the most common non-cutaneous cancer in men in the United States [6]. Information about multiple primary genitourinary cancers, which include PCa as primary or secondary, is very rare. Many articles published about MPN cancers are included in the literature as case reports and long-term follow-up is not available for PCa [7–10]. The presence of PCa in metachronous tumours is valuable in the light of this information. In this study, we aimed to evaluate this condition, which closely concerns the treatment and follow-up of patients, in terms of the presence of primary or secondary prostate cancer.

Methodology

In this retrospective cohort study was included patients with MPN diagnosed and treated in our clinic, between February 2000 and December 2019. This study was approved by the local Ethics Committee.
and conducted according to the principles of the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects.”

A total of 22 patients diagnosed with multiple primary genitourinary cancers in our clinic were evaluated. Multiple primary genitourinary cancers patients over 50 years of age diagnosed as primary or metachronous PCas were included in the study. Patients who were found to have missing data during data recording, evaluation or analysis, patients with RT or CTX history for any tumours, patients with a follow-up period of less than 1 year and patients under 50 years were excluded from the study. A total of 17 patients who met these criteria were included in the study.

Patients’ age at diagnosis, smoking status (pack-years), comorbidities, medications, PSA levels at the diagnosis of the primary and secondary tumour, primary and secondary tumour size (mm) or positive core number in a prostate biopsy, performed treatment for primary and secondary tumour, pathological results of treatment of primary or secondary tumour, pathological results of treatment of primary or secondary tumour (e.g. degree of invasion or International Society of Urological Pathology [ISUP] classification for PCa grade), the interval between primary and secondary tumour, presence of tumour recurrence or metastasis which develop in the follow-up period, and follow-up period were recorded. Biochemical recurrence was defined as an increase in PSA concentration to $\geq 0.2$ ng/mL with a second confirmatory value. Biochemical Recurrence Free Survival (BRFS) was defined from the date of the diagnosis to the date of the biochemical recurrence.

Patients with multiple primary genitourinary cancers were divided into two groups as group 1 and group 2. Group 1 patients consisted of primary PCa case + metachronous genitourinary cancer (bladder or kidney cancer). Group 2 patients consisted of primary genitourinary cancer (bladder or kidney cancer) + metachronous PCa cases. 11 patients in group 1 and 6 patients in group 2 were enrolled in the study. All of the above parameters were compared in both groups.

Data analyses were performed using SPSS Statistics 20.0 software (SPSS Inc., Chicago, IL). The normality hypothesis was tested using the Kolmogorov–Smirnov test during data analysis. All variables were non-normally distributed. Quantitative variables were expressed as the median and interquartile range (IQR). Qualitative variables were expressed as presence or absence percentage, and Chi-square test was applied. Mann–Whitney’s U-test was used to evaluate all non-normally distributed variables. A $p < 0.05$ was considered statistically significant in all analyses.

**Results**

A total of 17 patients were analyzed. The median (IQR) age of all patients at diagnosis was 67 (60.5–70.5) years. At the time of prostate cancer diagnosis, the median (IQR) PSA value was 7.2 (4.33–8.5) ng/mL. The median (IQR) time to metachronous tumour formation was 3.92 (1.12–8.65) years. The median (IQR) PSA value of all patients at the time of the metachronous tumour detection was 2.8 (0.38–5.35) ng/mL. The median (IQR) follow-up period of the patients was 10.42 (3.52–13.89) years.

In group 1, 11 patients were enrolled. The median (IQR) age of the patients at diagnosis was 63 (IQR: 60–68) years. The smoking rate was 36.36% among patients. The median (IQR) smoking history in group 1 was 0 (0–45) years. Four patients with smoking status were diagnosed with PCa and ISUP grade groups were 1, 2, and 4, respectively. 8 of 11 patients had at least one comorbid disease, while three patients did not have. The most common comorbid disease was hypertension and was present in 50% of patients who were diagnosed with PCas. Regular medication in patients with the comorbid disease was at least one drug and range from 1 to 10. Positive core involvement was a range from 1 to 6 cores in underwent 10 or 12-core systematic prostate biopsy. All patients’ pathological results, treatment methods and follow-up periods are described in Table 1. The median (IQR) follow-up time from primary to metachronous tumour was 4.00 (2.55–9.63) years. The median (IQR) follow-up period of the patients was 11.87 (8.04–14.22) years.

In group 2, 6 patients were enrolled. The median (IQR) age of the patients at diagnosis was 67 (65–73) years. The smoking rate was 50% among patients. The median (IQR) smoking history in group 1 was 20 (0–50) years. 3 of 6 patients with smoking status were TaLG bladder cancer. 4 of 6 patients had at least one comorbid disease, while 2 patients did not have. The most common comorbid disease was hypertension and was present in 75% of patients who were diagnosed with bladder cancer. Regular medication in patients with the comorbid disease was at least two drugs and range from 2 to 11. All patients’ pathological results, treatment methods and follow-up periods are described in Table 1. The median (IQR) follow-up time from primary to metachronous tumour was 1.31
Table 1. All patients' age, PSA levels, pathological diagnosis, treatment methods and follow-up period are described.

| Parameter | Age | PSA at primary tumour diagnosis | Primary tumour | Treatment of primary tumour | Time from primary to metachronous tumour (Day) | PSA at metachronous tumour diagnosis | Metachronous tumour | Size of tumour or core number of PCa cases | Treatment of metachronous tumour | Complications | Follow-up (Day) |
|-----------|-----|--------------------------------|----------------|----------------------------|-----------------------------------------------|------------------------------------|---------------------|------------------------------------------|--------------------------------|----------------|-----------------|
| GROUP 1   |     |                                |                |                            |                                               |                                    |                     |                                          |                                |                |                 |
| Patient 1 | 60  | ISUP 1                         | Goserelin + Flutamid | 3516 | 0.96 | TCC-TaLG + UUT TCC | 50mm | TUR-B + RNU | 7330 |
| Patient 2 | 57  | ISUP 1                         | Goserelin + Flutamid | 3014 | 0.69 | RCC-F2 | 55mm | RN | 3805 |
| Patient 3 | 67  | ISUP 1                         | RP              | 1431 | 0.01 | TCC-T1 | 30mm | TUR-B + 8 weeks MIT-C | 2953 |
| Patient 4 | 68  | ISUP 1                         | AS              | 931  | 3.81 | TCC-T1LG | 10mm | TUR-B | 4603 |
| Patient 5 | 79  | ISUP 1                         | Goserelin       | 1461 | 0.06 | TCC-TALG | 20mm | TUR-B | 5192 |
| Patient 6 | 68  | ISUP 1                         | AS              | 3301 | 4.71 | TCC-TALG | 10mm | TUR-B | 4737 |
| Patient 7 | 55  | ISUP 1                         | AS              | 1149 | 6.00 | RCC-F1 (BILL) | 34mm | BILATERALLY PN | 1365 |
| Patient 8 | 61  | ISUP 2                         | RP              | 3956 | 2.80 | TCC-TALG | 10mm | TUR-B | 5752 |
| Patient 9 | 76  | ISUP 1                         | Leuprolelin asetat | 236  | 0.01 | TCC-TALG | 12mm | TUR-B | 2936 |
| Patient 10| 63  | ISUP 4                         | RP              | 183  | 0.08 | TCC-TALG | 7mm | TUR-B | 510  |
| Patient 11| 63  | ISUP 4                         | RP              | 3693 | 2.79 | RCC-F2 | 30mm | PN | 4334 |
| GROUP 2   |     |                                |                |                |                                               |                                    |                     |                                          |                                |                |                 |
| Patient 12| 67  | RCC-F2                         | RN              | 1739 | 8.30 | ISUP 1 | 1 core | AS | Refused Treatment | 6615 |
| Patient 13| 73  | RCC-F2                         | RN              | 2258 | 4.27 | ISUP 1 | 2 core | WW | 4949 |
| Patient 14| 75  | TCC-TaLG                       | TUR-B           | 396  | 7.51 | ISUP 1 | 4 core | Goserelin | 849 |
| Patient 15| 65  | TCC-TaLG                       | TUR-B           | 539  | 7.20 | ISUP 1 | 2 core (80%) | RT | 1208 |
| Patient 16| 67  | TCC-TaLG                       | TUR-B           | 208  | 2.53 | ISUP 1 | 1 core | AS | 1817 |
| Patient 17| 53  | TCC-TaLG                       | TUR-B           | 422  | 4.45 | ISUP 1 | 1 core | AS | 997  |

ISUP: International Society of Urological Pathology; RP: radical prostatectomy; RCC: renal cell carcinoma; TCC: transitional cell carcinoma; TaLG: Ta Low Grade; T1LG: T1 Low Grade; AS: active surveillance; RN: radical nephrectomy; PSA: prostate-specific antigen; RNU: radical nephroureterectomy; TUR-B: transurethral resection of bladder; WW: watchful waiting; CKD: chronic kidney disease; MIT-C: Mitomycin-C; PN: partial nephrectomy; PCa: prostate cancer; Rec: Recurrence; UUT: upper urinary tract.
Table 2. Statistically analyses for both groups in terms of age, smoking status, PSA levels, presence of recurrence or metastasis and follow-up periods are summarized.

| Parameter                        | Group 1 (G1) | Group 2 (G2) | All patients |
|----------------------------------|--------------|--------------|--------------|
|                                  | n = 11       | n = 6        | n = 17       | p-Value |
| Age at diagnosis (Year)          | Median (IQR) | Median (IQR) | Median (IQR) | G1–G2   |
| 63 (60–68)                       | 67 (65–73)   | 67 (60.5–70.5)| 0.733        |
| Age (Year)                       | 80 (75–83)   | 78.5 (69–86) | 80 (71–84.5) | 0.960   |
| Smoking status (pack year)       | 0 (0–45)     | 0 (0–50)     | 0 (47.5)     | 0.660   |
| PSA (ng/mL)                      | 7.4 (4.4–8.7)| 5.82 (3.4–7.9)| 7.2 (4.33–8.5)| 0.108   |
| Follow-up (Years)                | 11.87 (8.04–14.22) | 4.14 (2.52–15.84)| 10.42 (3.52–13.89)| 0.315   |
| Recurrence or metastasis (-/+))  | 3 Biochemical recurrence 1 metastasis | None | 4 Biochemical recurrence or metastasis | 0.091 |

The median (IQR) follow-up period of the patients was 4.14 (2.52–15.84) years. The median age of patients was similar in both groups. The median smoking status (pack-years) was higher in group 2 than group 1. The median PSA level was higher in group 1 than group 2. The median follow-up time from primary to the metachronous tumour was higher in group 1 than group 2. In Group 1, two patients died during the follow-up period. While one of the patients died because of chronic kidney failure, and the other patient died because metastasis-related conditions of PCAs who refused the treatment of cancers. No statistically significant difference was observed in terms of patients’ age, smoking status, tPSA levels at diagnosis of PCAs and biochemical recurrence or metastasis between the two groups ($p = 0.68, 0.61, 0.11, 0.09$, respectively; Table 2).

The median BRFS time was 4.61 (1.65–13.79) years for 4/11 patients in group 1. Patient with first biochemical recurrence in group 1 died due to PCA metastasis-related problems in the 3rd month after recurrence. Biochemical recurrence or PCA metastasis was not detected in group 2.

**Discussion**

MPNs involving PCAs as primary or secondary tumours are not common [11]. MPN overall incidence is increasing in recent years. The incidence of metachronous tumour in urological tumours was reported to be 0.0096 in 2001 [12]. In a study conducted in 2018; Overall incidence of MPNs and genitourinary tumours-specific incidence were found as 0.72% and 1.26 [13]. If this risk will be assessed in terms of age, the estimated 10-year cumulative risk of second primary cancers for patients who were firstly diagnosed with cancer aged between 60 and 69 was as high as 13% [14]. The median age of both groups in our study was 67 years old and was in this risk group. We think that a different recommendation might be prepared for this age group in determining the follow-up intervals of patients.

Metachronous tumours usually occur due to the adverse effects of therapies used in the management of primary tumour. In this study, these patients were excluded as secondary to RT or CTX. Thus, we evaluated the primary or secondary cases with PCAs more clearly. In a study on smoking; patients with continued to smoke after primary tumours developed the second primary malignancy earlier as compared to those who did not smoke [15]. In our study; there was no difference between ISUP grade groups in terms of smoking status. Contrary to prospects there was less comorbid disorder in PCAs patients with biochemical recurrence and metastasis in our study and these were positive findings in terms of smoking and comorbid diseases.

Lee et al. reported that increased malignant behaviour and a worse prognosis in MPN occurred more than a single primary tumour [16]. Primary PCAs cases with ISUP grade group 1 (7/11) had a better prognosis for metachronous tumours. In only one case, tumour progression developed and radical cystoprostatectomy with ileal conduit was performed in the follow-up period. PCAs cases with ISUP grade group 2 and 4 (4/11) were followed up with biochemical recurrence or metastasis in group 1. But in group 2, patients with metachronous PCAs were ISUP grade group 1 and no progression was observed. We think that the results of this study for multiple primary genitourinary cancers are different from the results published by Lee et al. We support the idea that the ISUP grading group is crucial for identifying high-risk patients.

The prostate and bladder tissues have the same embryological origins. Despite many investigations, the carcinogenic pathway of co-existence of both tumours has not been established [12]. These pathways, which cannot be explained in synchronous tumours, are extremely difficult to explain in metachronous tumours. Genetic factors are a risk factor for secondary tumour development in patients with PCAs. The best known of these genetic factors is BRCA2 [17]. Therefore, patients who have a family history for breast cancer or malignant melanoma should have a close follow-up for metachronous PCAs. There was no familial history in cases with
metachronous PCa in our study and it may explain that prevent possible aggressive behaviour.

There are no currently available standard guidelines for MPNs treatment and the proposed recommendations mostly reflect consolidated expert opinion. Although the treatment type varies according to the patient’s performance status, it may be necessary to be aggressive in treatment.

BRFS was shorter in primary cases and high ISUP grade group was the main factor according to our results. Metachronous PCa cases with ISUP grade group 1 had no biochemical recurrence. However, in our study, as the ISUP grade group increased in primary PCa cases, the risk increased, whereas no significant risk was observed in terms of PCa progression in metachronous PCa cases. Therefore, it is not feasible to arrange an aggressive treatment in metachronous PCa cases if PCa cases with low ISUP grading group.

The study has several limitations. Even if this study is retrospective, it is considered a limitation, there are many case reports when the literature is examined, which makes this study valuable with its long-term results. In addition, another important aspect of this study is the evaluation of patients with multiple primary genitourinary cancers by excluding known etiological factors such as RT or CTX.

**Conclusion**

Presence of PCa in multiple primary genitourinary cancers requires careful treatment and follow-up in primary cases. While metachronous PCa may not be life-threatening disease according to our results; it may not also require close follow-up or aggressive treatment in patients with metachronous PCa.

**Ethical approval**

This retrospective cohort study was approved by the University of Health Sciences Hamidiye Clinical Research Ethics Committee (Hamidiye-KAEK 20/42). Informed consent is not obtained from patients to publish the data concerning this study.

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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