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Review

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Radiotherapy for Oligometastatic Prostate Cancer

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Abstract

The knowledge that disease progression after chemotherapy often occurs in areas affected by the disease at the time of diagnosis has given rise to the concept of oligometastasis. Although it is difficult to define oligometastatic disease clearly, most studies include cases with up to 3-5 metastases in this group. This review aimed to elucidate the role of radiotherapy in oligometastatic prostate cancer, identify appropriate radiotherapy modalities, and establish appropriate dose/fraction schemes. We can discuss radiotherapy for oligometastatic prostate cancer under two main headings: metastasis-directed therapy (MDT) and primary treatment. Most studies on MDT in patients with oligometastatic prostate cancer are retrospective; however, in the results, it is noteworthy that a group of patients benefit from MDT within the classification defined as "oligometastasis". Studies on primary-directed radiotherapy for oligometastatic prostate cancer have revealed the potential benefits of curative treatment. These results should be supported by prospective phase 3 studies. We observed that stereotactic body radiotherapy (SBRT) is a frequently used radiotherapy technique for oligometastatic prostate cancer. The capability of the treatment machine, the location and size of the metastasis, and patient immobilization should be taken into consideration for dose/fraction selection. MDT and primary-directed treatment can slow disease progression in patients with oligometastatic prostate cancer. SBRT is the most commonly preferred treatment modality for this purpose. Prospective studies are needed to clearly define the patient group that will benefit from treatment.

Keywords: Prostate cancer, oligometastatic, radiotherapy

Introduction

Androgen deprivation therapy (ADT), chemotherapy, and palliative radiotherapy constitute the backbone of metastatic prostate cancer treatment (1,2). The knowledge that disease progression after chemotherapy often occurs in areas affected by the disease at the time of diagnosis has given rise to the concept of oligometastasis. The concept of oligometastasis was first introduced by Hellman and Weichselbaum (3). In their 1995 article, the authors defined oligometastatic disease as cancer with limited metastasis burden (3). Although it is not possible to make a clear definition of the term oligometastatic disease, in most studies, cases with a maximum of 3-5 metastases are included in the classification of oligometastatic disease (4-6). The European Organization for Research and Treatment of Cancer and the European Society for Radiation Oncology published a consensus that defined oligometastatic disease as limited metastatic disease (6,7). Presently, discussing curative treatment options for suitable metastatic patients has become part of the daily routine. This review aimed to elucidate the role and efficacy of radiotherapy in oligometastatic prostate cancer, as well as identify appropriate radiotherapy modalities and dose/fraction schemes.

Role of Radiotherapy in Oligometastatic Prostate Cancer

The diagnosis of metastatic prostate cancer may vary depending on the radiological modality used. Radiological techniques, such as choline positron emission tomography/computed tomography (PET/CT), prostate-specific membrane antigen (PSMA) PET/CT, and whole body magnetic resonance imaging (MRI) (8) can now detect metastases that conventional examinations cannot detect (8). When we look at studies on metastatic prostate cancer, there are two main distinctions: diseases with low metastatic burden that benefit from local ablative treatment and diseases with high tumor burden (9-12). In the Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) study, metastatic patients with four or more bone metastases and at least one of them outside the axial skeleton or with visceral metastases were defined as having high tumor burden disease, whereas the remaining metastatic group was considered to have low tumor burden (9). In the LATITUDE study, metastatic patients with three or more bone metastases, visceral metastases, or at least two of the International Society of Urological Pathology-4 disease factors were considered to

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have a high tumor burden, whereas metastatic patients who did not fall into this group were considered to have a low tumor burden (10). The European Association of Urology accepts both definitions (11). We can discuss radiotherapy for oligometastatic prostate cancer under two main headings: metastasis-directed therapy (MDT) and treatment of primary cancer.

Direct Treatment for Metastasis in Patients with Oligometastatic Prostate Cancer

Since the concept of oligometastasis was introduced, studies have been conducted on whether direct treatments for metastases in oligometastatic prostate cancer prolong the duration of clinical progression and delay the time to start ADT (13,14). When we look at the literature, it is evident that the majority of the information on this subject is based on retrospective data (15). In the phase 2 study conducted by Ost et al. (14), prostate cancer patients who relapsed with a maximum of 3 extracranial lesions after receiving curative treatment were divided into 2 groups: observation or MDT for all metastatic foci. The number of lesions was determined using choline PET/CT. Surgery or stereotactic body radiotherapy (SBRT) was the preferred MDT modality. The study included 62 patients, and the primary endpoint was ADT-free survival. At 3-year follow-up, ADT-free survival was 21 months in the MDT arm and 13 months in the observation arm. Furthermore, the MDT arm had a significantly longer time to prostate-specific antigen (PSA) progression (6-10 months). Both groups showed similar quality of life, and none experienced treatment-related grade 2-5 side effects. Although not starting ADT in patients with metastatic prostate cancer is a controversial issue, delaying the start of ADT as much as possible by applying treatment modalities, such as SBRT, in this patient group is on the agenda due to side effects.

Similar to Ost et al.'s (14) study, the ORIOLE phase 2 study (16) included patients with metastatic prostate cancer who relapsed after definitive treatment. The study included patients with 1-3 asymptomatic metastases with a metastasis size of 5 cm. The number of metastases was determined by CT, MRI, and/or radionuclide bone scan. The study divided the patients into two main groups: the SBRT and observation arms, with the primary endpoint being the rate of progression within 6 months. The SBRT regimens applied were 19.5-48 Gy/3-5 fractions. Patients were considered to have progressed if one or more of the following factors occurred: PSA progression (≥2 ng/dL), radiological progression, symptomatic progression, the need to initiate ADT, or death. The study analyzed 80 patients and found that the rate of patients experiencing progression at 6 months was 19% in the SBRT arm and 61% in the observation arm, significantly favoring the SBRT arm. The proportion of patients experiencing PSA progression was also significantly lower in the SBRT arm (11% vs. 50%). In the SBRT arm, the median progression-free survival (PFS) was significantly longer. In addition to these findings, the fact that no grade 3 or higher side effects were observed in any of the evaluated patients indicated the treatment's tolerability. In both of the studies mentioned above, MDT was found to be a safe treatment with a low incidence of side effects.

In the The Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases (SABR-COMET) phase 2 study (17), 99 patients with oligometastatic cancer from various tumor groups, including lung, colorectal, breast, and prostate cancer, were assigned to receive either palliative standard of care treatment alone or standard of care plus SABR for all metastatic lesions. Patients with a maximum of 5 metasteses were included. Diagnostic imaging methods included MRI or CT for cranial scanning, PET/CT or whole-body CT and bone scan for the entire body, and MRI imaging for the vertebrae. SABR regimens of 30-60 Gy/3-8 fractions were applied. The primary endpoint was overall survival, which was higher in the SABR arm (41 vs. 28 months). One of the striking findings of the study was that the rate of grade 2 and higher side effects was significantly more frequent in the SABR arm than in the BR arm (29% vs. 9%). Additionally, 3 patients (4.5%) in the SABR arm died from treatment. Although the study demonstrated that SABR was an effective treatment in patients with oligometastatic tumors, it was emphasized that attention should be paid to toxicity.

Decaestecker et al. (18) conducted a prospective study on patients with prostate cancer who relapsed after receiving local curative treatment. The study included patients with a maximum of three metastases, and PET/CT was used to detect metastases. Patients were treated with SBRT regimens of 30 Gy/3 fractions or 50 Gy/5 fractions. In total, 70 lesions in 50 patients were treated. The primary endpoint of the study was ADT-free survival, with 1- and 2-year ADT-free survival rates of 82% and 60%, respectively. The 2-year local control rate was 100%, and the median PFS was 19 months. In addition to the efficacy of the treatment, no grade 3 or higher side effects were observed, indicating low toxicity. This prospective study with a low toxicity profile highlighted the positive impact of SBRT against the progression of oligometastatic prostate cancer, which is extremely valuable.

Another prospective study (19) evaluated prostate cancer patients who relapsed after definitive treatment, with a maximum of 5 metastases. In cases before 2014, MRI, bone scan, and choline PET/CT were used to detect metastases; while PSMA PET/CT was used for cases after 2014. In this study, which included 199 patients, an SBRT regimen of 50 Gy/10 fractions was administered to the lesions. The primary endpoint was the proportion of patients who did not require treatment escalation within 2 years of SBRT. The rate of patients who did not require treatment escalation within 2 years was 51.7%, and there was no significant difference in this rate between patients with 1-3 metastases and those with 4-5 metastases. PSA decreased in 75% of patients. No patient showed toxicity above grade 2. The finding that SBRT delayed treatment escalation with a low side effect profile in patients with oligometastatic prostate cancer attracted attention as evidence supporting Decaestecker et al.'s (18) prospective study.

In a systematic review of 56 studies on radiotherapy for oligometastatic prostate cancer (15), local control rates were found to be high following the application of MDT for oligometastatic disease. However, since the majority of studies were retrospective, it was stated that prospective phase 3 studies were needed. The diverse patient groups included in the studies made it difficult to provide a clear definition of the concept of oligometastasis. However, in most studies, patients with up to 3-5 metastases were included in this definition.

The review by Lancia et al. (20) stated that MDT delays the initiation of ADT and prolongs PFS, but the studies did not demonstrate its effect on overall survival. In a phase 2 study of patients with oligometastatic castration-resistant prostate cancer (21), patients who received abiraterone plus SBRT for all metastatic foci had an increased PFS compared with those who received abiraterone alone. In this study, patients with 3 or fewer non-visceral metastases were considered oligometastatic. A systematic review by Lim et al. (22) revealed an increase in PFS with MDT in patients with 3 or fewer non-visceral metastases. A systematic review by Le Guevelou et al. (23) found an increase in PFS with SBRT in patients with oligometastatic castration-resistant disease. Important studies on MDT in prostate cancer and their results are shown in Table 1.

Based on these encouraging studies, it becomes clear that there is a group that benefits from MDT within the group defined as "oligometastasis". It is obvious that these results should be supported by prospective phase 3 studies, and a clearer definition of oligometastasis is needed.

Radiotherapy for Primary Oligometastatic Prostate Cancer

In addition to MDT, the approach to the primary area of oligometastatic prostate cancer remains controversial. One of the most important studies addressing this issue is the multicenter randomized controlled HORRAD study (24). In this study, ADT and ADT + primary-directed RT were compared among patients with prostate cancer and primary bone metastases. Radiotherapy regimens of 70 Gy/35 or 57.76 Gy/19 fractions were applied. The study evaluated 432 patients and found that although combined treatment did not increase overall survival at a median follow-up of 47 months, it could be beneficial for patients with low tumor burden.

In the retrospective analysis conducted by Rusthoven et al. (25), ADT vs. The ADT + RT or radical prostatectomy (RP) arms were compared among patients with newly diagnosed metastatic prostate cancer. A total of 6382 patients were included, and it was observed that the RT + ADT arm exhibited increased overall survival compared with the ADT alone arm at 5-year follow-up. In another analysis, no difference in survival was found between the ADT + RT and ADT + RP arms, and both treatment modalities were found to be superior in terms of survival compared with ADT alone.

The randomized controlled phase 3 STAMPEDE (26) study evaluated newly diagnosed metastatic prostate cancer. Patients were divided into standard treatment (ADT ± docetaxel) and standard treatment + radiotherapy groups to the primary arms. Radiotherapy dose schedules of 55 Gy/20 or 36 Gy/6 fractions (1 fraction per week) were applied. This study analyzed 2061 patients and found that although radiotherapy increased recurrence-free survival, it did not increase overall survival. Subgroup analysis revealed that radiotherapy improved overall survival in patients with low tumor burden disease. The distinction between low and high tumor burden was made according to CHAARTED criteria. Considering these findings, it is clear that curative radiotherapy for primary oligometastatic prostate cancer may be beneficial.

Table 1. Important studies on MDT in prostate cancer and their results

Studies	Study design/ phase	Definition of oligometastasis	Number of patients	Arms	MDT regimens	SBRT regimens	Primary endpoint	Conclusion
Decaestecker et al. (13)	Phase 2	≤3 bone or lymph node lesions		Active surveillance vs. MDT	SBRT or surgery	30 Gy/3 fractions	ADT-free survival	
Ost et al. (14)	Phase 2	≤3 extracranial lesions	62	Observation or MDT	SBRT or surgery	30 Gy/3 fractions	ADT-free survival	13-21 months
Phillips et al. (16)	Phase 2	≤3 asymptomatic lesions, size <5 cm	54	Observation or MDT	SBRT	19.5-48 Gy/3-5 fractions	Rate of patients progressed within 6 months	61-19%
Palma et al. (17)	Phase 2	≤5 lesions	99	Standard of care or MDT	SBRT	30-60 Gy/3-8 fractions	Overall survival	28-41 months
Decaestecker et al. (18)	Phase 2	≤3 lesions	50	MDT	SBRT	30 Gy/3 fractions or 50 Gy/5 fractions	1 and 2 year ADT-free survival	82-60%
Bowden et al. (19)	Phase 2	≤5 lesions	199	MDT	SBRT	50 Gy/10 fractions	The proportion of patients did not require treatment escalation within 2 years of SBRT	51.70%
Francolini et al. (21)	Phase 2	≤3 non-visceral lesions	157	Abiraterone vs Abiraterone + MDT	SBRT	Rate of biochemical response	Rate of biochemical response	68.3-92%

MDT: Metastasis-directed therapy, SBRT: Stereotactic body radiotherapy, ADT: Androgen deprivation therapy

Radiotherapy Techniques and Dose/Fraction Regimes for Oligometastatic Prostate Cancer

While SBRT is often preferred for MDT in patients with oligometastatic prostate cancer, moderately hypofractionated or normofractionated regimens can also be preferred (14-16). Studies have shown that many different dose/fraction regimens are used for MDT. Dose schedules of 15-24 Gy/1 fraction, 24-36 Gy/3 fractions, 30-50 Gy/5 fractions stand out as SBRT regimens that can be preferred for MDT. Among these regimens, the most preferred regimen is the 30 Gy/3-fraction regimen. If we look at the MDT doses applied to lymph nodes, we see that after 45-50 Gy elective nodal irradiation with conventional fractionation, 63-74 Gy with boost to the affected area or 24-50 Gy/3-10 fractions with SBRT are preferred (15).

Ost et al.'s (14) study found that PFS increased when the biological effective dose was >100 Gy (27). Schick et al.'s (28) study concluded that the biochemical recurrence-free survival rate increased when the applied dose was EQD2 >64 Gy (alpha/beta: 2 Gy). Muldermans et al.'s (29) study found that the local control rate was higher in the group administered the 18 Gy/1 fraction regimen compared with the 16 Gy/1 fraction group.

Although existing studies provide us with clues about the regimen that should be selected, it is obvious that more studies are needed to determine the ideal dose/fraction regimen. Regarding the dose/fraction regimen to choose, factors such as the capability of the treatment machine, experience of the treatment team, the location and size of the area to be treated, and patient immobilization should be taken into account. Although the risk of serious toxicity with SBRT is extremely low, clinicians should not ignore the risk of treatment-related toxicity.

Conclusion

Although there is currently no definitive definition of the concept of "oligometastasis", MDT and primary-directed treatment can help slow down disease progression and contribute to the treatment process in prostate cancer, which is considered oligometastatic. SBRT is the most preferred treatment modality for this purpose. Various dose/fraction regimens are available in the literature. Treatment machine use, clinical, and patient-related factors should be considered when selecting the most appropriate regimen. More prospective studies are needed to clearly define the patient group that will benefit from treatment and to determine the ideal treatment for this group.

Footnote

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Short Quiz

1. According to Ost et al.'s study, above which value does BED increase PFS?

A. 70
B. 80
C. 90
D. 100

2. Which regimen is the most frequently used dose-fraction scheme for oligometastatic prostate cancer?

A. 50 Gy/5 fraction
B. 30 Gy/3 fraction
C. 15 Gy/1 fraction
D. Gy/3 fraction

Original Article

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Impact of Positive Surgical Margins on Renal Cell Carcinoma Recurrence

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Abstract

Objective: To investigate the impact of positive surgical margins (PSM) on local relapse and metastasis in patients undergoing partial nephrectomy (PN).
Materials and Methods: We retrospectively analyzed the data of 43 patients who underwent PN between June 2019 and January 2024 and met the inclusion criteria. Patients were divided into two groups: PSM and negative surgical margin (NSM). We analyzed preoperative patient characteristics, surgical details, and pathological findings. We compared the incidences of local relapse, ipsilateral radical nephrectomy, and metastasis between the two groups during follow-up.
Results: The median follow-up duration was 24.5 months in the PSM group and 16 months in the NSM group, with no significant difference in follow-up duration ($p>0.05$). Ischemia times were significantly longer in the PSM group (26.5 minutes vs. 18 minutes, $p=0.04$) and there was greater intraoperative blood loss (700 mL vs. 300 mL, $p<0.001$). No significant differences were observed between the groups regarding local relapse, metastasis, or ipsilateral radical nephrectomy ($p>0.05$). Histological type, Fuhrman grade, and pathological T-stage did not differ significantly between the groups ($p>0.05$).
Conclusion: PSM is associated with longer ischemia times and increased intraoperative bleeding. However, despite the higher recurrence rates associated with PSM, no statistically significant differences were observed in local relapse or metastasis when compared to NSM. Future research should focus on larger cohorts and extended follow-up to better understand the impact of surgical margins on patient outcomes.
Keywords: Local recurrence, metastasis, negative surgical margins, partial nephrectomy, positive surgical margins

Introduction

In recent years, due to advancements and the widespread use of imaging techniques, the detection of smaller and earlier-stage renal masses, both incidentally and symptomatic, has increased. The standard curative treatment for localized renal tumors is surgery. However, the choice of surgical procedure depends on the tumor's size, location, and stage. For cT1 and selected cT2 tumors, partial nephrectomy (PN) is preferred when considering the importance of preserving kidney function to maintain oncological outcomes and quality of life (1). It has been reported that in localized renal tumors, kidney function is better preserved after PN than after radical nephrectomy (RN), and morbidity related to cardiovascular disorders is reduced (2). In patients undergoing PN, positive surgical margins (PSM) can be observed at rates ranging from 0% to 11%, regardless of the surgical technique used (open, laparoscopic, robotic) (3,4). PSM are a subject of debate in terms of prognosis and follow-up plans because they may lead to poor outcomes in certain histological subtypes.

Some researchers have reported that PSM in renal cell carcinoma (RCC) does not affect cancer-free survival (5). The oncological outcomes of PSM remain controversial. PSM, especially in high-grade patients, increases the risk of local relapse. In patients with PSM, the incidence of local relapse is 16% compared with 3% in patients with negative surgical margins (NSM) (6).

The aim of this study was to investigate the impact of surgical margins on local relapse and metastasis in patients with PN.

Materials and Methods

This study retrospectively examined the data of 57 patients who underwent preoperative thoracoabdominopelvic computed tomography (CT) or abdominal magnetic resonance imaging

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(MRI) combined with thoracic CT between June 2019 and January 2024 and who underwent PN due to a preliminary diagnosis of localized renal malignancy.

The inclusion criteria were as follows: minimum follow-up of 6 months, malignant pathology, PSM, NSM, and complete follow-up data. The exclusion criteria were benign pathologies, such as oncocytoma and angiomyolipoma, clinical stage cT3-4, cN+, or cM+, and incomplete or missing data for the study. After excluding 14 patients who met the exclusion criteria, the study was designed with 43 patients.

Preoperative factors evaluated in the included patients included age, sex, laterality, clinical tumor size and location, renal nephrometry score, and serum creatinine levels. Perioperative renal ischemia status, surgical technique, intraoperative bleeding, and non-bleeding intraoperative complications were also assessed.

All specimens were evaluated by uro-pathologists at our institution for analysis. Pathological findings included histological types, such as clear cell RCC (ccRCC), papillary RCC (pRCC), and chromophobe RCC, as well as pathological T-stage, tumor size, Fuhrman grade, and surgical margins. During follow-up, local relapse, ipsilateral RN, and metastasis were evaluated. Patients with PSM were grouped into group 1, and patients with NSM were grouped into group 2. Between-group comparisons were made regarding age, sex, laterality, tumor size and location, renal nephrometry score, preoperative serum creatinine levels, histological type, pathological T-stage, Fuhrman grade, pathological tumor size, surgical margins, and occurrence of local relapse, ipsilateral RN, and metastasis. The median follow-up duration was calculated as the median time from surgery to the last follow-up visit.

The study protocol was approved by the Clinical Research Ethics Committee of Gazi University Faculty of Medicine (approval number: 23/01/2023-82, date: 27.01.2023).

Surgical Technique

Open PN: A subcostal incision was made in the lateral decubitus position to free the kidney from surrounding tissues transabdominally. After controlling the renal hilum, the renal artery and vein were clamped en bloc. The tumor was then resected under cold ischemia. Post-resection, the tumor bed and parenchyma were repaired in two layers. Hemostasis was achieved using a hemostatic matrix kit (Surgiflo, ETHICON) and absorbable hemostat (Surgicel, ETHICON). A drain was placed in the renal bed, and the procedure was concluded.

Laparoscopic PN: In the lateral decubitus position, insufflation was performed with a Veress needle to achieve an intra-abdominal pressure of 15 mmHg. After placing a total of four trocars, including one for the camera, the kidney was freed from surrounding tissues, and control of the renal hilum was established. The renal artery and vein were clamped en bloc, and the tumor was resected under warm ischemia. Post-resection, the tumor bed and parenchyma were repaired in two layers. Hemostasis was achieved using a hemostatic matrix kit (Surgiflo, ETHICON) and absorbable hemostat (Surgicel, ETHICON). A drain was placed in the renal bed, and the procedure was concluded.

Robot-assisted laparoscopic PN (RAPN): In the lateral decubitus position, insufflation was achieved using a Veress needle to reach an intra-abdominal pressure of 15 mmHg. After placing a total of five trocars, including one for the camera, the kidney was freed from surrounding tissues, and control of the renal hilum was established. The renal artery and vein were clamped en bloc, and the tumor was resected under warm ischemia. Post-resection, the tumor bed and parenchyma were repaired in two layers. Hemostasis was achieved using a hemostatic matrix kit (Surgiflo, ETHICON) and absorbable hemostat (Surgicel, ETHICON). A drain was placed in the renal bed, and the procedure was concluded.

Patients were evaluated every 3 months during the first year after surgery and then every 6 months thereafter. Follow-up evaluations included medical history taking, physical examinations, routine laboratory blood tests, chest radiography, and abdominal imaging (CT or MRI). Follow-up assessments for both PSM and NSM cases were conducted at the same time-points.

Statistical Analysis

Statistical analysis was performed using SPSS software version 22. Categorical data across groups were compared using Fisher's exact test, and continuous variables were compared using the Mann-Whitney U test. Statistical significance was set for p-values less than 0.05.

Results

The median age of patients in the PSM group was 52.5 years (range: 44-58), while in the NSM group it was 57 years (range: 32-77). There were no statistically significant differences between the groups regarding age, sex, laterality, or median preoperative serum creatinine levels (all $p>0.05$; Table 1).

The median follow-up duration was 24.5 months (7-47) in the PSM group and 16 months (6-60) in the NSM group. There was no statistically significant difference between the groups in terms of follow-up duration ($p>0.05$) (Table 1).

The median ischemia time was 26.5 minutes (23-32) in the PSM group and 18 minutes (8-33) in the NSM group. The ischemia time was significantly longer in the PSM group ($p=0.04$) (Table 1).

The median intraoperative blood loss was 700 mL (600-900) in the PSM group and 300 mL (200-700) in the NSM group. Intraoperative blood loss was significantly higher in the PSM group ($p<0.001$) (Table 1).

There were no statistically significant differences between the two groups regarding intraoperative complications, tumor location, renal nephrometry score, endophytic nature of the tumor, or imaging-based tumor size ($p>0.05$, $p>0.05$, $p>0.05$, $p>0.05$ and $p>0.05$, respectively) (Table 1).

There were no statistically significant differences between the groups regarding histological tumor type, Fuhrman grade, pathological T-stage, or pathological tumor size ($p>0.05$, $p>0.05$, $p>0.05$ and $p>0.05$, respectively) (Table 2).

In the PSM group, during a median follow-up of 24.5 months, 1 patient (25%) experienced local relapse, and the same

patient 1 (25%) also had synchronous metastases. Patient 1 (25%) underwent ipsilateral RN surgery. In the NSM group, during a median follow-up of 16 months, none of the patients experienced local relapse, but 1 patient (2.6%) had metastasis, and no patients (0%) underwent ipsilateral RN. There were no significant differences between the groups in terms of local relapse, metastasis, and ipsilateral RN (p>0.05, p>0.05 and p>0.05, respectively) (Table 3).

Discussion

PSMs can be considered residual cancer cells in the resection area. However, these residual cells might undergo necrosis due to renal ischemia, making them potentially clinically insignificant. Additionally, because pathologists can only examine one side of the specimen, cancer cells corresponding to PSM might not be present in the resection bed. In NSM, although there is a

Table 1. Patient characteristics and perioperative findings

		PSM n (4)	NSM n (39)	p-value
Age, year (median, min-max)		52.5 (44-58)	57 (32-77)	0.319
Follow-up, month (median, min-max)		24.5 (7-47)	16 (6-60)	0.454
Gender n (%)	Female	0 (0%)	17 (43.6%)	0.140
	Male	4 (100%)	22 (56.4%)	
Tumor side n (%)	Right	3 (75%)	21 (53.8%)	0.618
	Left	1 (25%)	18 (46.2%)	
Renal nephrometry score (median, min-max)		5.5 (4-7)	5 (4-8)	0.479
Endophytic biomass, n (%)		2 (50%)	12 (30.8%)	0.585
Imagiological tumor size, cm (median, min-max)		37.5 (19-57)	37 (12-75)	0.762
Tumor location n (%)	Superior pole	1 (25%)	9 (23.1%)	0.996
	Inferior pole	2 (50%)	20 (51.3%)	
	Mezorenal area	1 (25%)	10 (25.6%)	
Surgical approach n (%)	Open	2 (50%)	31 (79.5%)	0.374
	LPN	1 (25%)	3 (7.7%)	
	RAPN	1 (25%)	5 (12.8%)	
Ischemia time, minute (median,min-max)		26.5 (23-32)	18 (8-33)	0.04*
Preoperative creatinine mg/dL (median, min-max)		0.9 (0.9-1.6)	0.9 (0.5-2.8)	0.361
Intraoperative blood loss, mL (median, min-max)		700 (600-900)	300 (200-700)	<0.001*
Intraoperative complications, n (%)		3 (75%)	10 (25.6%)	0.075

PSM: Positive surgical margin, NSM: Negative surgical margin, LPN: Laparoscopic partial nephrectomy, RAPN: Robotic-assisted laparoscopic partial nephrectomy, min-max: Minimum-maximum, *Statistically significant p-value

Table 2. Pathological findings

		PSM n (4)	NSM n (39)	p-value
Histology n (%)	ccRCC	4 (100%)	35 (89.7%)	0.798
	pRCC	0 (0%)	3 (7.7%)	
	chrRCC	0 (0%)	1 (2.6%)	
T stage n (%)	T1a	2 (50%)	28 (71.8%)	0.571
	T1b	2 (50%)	10 (25.6%)	
	T2a	0 (0%)	1 (2.6%)	
Fuhrman grade n (%)	I	2 (50%)	10 (25.6%)	0.824
	II	1 (25%)	15 (38.5%)	
	III	1 (25%)	13 (33.3%)	
	IV	0 (0%)	1 (2.6%)	
Tumor size, cm (median, min-max)		37.5 (15-55)	35 (8-73)	0.763

PSM: Positive surgical margin, NSM: Negative surgical margin, ccRCC: Clear cell renal cell carcinoma, pRCC: Papillary renal cell carcinoma, chrRCC: Chromosomal renal cell carcinoma

Table 3. Follow-up variables

	PSM n (4)	NSM n (39)	p-value
Local relapse, n (%)	1 (25%)	0 (0%)	0.093
Metastasis, n (%)	1 (25%)	1 (2.6%)	0.179
Ipsilateral RN, n (%)	1 (25%)	0 (0%)	0.093

PSM: Positive surgical margin, NSM: Negative surgical margin, RN: Radical nephrectomy

possibility of up to 5% false-negative reports, NSM does not guarantee the absence of local relapse (7,8).

Bensalah et al. (9) reported that only 39% of patients who underwent reoperation due to PSM had residual tumors identified on pathological examination. They stated that new techniques or tumor markers are necessary to more accurately assess surgical margins in their studies.

PSM after PN has been reported at rates ranging from 0.1% to 10.7% (10). In our study, the rate of PSM was 9.3%, which is consistent with the literature. Takagi et al. (11) reported that the average time to recurrence after PN was 19 months. In our study, the time to recurrence in one of the four patients with PSM was 16 months. However, due to the limited number of patients, we could not determine a threshold value.

In the literature, there is no consensus on whether there is a statistical relationship between positive and NSM and recurrence rates or specific survival. Bernhard et al. (12) conducted multivariate analysis during an average follow-up of 27 months and demonstrated an association between PSM and local recurrence. Similarly, Wood et al. (6) showed a strong association between PSM and local relapse after PN, with an average follow-up of 23 months. They reported a relapse rate of 15.9% in the PSM group compared with 3% in the control group. Khalifeh et al. (3) reported in their study that during an average follow-up of 13 months, 9 out of 21 patients with PSM (42.9%) experienced recurrence, and 4 patients (19.1%) developed metastases. They interpreted these findings as indicating a strong association between PSM and recurrence (3). In our study, only 1 recurrence occurred in the PSM group. Due to the limited number of patients, statistically strong results were not obtained.

Shah et al. (13) demonstrated that PSM is an independent risk factor for recurrence. Their subgroup analysis revealed that PSM was a risk factor for recurrence in pathologically high-risk tumors (pT2-3a or Fuhrman grade III-IV) but not in low-risk tumors (pT1 or Fuhrman grade I-II) (13). Similarly, Marchiñena et al. (14) found that PSM and high-grade tumors (Fuhrman grade III-IV) are independent predictors of local recurrence. It is known that tumors with a high Fuhrman grade are more aggressive and are thought to have a higher risk of recurrence. However, due to the limited number of patients in our study cohort, we were unable to evaluate the correlation between Fuhrman grade and recurrence.

In a study by Carvalho et al. (15), it was concluded that high-risk tumors and limited surgical experience are risk factors for PSM. Although they could not demonstrate a negative impact of PSM on survival, they observed a trend toward increased local recurrence and metastasis.

In a matched pair analysis study by Bensalah et al. (9), which included 101 patients with PSM and 102 patients with NSM, they found that PSM had no impact on 5-year recurrence-free survival (RFS), 5-year cancer-specific survival (CSS), or 5-year overall survival (OS). Rothberg et al. (16) reported that, during an average follow-up of 18.8 months, the oncological outcomes were not worse in patients with PSM than in those with NSM.

Morrone et al. (17) evaluated patients undergoing RAPN and found no statistical relationship between PSM and RFS or OS. However, multivariate analysis showed that higher RENAL scores were associated with NSM. They proposed that this paradoxical finding might be due to the difficulty in detecting small masses in the renal parenchyma or increased surgeon confidence in easier cases (17). In our study, the longer ischemia time and increased intraoperative blood loss in the PSM group could be attributed to the difficulties encountered during tumor resection, which could prevent the achievement of NSM.

In a matched pair analysis study by Radfar et al. (18), with an average follow-up period of 24 months, they found that tumor recurrence occurred more frequently in the PSM group. However, the authors also noted that this did not affect OS compared with the NSM group (18).

Yoo et al. (19) found that 10 year RFS was significantly higher in patients with ccRCC than in those with pRCC. They attributed this finding to the greater prevalence of recurrence in the pRCC group compared with the ccRCC group at least 5 years after surgery (19). In our study, the average follow-up period was only 20 months, and all patients with PSM had ccRCC. Therefore, we were unable to evaluate tumor recurrence and its relationship with histological type beyond the 5-year postoperative period.

Study Limitations

First, as this was a retrospective study, there was a possibility of selection bias and information inaccuracies. Second, the small number of patients and short follow-up durations may have limited our ability to obtain objective results. Additionally, because our data represent results from a single center, they may not be generalizable. Additionally, because our data reflected the experience of multiple surgeons, varying levels of surgical expertise might have influenced our results. The use of different ischemia techniques (warm vs. cold) might have affected the results. Importantly, key parameters, such as CSS, RFS, and OS, were not evaluated in relation to PSM. An analysis of survival might have provided more in-depth insights into the influence of PSM on recurrence. Furthermore, the size of the PSM area was not assessed.

Conclusion

The current study aimed to investigate the impact of PSM and NSM on local relapse and metastasis among patients undergoing PN. Although our results support some findings in the literature, the limited number of patients prevented us from reaching definitive conclusions in some statistical assessments. We hypothesized that the high incidence of surgical margins in patients with prolonged ischemia time and increased intraoperative blood loss may be due to difficulties encountered during tumor resection.

In conclusion, the effect of PSM on local relapse and metastasis remains controversial. However, our study revealed higher recurrence rates in the PSM group. It should be noted that PSM poses a higher risk in high-grade tumors, and careful monitoring of this patient group is necessary. When supported by larger patient cohorts and long-term follow-up studies, our findings provide clearer insights into the impact of surgical margins on oncological outcomes.

Footnote

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Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: E.C.B., B.E., M.K., N.K., Ç.C., U.A., S.Ç., S.S., Concept: E.C.B., B.E., S.Ç., S.S., Design: E.C.B., M.K., Ç.C., U.A., S.Ç., Data Collection or Processing: B.E., M.K., N.K., Ç.C., U.A., Analysis or Interpretation: E.C.B., B.E., Ç.C., U.A., Literature Search: M.K., N.K., Ç.C., U.A., S.Ç., S.S., Writing: E.C.B., B.E., S.Ç., S.S.

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Contemporary Role of Urine Cytology in Bladder Cancer

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Abstract

Objective: The objective of this study was to assess the efficacy of urine cytology in predicting definitive pathology in patients undergoing transurethral bladder tumor resection.

Materials and Methods: Patients who underwent transurethral bladder tumor resection between January 2019 and April 2022 were included. Urine cytology was performed via the bladder wash of the first urine sample as the initial procedure during cystoscopy. Then, transurethral resection of the bladder tumor was performed. The demographic characteristics of the patients, including age and sex, were recorded. The diagnostic accuracy of urine cytology for bladder tumor detection was calculated using the Paris System for Reporting Urinary Cytology.

Results: A total of 229 patients who underwent endoscopic bladder tumor resection for urothelial carcinoma comprised the study group. Among patients, 193 (84.28%) were male and 36 (15.72%) were female. Urine cytology revealed "negative for high-grade urothelial carcinoma" in 44.11% of the patients, and "low-grade urothelial carcinoma" in 27.31% of the cases as the most common first two findings. The definitive pathological examination after endoscopic surgery revealed benign histology in 23.75% of the patients, whereas the remaining patients had urothelial carcinoma. The overall efficacy of urine cytology in detecting urothelial tumors was 72.89% sensitivity and 90.47% specificity.

Conclusion: Urine cytology can predict the final pathology of bladder urothelial carcinoma with limited sensitivity.

Keywords: Urine cytology, high-grade, bladder cancer, urothelial carcinoma, hematuria

Introduction

Cystoscopy is currently the preferred tool for both diagnosis and follow-up of bladder cancer. However, it is invasive and is associated with significant morbidity. Cytologic examination of urine sediment is an easy-to-obtain test for diagnosing malignant diseases of the urinary tract (1). Urine cytology includes the diagnosis/monitoring of urothelial tumors and evaluation of hematuria (1). It is highly sensitive in high-grade (HG) tumors but is less sensitive in low-grade (LG) tumors. The overall sensitivity of cytology is 48% (1). It was 16% for LG tumors and 84% for HG tumors (1). Furthermore, its low sensitivity ranges from 28% to 100% for different series (2). On the other hand, urine cytology has remarkable specificity, exceeding 90% (3). These findings suggest that urine cytology is largely subjective, and the ability to detect cancer cells is dependent on the experience of cytologists, particularly in detecting LG atypia tumors (4). Consequently, significant variability in cytology results has been reported among the 10 centers and ranges from poor (63%) to excellent (89%) (5). The Paris System (TPS) for Reporting Urinary Cytology, which was proposed in 2016 and updated in 2022, has standardized the diagnostic criteria for HG urothelial carcinoma and provided promising results (6,7). In order to detect the utilization yield of this new TPS, recent clinical trial results are required. The objective of this retrospective study was to document the efficacy of urine cytology in predicting definitive pathology in patients who underwent transurethral bladder tumor resection.

Material and Methods

A total of 240 patients who underwent endoscopic bladder tumor resection between January 2019 and April 2022. The group consisted of patients with either tumor recurrence during follow-up cystoscopy or initial diagnosis of bladder cancer. The exclusion criteria were renal cell carcinoma, prostate cancer, and any other histological subtype that differed from urothelial

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cancer. Two cases of bladder small cell carcinoma and four cases of prostate adenocarcinoma were excluded. Another 3 cases who had different histological characteristics (chronic lymphocytic leukemia/small lymphocytic lymphoma, colon adenocarcinoma, and leiomyosarcoma) were also not included. According to urine cytology results, two cases that were found inadequate in terms of cellularity were also excluded. Finally, 229 patients with urothelial pathology constituted the study group. This retrospective study was approved by the Clinical Research Ethics Committee of Marmara University (protocol number: 09.2024.444, date: 08.12.2023).

Transurethral bladder surgery was performed when the urine culture result was negative in all patients. The demographic characteristics of the patients, including age and sex, were recorded. Urine cytology was performed via the bladder wash of the first urine sample as the initial procedure during cystoscopy. A sterile 0.9% saline solution was used for bladder washing. This fresh sample was sent to the cytopathologist without further procedures. At the pathology laboratory, urine samples were immediately centrifuged at 2,000 rpm for 10 min, and ThinPrep® liquid-based cytology slides were prepared from the sediment. All samples with low cellularity were re-centrifuged at 2,000 rpm for 5 minute. The slides were then stained using the positive airway pressure method. The slides were reported using the TPS. A single dedicated cytopathologist (M.H.T.) evaluated all urine samples. Then, transurethral resection of the bladder tumor was performed. Local pathological staging was performed according to the tumor-node-metastasis (TNM) 2017 by the same pathologist.

The 2017 TNM classification system was used for pathological staging, and the results were divided into Ta, T1, T2, and carcinoma *in situ* (CIS) categories according to T (tumor) stage (8). The 2016 World Health Organization grading system was used for pathological grading, and the results were divided into LG and HG categories (9). According to the transurethral resection-MT pathology results, patients were evaluated in 9 categories: 0) Benign pathologies (inflammation, granulation, edema, etc.) 1) TaLG, 2) TaHG, 3) T1LG, 4) T1HG, 5) T2HG, 6) CIS, 7) Focal dysplasia, 8) Others.

2016 TPS category groups were used for cytological evaluation (10). Cytological findings were evaluated in 7 categories: 1) Adequacy/unsatisfactory, 2) Negative for high-grade urothelial carcinoma (NHGUC), 3) Atypical urothelial cell (AUC), 4) Suspicious for high-grade urothelial carcinoma (SHGUC), 5) Low-grade urothelial carcinoma (LGUC), 6) High-grade urothelial carcinoma (HGUC), 7) Others.

The diagnostic yield of urine cytology based on the TPS for predicting final pathology was assessed using sensitivity and specificity.

Statistical Analysis

Data were analyzed using the IBM Statistical Package for the Social Sciences version 22 (IBM SPSS Statistics for Windows, Chicago, IL, USA). The normality of the distribution of variables was evaluated using the Shapiro-Wilk test. The independent and dependent groups were compared using the Mann-Whitney U test and Wilcoxon signed-rank test, respectively. A p-value <0.05 was set as statistically significant.

Results

Among the included patients, 193 (84.28%) were male and 36 (15.72%) were female. The mean age was 65.88+11.91 and 68.12+10.95 for male and female patients, respectively. Out of the total, 103 patients (45%) presented with hematuria, 23 patients (10%) were incidentally diagnosed, 34 patients (35%) presented with lower urinary tract symptoms (LUTS), and data for 69 were unavailable. A smoking history was noted in 119 patients (52%). Primary bladder cancer was identified in 132 patients (57%), while 97 patients (42%) were diagnosed with secondary bladder cancer.

Out of the total, 50 patients (22%) were classified as low risk, 98 patients (43%) as intermediate risk, and 91 patients (35%) as high risk. Considering the past therapy, 17 patients had a history of intravesical chemotherapy, and 25 patients had a history of intravesical BCG only 7 patients had a history of upper urinary tract urothelial carcinoma with a history of nephroureterectomy.

The investigation of urine cytology revealed NHGUC in 44.11% of the patients, LGUC in 27.31%, HGUC in 13.86%, AUC in 6.72%, and SHGUC in 5.88% of the samples as the first 5 ranks of cytological diagnosis based on TPS criteria. The detailed results are presented in Table 1. Within the excluded patients with different final histologies from urothelial carcinoma, 5 had "others", 3 had NHGUC and 1 had AUC as the cytology result.

The histological evaluation of tissues obtained from endoscopic resection revealed that 23.75% of the patients had benign pathologies, 27.91% had Ta LG, 7.5% had Ta HG, 1.2% had T1 LG, 17.91% had T1 HG, 12.91% had T2 HG, CIS in 2.5% of the cases, and focal dysplasia in 2.5% of the patients. Half of the CIS cases were primary CIS; and the remaining 3 cases had concomitant T1 HG. The findings based on the final pathological findings of the specimens are presented in Table 2.

The efficacy of negative urine cytology in 105 patients in predicting final pathology after transurethral resection was reported as benign in 52 (49.5%) patients, Ta LG in 31 (29.5%) patients, Ta HG in 4 (3.8%) patients, T1 HG in 4 (3.8%) patients, and T2 HG in 6 (5.7%) patients. The corresponding results of

Table 1. Urine cytology findings

Urine cytology results based on the TPS criteria	Number (n)	%
None	1	0.41
Unsatisfactory specimen	1	0.41
Negative for HGUC	105	44.11
Atypical urothelial cells	16	6.72
Suspecious for HGUC	14	5.88
LGUC	65	27.31
HGUC	33	13.86
Others	5	2.1
Total	240	100

TPS: The Paris System for Reporting Urinary Cytology, HGUC: High-grade urothelial carcinoma, LGUC: Low-grade urothelial carcinoma

cytology with definitive pathology are presented in Table 3. The second major subgroup based on the TPS classification was LGUC, which included 65 patients. Final pathological examination revealed a urothelial tumor in all cases (6 patients had LGUC and 59 cases had HGUC or CIS). HGUC was the third most common category according to cytology results, including 33 patients. Final pathological examination revealed LGUC in 24, HGUC in 8, and CIS in 1.

Table 2. Final pathological findings

Local pathological results based on TNM classification (2017)	Number (n)	%
Benign pathologies (inflammation, granulation, edema, etc.)	57	23.75
Ta LGUC	67	27.91
Ta HGUC	18	7.5
T1 LGUC	3	1.2
T1 HGUC	43	17.91
T2 HGUC	31	12.91
Carcinoma *in situ*	3+3*	2.5
Focal dysplasia	6	2.5
Others	9	3.75
Total	240	100

HGUC: High-grade urothelial carcinoma, LGUC: Low-grade urothelial carcinoma, TNM: Tumor-node-metastasis, *: Three patients had primary Carcinoma *in situ*, the remaining 3 had concomitant

The overall efficacy of urine cytology in predicting final pathology based on the presence of urothelial tumor demonstrated 72.89% sensitivity and 90.47% specificity (Table 4). The positive predictive value (PPV) and negative predictive value (NPV) of urine cytology for bladder tumors were calculated as 95.27% and 55.88%, respectively.

Discussion

Urothelial carcinoma is one of the most common organ cancers, with a remarkable incidence rate (11). Most cases present as non-muscle-invasive disease and initially underwent endoscopic tumor resection with remarkably high recurrence rates despite intravesical treatment (12). Therefore, strict surveillance is essential. Current practice in the follow-up of patients with superficial bladder cancer requires regular checkup cystoscopies, and the schedule is maintained when recurrence occurs. Consequently, cystoscopy remains the gold standard follow-up protocol for bladder cancer (12). However, cystoscopy is costly and uncomfortable. In addition, it creates a great burden for busy reference hospitals. On the other hand, some tumors can be missed by cystoscopy. Therefore, there is clearly a need for non-invasive urine markers that can help reduce the number of cystoscopies and increase diagnostic accuracy.

Urine cytology is an important non-invasive technique for the screening, diagnosis, and follow-up of patients with urothelial carcinoma. A standardized evaluation of urine cytology would hypothetically replace cystoscopy, or at least the cystoscopy interval would be prolonged when there is a negative cytology result.

Table 3. Corresponding final pathological results of the cytology subgroups

Cytology	Final pathology									
	Benign	TaLG	TaHG	T1LG	T1 HG	T2 HG	CIS	Dysplasia	Other	Total
Negative for HGUC	52	31	4	0	4	6	0	5	3	105
Atypical urothelial cells	3	7	0	0	2	2	0	1	1	16
Suspecious for HGUC	2	1	2	0	5	1	3	0	0	14
LGUC	0	6	10	0	26	21	2	0	0	65
HGUC	0	21	2	3	5	1	1	0	0	33
Others	0	0	0	0	0	0	0	0	5	5
Total	57	66	18	3	42	31	6	6	9	238

HGUC: High-grade urothelial carcinoma, LGUC: Low-grade urothelial carcinoma, HG: High-grade, LG: Low-grade, CIS: Carcinoma *in situ*

Table 4. Evaluation of cytology parameters for predicting final pathology

Cytology	Final pathology			
	(+) (Ta, T1, T2, CIS)	(-) (benign, dysplasia)	Total	
(+) (atypical urothelial cells) (suspecious for HGUC, LGUC, HGUC)	121	6	127	PPV 95.27%
(-) (negative for HGUC)	45	57	102	NPV 55.88%
Total	166	63	229	
	Sensitivity 72.89%	Specificity 90.47%		

HGUC: High-grade urothelial carcinoma, LGUC: Low-grade urothelial carcinoma, CIS: Carcinoma *in situ*, PPV: Positive predictive value, NPV: Negative predictive value

However, despite advancements in laboratory systems for processing urine specimens, difficulties remain in some cases, and accurate interpretation of certain cells in urine is a major challenge for cytopathologists (7). The evaluation of urine cytology to detect tumor cells is largely subjective, and the ability to detect cancer cells depends on the experience of cytopathologists (13). Therefore, tremendous efforts have been made to standardize urine cytology. Particularly, "atypical cells" are commonly reported and have various diagnostic suggestions (7). TPS was developed to address these problems of variations in cytology evaluation to provide a relatively universal interpretation. TPS was conceived during the International Academy of Cytology Congress held in Paris in May 2013 to ensure uniformity in reporting of urine cytology (10). Recent molecular and genetic studies suggest that these are two separate diseases; first, LGUC with an overall good prognosis and HG cancer with a significant mortality rate (6). Therefore, the conclusion of the first meeting of the TPS working group was that the new reporting system should focus primarily on the detection of HGUC while minimizing LGUC detection. Then, the efforts of this working group proposed an improvement in the reporting system that includes specific diagnostic categories and cytomorphologic criteria for reliable diagnosis of HGUC in 2016 (6).

The new TPS modification in 2016 has been widely accepted and tested by several studies. Rohra et al. (14) reported that the new TPS particularly lowered the rate of atypia based on 486 urine samples with a high rate of HGUC. Another comparison of the evaluation of urine cytology based on pre-TPS and the new TPS classification clearly demonstrated that TPS has an increasing PPV for HGUC (15). It was confirmed that the TPS is an objective template for reporting urine cytology and is particularly useful for identifying HGUC cases (16). The results of the current trial also demonstrated that the new TPS had reasonable specificity for detecting HGUC.

The initial step in optimal urine cytology is proper collection. It has been documented that the sensitivity of instrumented urine cytology is significantly higher than that of the voided cytology (17). Another trial indicated that, in the absence of atypical or malignant cells, an adequate bladder barbotage specimen should have a minimum of 2644 (20 per 10 high-power fields) well-visualized, well-preserved urothelial cells as the cut-off value (18). On the other hand, it was shown that volume was an important component in the evaluation of adequacy for voided urine cytology specimens, and at least 30 mL of urine is required for an adequate test (19). In this study, we preferred bladder wash-out specimens with a volume of 50 mL based on these studies. Only 2 samples were found inadequate in terms of cellularity.

One of the most challenging categories in urine cytology reporting is the "AUC". The AUC category may represent diagnosis that "favor a reactive process" or "is uncertain whether reactive or neoplastic" (20). Strict criteria were proposed by the TPS to define the AUC category and reduce the number of uncertain diagnoses. In four prospective studies, a decrease in AUC category diagnosis rates, ranging from 0.9% to 13%, was observed after the use of the TPS criteria (21,22). In these studies, the overall AUC diagnosis rate after TPS varies between 14.4% and 26%, and the percentage of patients diagnosed with AUC and ultimately diagnosed with HGUC increased (from 33% to 53%). In our study, the AUC category constituted 6.72% of the cytology reports, and according to the surgical pathology results, 25% of these patients were diagnosed with HGUC, which demonstrated similar findings to the literature.

As the main focus of urine cytology is the diagnosis of high-grade urothelial carcinoma and given the great sensitivity of cytology in detecting these tumors, HGUC is the most important category of cytologic interpretation. In a review of the published literature, Pastorello et al. (23) showed that the diagnosis rates of SHGUC and HGUC ranged from 0.2% to 6.6% and 2.2% to 14.1%, respectively. The calculated risk of high-grade malignancy (ROHM) ranged from 33.3 to 100% for SHGUC and 58.8 to 100% for HGUC. Furthermore, the reported sensitivity of TPS ranged from 40% to 84.7%, specificity from 73% to 100%, PPV from 62.3% to 100%, and NPV from 46% to 90% (23). In our study, according to the cytology results, the diagnostic rates for SHGUC and HGUC were 5.88% and 13.86%, respectively. Interestingly, the ROHM rate for HGUC was 27.2%. In fact, all cases in the HG category had a diagnosis of urothelial carcinoma, including LG, HG, and CIS based on the final pathologic results; however, LG urothelial tumors account for the majority of the cases. The overall efficacy of urine cytology for the detection of urothelial tumors demonstrated 72.89% sensitivity, 90.47% specificity, 95.27% PPV, and 55.88% NPV in this study. Our results are similar to those in the literature.

Study Limitations

The main limitation of this trial is that it is a retrospective study. Some data regarding patient characteristics, such as obesity, are missing. Nevertheless, the current trial reflected the current role of cytology in daily practice.

Conclusion

Urine cytology is a non-invasive diagnostic procedure for the primary diagnosis and follow-up of patients with urothelial carcinoma. The results of the current study confirmed that urine cytology has acceptable sensitivity and specificity for detecting HG tumors but is less sensitive for LG tumors. Our findings suggest that although TPS has standardized the diagnostic criteria in particular focusing on detecting HG tumors and improved the quality of reporting and clinical utility of urinary cytology; there is no sufficient data for cytology to replace cystoscopy in the diagnosis and follow-up of patients with bladder cancer.

Footnote

Publication: The results of the study were not published in full or in part in form of abstracts.

Contribution: There is not any contributors who may not be listed as authors.

Conflict of Interest: No conflict of interest was declared by the authors.

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Ethics Committee Approval: This retrospective study was approved by the Clinical Research Ethics Committee of Marmara University (protocol number: 09.2024.444, date: 08.12.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: M.K., M.Ç., M.H.T., D.F., K.Ç., Concept: K.Ç., Design: M.K., K.Ç., Data Collection or Processing: M.Ç., M.H.T., Analysis or Interpretation: M.K., M.Ç., M.H.T., D.F., Literature Search: M.K., M.Ç., M.H.T., Writing: M.K., K.Ç.

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Original Article

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Comparison of Prostate Specific Antigen and Neuropeptide Y Parameters in Patients with Prostate Cancer

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Abstract

Objective: Prostate cancer is a solid tumor that can be fatal in men. Early detection and proper management are essential for improving outcomes and reducing mortality rates associated with this disease. This study aimed to evaluate the potential of neuropeptide Y (NPY) as a biomarker to enhance the effectiveness of prostate specific antigen (PSA) testing in diagnosing and predicting prostate cancer prognosis. NPY, a well-known sympathetic neurotransmitter, possesses growth-promoting and angiogenic properties in various cell types, including those relevant to prostate cancer. Additionally, NPY has been linked to neuroendocrine differentiation of prostate cancer cells. By comparing the efficacy of PSA testing alone with the addition of NPY, this study aimed to determine whether NPY could offer additional predictive value for prostate cancer progression and prognosis.

Materials and Methods: This study involved 90 patients each diagnosed with localized prostate cancer (LPC), metastatic prostate cancer (mPC) at diagnosis, and metastatic castration-resistant prostate cancer (mCRPC) who visited our urology clinic between 2022 and 2023. Blood samples were collected from all participants between 08:00 and 09:00 after a 12 hour fast. In the LPC and mPC groups, samples were collected upon diagnosis, whereas in the mCRPC group, samples were collected upon development of treatment resistance. NPY levels in blood samples were analyzed using enzyme-linked immunosorbent assay method. Serum NPY levels were compared between the LPC, mPC, and mCRPC groups.

Results: PSA values were calculated as 12.6 (7.08-32.47) ng/L in the LPC group, 159 (73.1-405.2) ng/L in the mPC group, and 38.33 (18.4-132) ng/L in the mCRPC group, with a statistically significant difference between the groups ($p<0.001$). The average NPY values were 351.3±162.7 ng/L in the LPC group, 276.5±85 ng/L in the mPC group, and 272.13±94.7 ng/L in the mCRPC group. NPY values were found to be statistically significantly higher in the LPC group ($p=0.018$).

Conclusion: The serum NPY levels were notably elevated in the LPC group compared with the mPC and mCRPC groups. This finding implies a potential association between low NPY levels and mPC as well as mCRPC.

Keywords: Prostate cancer, PSA, NPY, neuropeptide-Y

Introduction

Prostate cancer is the prevailing form of solid tissue cancer among men in Western societies. Prostate specific antigen (PSA) testing and screening have led to higher rates of early detection and decreased incidences of metastasis and fatalities associated with the disease (1). PSA, while specific to the prostate, lacks specificity to prostate cancer and can be elevated in benign conditions like benign prostatic hyperplasia (BPH) and prostate infections. This highlights the necessity of identifying new biomarkers with higher specificity and sensitivity for prostate cancer diagnosis. These potential biomarkers must undergo rigorous validation to ensure their accuracy and effectiveness in the detection and monitoring of prostate cancer. These markers should aid in patient classification, enable personalized treatment planning, and prevent overdiagnosis and overtreatment of clinically insignificant prostate cancers, thus safeguarding patients' quality of life.

The neuropeptide Y (NPY) family comprises three peptides: NPY, polypeptide YY, and pancreatic polypeptide. The NPY plays an

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integral role in peripheral organs, including vasoconstriction and food intake regulation. In humans, NPY exerts its effects through four G protein coupled receptors: Y1, Y2, Y4, and Y5. NPY1, Y2, and Y5 receptors play crucial roles in oncogenesis and angiogenesis (2).

The relationship between NPY levels and cancer progression is complex and somewhat controversial. Although active NPY is primarily known for its roles in appetite stimulation, vasoconstriction, and stress behavior regulation, its involvement in cancer progression is multifaceted. NPY is strongly linked to the development of certain tumors, including neural crest-derived tumors, breast cancer, and prostate cancer. It appears to promote cancer progression by facilitating processes such as proliferation, invasion, metastasis, and angiogenesis (3). The precise mechanisms governing the role of NPY in the development and progression of cancer are still unclear. Further research is essential to comprehensively assess its influence on tumor biology.

NPY and other neuroendocrine modulators have been identified in prostate cancer, suggesting a potential role for neuroendocrine signaling pathways in the development of the disease (4). In addition to its critical role in regulating several physiological processes, NPY promotes cell proliferation and has been implicated as a growth-promoting factor in several malignancies, including prostate cancer (5,6). Indeed, it has been suggested that NPY is synthesized at higher levels in cancerous prostate tissue than in benign prostate tissue and cancerous tissues from other organs (4-7). Despite the available data, the precise effect of NPY on prostate cancer diagnosis and progression remains unclear. Further research is needed to fully elucidate the role of NPY in the development and progression of prostate cancer and its potential use as a biomarker or therapeutic target in the management of prostate cancer.

This study demonstrated the potential of NPY levels as a new marker for predicting the risk of prostate cancer. To achieve this goal, we compared serum PSA levels with serum NPY levels in patients with prostate cancer. Early diagnosis, treatment effectiveness, and prevention of recurrence and progression are crucial aspects of prostate cancer management. Therefore, clinicians need to identify specific and sensitive markers for early diagnosis. By assessing the utility of NPY values alongside PSA levels, we sought to enhance risk stratification in patients with prostate cancer and improve clinical decision-making during their management.

Materials and Methods

The study involved 90 patients each diagnosed with localized 30 prostate cancer [localized prostate cancer (LPC)], 30 metastatic prostate cancer (mPC) at diagnosis, and 30 metastatic castration-resistant prostate cancer (mCRPC) who visited the urology clinic between 2022 and 2023.

All participants provided informed verbal and written consent before participation. Age, PSA levels, digital rectal examination (DRE) findings, and pathological findings were systematically collected and recorded for each participant. Clinical staging was conducted following the 2017 tumor, lymph node, metastasis classification, considering DRE findings and imaging results. Pathological staging was based on pathological reports, and Gleason scores from prostate biopsy and radical prostatectomy specimens were graded using the 2014 International Society of Urological Pathology (ISUP) grading system. Additionally, patients were classified according to the D'Amico risk classification, considering serum PSA levels, Gleason scores, and clinical stages. Venous blood samples were collected from all participants between 08:00 and 09:00 a.m. following a 12 hour fast. Blood samples were collected upon diagnosis in the LPC and mPC groups and upon treatment resistance in the mCRPC group. After centrifugation at 3000 rpm for 15 minutes, serum samples were separated and stored at -80 °C in the Biochemistry Laboratory of Sivas Cumhuriyet University Faculty of Medicine Health Services Application and Research Hospital for analysis. NPY levels in serum samples were determined using enzyme-linked immunosorbent assay (ELISA) method. Absorbance was measured at 450 nm using an ELISA reader (Thermo Scientific Multiskan FC). Serum NPY levels were measured using a Human NPY ELISA Kit (Bioassay Technology Laboratory) after dilution at a ratio of 1:5, following the procedures specified in the kit package insert. The kit has a sensitivity of 2.36 ng/L and a measurement range of 5-2000 ng/L, with an inter-assay precision coefficient of variability of less than 10%.

Statistical Analysis

The data were analyzed using the SPSS software (SPSS Inc., Chicago, IL). Parametric tests were used for data evaluation when the assumptions, such as the normal distribution assessed using the Kolmogorov-Smirnov test, were satisfied. ANOVA followed by Tukey's post-hoc test was used to compare measurements from more than two independent groups. Non-parametric tests, such as the Kruskal-Wallis test and Mann-Whitney U test, were used to compare measurements from more than two independent groups when the assumptions for parametric tests were not met. Additionally, the chi-square test was employed with assurance to analyze the count data. The significance level was set at a confidence level of 0.05.

All subjects provided informed consent for study participation before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Sivas Cumhuriyet University Ethics Committee (decision no: 2022-01/02, date: 11.01.2022).

Results

In our study, the mean age of the LPC group was 67.6±6.4, while the mean ages of the mPC and mCRPC groups was 73.1±9.1 and 72.7±7.9, respectively. The LPC group was significantly older than the other two groups (p=0.013) (Table 1).

PSA values were calculated for the patient groups as follows: 12.6 (7.08-32.47) ng/L in the LPC group, 159 (73.1-405.2) ng/L in the mPC group, and 38.33 (18.4-132) ng/L in the mCRPC group. A statistically significant difference was found between the groups (p<0.001). NPY values were also calculated for the patient groups: 351.3±162.7 ng/L in the LPC group, 276.5±85 ng/L in the mPC group, and 272.13±94.7 ng/L in the mCRPC group. The LPC group had significantly higher NPY values (p=0.018) (Table 1).

Table 1. Comparing age, PSA, NPY, PNI, and ISUP grades among groups				
	LPC (n=30)	mPC (n=30)	mCRPC (n=30)	p-value
Age (years)	67.6±6.4[a]	73.1±9.1[b]	72.7±7.9[b]	0.013
PSA (ng/L)	12.6 (7.08-32.47)[a]	159(73.1-405.2)[b]	38.33(18.4-132)[c]	<0.001
NPY (ng/L)	351.3±162.7[a]	276.5±85[ab]	272.13±94.7[b]	0.018
PNI	15 (50%)[a]	15 (50%)[a]	29 (96.7%)[b]	<0.001
ISUP 1	11 (36.7%)	0 (0%)	0 (0%)	
ISUP 2	7 (23.3%)	2 (6.7%)	0 (0%)	
ISUP 3	5 (16.7%)	6 (20%)	4 (13.3%)	
ISUP 4	6 (20%)	9 (30%)	10 (33.3%)	
ISUP 5	1 (3.3%)	13 (43.3%)	16 (53.3%)	
PSA: Prostate specific antigen, NPY: Neuropeptide Y, PNI: Perineural invasion, ISUP: International Society of Urological Pathology, LPC: Localized prostate cancer, mPC: Metastatic prostate cancer, mCRPC: Metastatic castration-resistant prostate cancer				

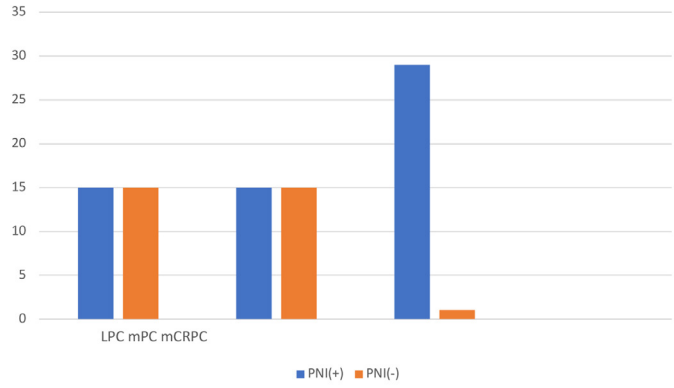

Figure 1. Distribution of PNI positivity between groups

PNI: Perineural invasion, LPC: Localized prostate cancer, mPC: Metastatic prostate cancer, mCRPC: Metastatic castration-resistant prostate cancer

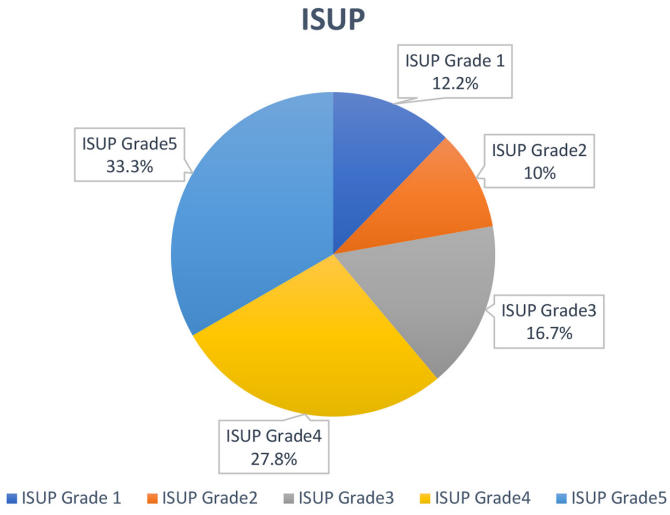

Figure 2. ISUP grade distribution in all patients

ISUP: International Society of Urological Pathology

Perineural invasion (PNI) was present in 50% of LPC patients, 50% of mPC patients, and 96.7% of mCRPC patients. The mCRPC group demonstrated a statistically significant increase in PNI compared with the other two groups (p<0.001) (Table 1, Figure 1).

A comprehensive evaluation of all patients according to ISUP grade revealed the following distribution: ISUP grade 1 (11.2%), ISUP grade 2 (10%), ISUP grade 3 (16.7%), ISUP grade 4 (27.8%), and ISUP grade 5 (33.3%) (Table 2, Figure 2).

There were no statistically significant differences between the patients in terms of ISUP Grade scores and NPY values (p=0.193) (Table 2). However, pairwise comparisons indicated a statistically significant difference between ISUP grades 1 and 2, as well as between ISUP grades 1 and 5 (p=0.031 and p=0.047, respectively) (Figure 3).

When the LPC and mPC patient groups were compared, PSA values were found to be significantly higher in the mPC group (p<0.001). NPY values were found to be statistically significantly higher in the LPC group (p=0.031) (Table 3, Figure 4).

When the LPC and mCRPC patient groups were compared in terms of NPY, the NPY values were found to be significantly higher in the LPC group (p=0.026) (Table 4, Figure 4).

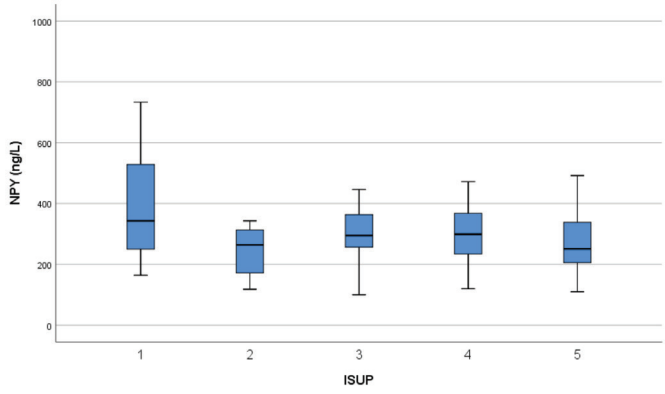

Figure 3. Relationship between ISUP Grade and NPY (box-plot graph)

ISUP: International Society of Urological Pathology, NPY: Neuropeptide Y

Table 2. Comparing ISUP Grade scores and NPY levels among all patients						
ISUP grade	**1**	**2**	**3**	**4**	**5**	**p-value**
N	11 (12.2%)	9 (10%)	15 (16.7%)	25 (27.8%)	30 (33.3%)	
NPY	343 (244-557)	264 (171-313.5)	295 (251-367)	299 (233-370)	251 (203-343)	0.193
NPY: Neuropeptide Y, ISUP: International Society of Urological Pathology						

Table 3. Comparison of age, PSA, NPY, and ISUP grades between the LPC and mPC groups			
	LPC (n=30)	**mPC (n=30)**	**p-value**
Age (years)	67.6±6.4	73.1±9.1	0.009
PSA (ng/L)	12.6 (7.08-32.47)	159 (73.1-405.2)	<0.001
NPY (ng/L)	351.3±162.7	276.5±85	0.031
ISUP 1	11 (36.7%)	0 (0%)	<0.001
ISUP 2	7 (23.3%)	2 (6.7%)	
ISUP 3	5 (16.7%)	6 (20%)	
ISUP 4	6 (20%)	9 (30%)	
ISUP 5	1 (3.3%)	13 (43.3%)	
PSA: Prostate specific antigen, NPY: Neuropeptide Y, ISUP: International Society of Urological Pathology, LPC: Localized prostate cancer, mPC: Metastatic prostate cancer			

Table 4. Comparison of NPY levels between the LPC and mCRPC patient groups			
	LPC (n=30)	**mCRPC (n=30)**	**p-value**
NPY (ng/L)	351.3±162.7	272.13±94.7	0.026
NPY: Neuropeptide Y, LPC: Localized prostate cancer, mCRPC: Metastatic castration-resistant prostate cancer			

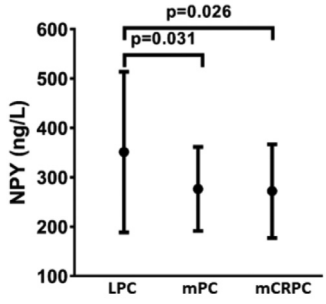

Figure 4. Relationship between LPC, mPC, and mCRPC and NPY

LPC: Localized prostate cancer, mPC: Metastatic prostate cancer, mCRPC: Metastatic castration-resistant prostate cancer, NPY: Neuropeptide Y

Discussion

Prostate cancer is a significant health challenge for men worldwide, with 81.4 million cases of the second most frequently diagnosed cancer in men reported in 2020 (8). Studies indicate that approximately one in every seven men will receive a prostate cancer diagnosis during their lifetime (9). Presently, screening for prostate cancer is a risk-based approach. While PSA and DRE serve as primary screening tools, the limitations of PSA, as it is organ-specific rather than cancer-specific and can increase in non-cancerous conditions, restrict its clinical utility. Consequently, numerous studies aim to enhance the sensitivity and specificity of PSA and to identify new, more ideal markers for prostate cancer diagnosis. The NPY family comprises three peptides: NPY, polypeptide YY, and pancreatic polypeptide. In addition to its vital role in regulating various physiological functions like vasoconstriction and food intake stimulation, NPY has been implicated in stimulating cell proliferation and acting as a growth-promoting factor in several malignancies (5,6). A study examining 400 pathology samples across different organs observed predominant staining for pro-NPY in prostate cancer. NPY has been implicated in the development of certain tumors, including neural crest-derived tumors, breast cancer, and prostate cancer, by promoting processes such as proliferation, invasion, metastasis, and angiogenesis (4). However, there is a paucity of studies investigating the relationship between PSA and NPY in prostate cancer. Recent studies have highlighted the expression of the Y1-R gene and protein in prostate cancer cells, suggesting the involvement of NPY in the regulation of tumor growth (10,11). Therefore, data on NPY levels in patients with prostate cancer at various stages are warranted. In this study, we investigated the relationship between PSA and NPY levels in serum samples collected from prostate cancer patients at various clinical and pathological stages.

PNI is a frequent indicator of tumor metastasis and can be identified in various malignancies, including prostate cancer (12). The presence of PNI is associated with an increased risk of extraprostatic spread. Although PNI defines PSA recurrence following radical prostatectomy, it has been suggested that it does not influence the preoperative Gleason score, irrespective of PSA levels and clinical stage (13). Passavanti et al. (14) evaluated radical prostatectomy specimens from 94 patients and reported a PNI positivity rate of 53%. Moreover, their research did not reveal any statistically significant correlation between PSA and

PNI (14). In a study involving 364 patients who underwent radical prostatectomy, PNI positivity was observed in 287 individuals (79%). Interestingly, the study results indicated no significant relationship between PNI and preoperative PSA levels (p=0.96) (15). In line with these findings, our study evaluated patients in the LPC group, and the PNI positivity rate was 50%. Similar to previous studies, no statistically significant relationship was identified between PSA and PNI in these patients (p=0.148). In this study, no statistically significant relationship was observed between NPY levels and PNI in the LPC group (p=0.222). Although there may be differences in tissue characteristics, the results of our study are supported by Alshalalfa et al. (16), who studied both localized and mPC patients. Based on these findings, it appears that there is no significant association between NPY and PNI, suggesting that NPY can independently predict the negative features of prostate cancer regardless of PNI status.

In a study conducted by Niu et al. (17) involving 402 patients with prostate cancer, significant differences were observed in the expression of the NPY gene across various T stages and Gleason scores (17). In our study, we divided 90 patients according to ISUP Grade scores. However, when comparing NPY scores across ISUP grades, we did not find a significant difference between ISUP grades (p=0.193). In pairwise comparisons, we found a statistically significant difference between ISUP grade 1 and ISUP grade 2, and between ISUP grade 1 and ISUP grade 5 (p=0.031 and p=0.047, respectively). Our findings suggest that low NPY values in prostate cancer are correlated with high-grade disease. Therefore, patients with low NPY values may require closer monitoring for tumor aggressiveness.

Accumulating evidence suggests that NPY plays a role in aging and determining lifespan (18). It is known that NPY levels decrease with age. However, determining this decline solely by age is not sufficient to evaluate tumor aggressiveness in patients with prostate cancer. Indeed, it has been observed that as the ISUP grade increases, NPY levels decrease. This indicates that NPY is an independent biomarker of tumor aggressiveness in prostate cancer.

The study, conducted in localized and mPC patients, found that although NPY expression was generally higher than that in other solid tumors, low NPY expression may serve as a negative predictor of aggressive disease and progression in prostate cancer. In the Gleason score-matched groups, lower NPY expression was correlated with more aggressive disease phenotypes. In addition, tumors with the lowest decile of NPY expression had significantly higher rates of metastasis (16). In the same study, low NPY expression was linked to shorter metastasis-free survival and progression-free survival (PFS). Additionally, the study revealed lower NPY expression in castration-resistant mPC than in primary tumors. A gradual decrease in NPY expression was observed in correlation with castration and neuroendocrine developmental status.

In a study involving patients with castration-resistant prostate cancer, those who tested positive for NPY were found to have a 4.2 times higher risk of treatment failure (p<0.01) and a 3.2 times shorter PFS (p<0.001) compared with those who tested negative (19). In our study, patients were categorized into LPC, mPC, and mCRPC groups. Significant differences in NPY values were observed between the LPC and mPK and mCRPC groups. Specifically, NPY levels were higher in the LPC group than in the mPC and mCRPC groups. Based on these findings, we observed lower NPY values in advanced stage and mPC, which aligns with existing literature. We propose that low NPY levels during prostate cancer diagnosis may serve as a predictor of metastatic disease. Therefore, patients with low NPY levels that are not initially metastatic should undergo detailed examination to assess the risk of progression to metastatic disease.

Study Limitations

Despite our efforts, several limitations were encountered in our study. These include the heterogeneity among patient groups, the relatively small sample size compared with other studies in the literature, and the absence of a BPH or healthy control group for comparison. Additionally, while most studies in the literature utilize cell or tissue samples, our study employs serum samples, which may introduce differences in the results due to sample type. However, despite these limitations, the results of our study are consistent with existing literature, and we believe that they contribute valuable insights that can enhance current knowledge and guide future research endeavors in this field. We believe that our study will contribute to our national data regarding the classification of prostate cancer and its relationship with NPY.

Conclusion

In conclusion, prostate cancer remains a significant global health concern, prompting extensive research into its diagnosis and treatment. Many studies have focused on improving the sensitivity and specificity of PSA as well as identifying biomarkers such as NPY. Unlike previous studies, our research examined serum NPY levels using a faster and less invasive method applicable to clinical practice. Our findings revealed lower serum NPY levels in patients with metastatic and castration-resistant mPC than in those with localized disease. Additionally, higher NPY levels were observed in patients with lower ISUP grades, suggesting a potential role for NPY in both clinical and pathological staging of prostate cancer.

Although our study highlights the potential utility of NPY in prostate cancer diagnosis and its association with disease progression, serum PSA levels remain more sensitive indicators of tumor burden and pathological staging. Therefore, we propose that NPY may complement PSA for predicting metastatic disease rather than serving as a standalone agent. Some prostate cancers do not produce significant levels of PSA, which can result in false-negative results. Furthermore, patients with mCRPC may exhibit low PSA levels because of the effects of castration. In light of these considerations, a more comprehensive view of the patient's condition can be obtained using the use of both biomarkers to monitor disease progression and response to treatment. This approach can facilitate more informed clinical decisions, more effective and personalized patient care, and more accurate patient stratification. We anticipate that our findings will stimulate further research into the use of NPY as a diagnostic marker for prostate cancer, encouraging more comprehensive studies with larger sample groups in the future.

Footnote

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Authorship Contributions

Surgical and Medical Practices: A.Ö., H.S., A.A., İ.E.E., E.Ko., Concept: A.Ö., H.S., A.A., İ.E.E., E.K., E.Ko., Design: A.Ö., H.S., A.A., S.B., İ.E.E., E.K., Data Collection or Processing: A.Ö., S.B., İ.E.E., E.K., Analysis or Interpretation: A.Ö., S.B., E.K., E.Ko., Literature Search: A.Ö., H.S., A.A., E.Ko., Writing: A.Ö., H.S., S.B., E.Ko.

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Case Report

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Prostate Metastasis from Gastric Malignancy: A Rare Case Report and Literature Review

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Abstract

Metastasis of gastric cancer to the prostate gland is extremely rare. Here, we report a unique case of prostate metastasis from gastric malignancy, diagnosed through a transrectal ultrasound-guided prostate biopsy four years after subtotal gastrectomy. We believe this case highlights the importance of vigilant follow-up for detecting uncommon metastatic events.
Keywords: Gastric cancer, metastases, prostate, seconder prostate neoplasm

Introduction

Signet ring cell adenocarcinomas (SRCCs) are a rare histological subtype of adenocarcinomas with a poor prognosis, typically because of advanced disease at diagnosis. The SRCCs are characterized by an abundance of intracytoplasmic mucin that displaces the nucleus to the cell's periphery.

This cell type is observed in >50% of these tumors. While SRCCs are more common in the gastrointestinal tract, especially the stomach, they may also arise in other locations, such as the colon, esophagus, rectum, lung, bladder, pancreas, and prostate. In particular, primary SRCC of the prostate is remarkably rare (0.4% of all SRCC cases) (1), and only a few reported cases of gastric SRCC metastasis to the prostate are available in the literature (2-10). This case report presents this rare entity from a histopathological perspective.

Case Report

A 61-year-old man was previously diagnosed with gastric SRCC and underwent subtotal gastrectomy, eight chemotherapy cycles, and six rounds of radiotherapy four years ago. He is currently experiencing frequent urination, interrupted urination, and dripping. In a contrast-enhanced chest computed tomography (CT) examination, newly developed parenchymal and subpleural nodules, which were not present in the previous examination, were observed in both lungs. In a contrast-enhanced abdominal CT examination, an indeterminate density area with vague borders was spotted in the mesentery of the small intestine on the right side, at the level of the bladder trigone. Additionally, an asymmetrical wall thickening in a plaque-like shape, reaching approximately 1.2 cm in size, was observed at the level of the prostate base, which also involved the intramural segments of both ureters. A contrast-enhanced magnetic resonance imaging of the prostate showed a prostate gland size of 4.9 x 5.7 x 5.7 cm and a prostate volume of 83.32 cubic cm. Multiple hyperplastic nodules and numerous multifocal non-encapsulated T2A hyperintense foci were observed in the transitional zone, with diffusion restriction at these locations. In addition, several spherical lymphadenopathies with diffusion restriction, the largest of which was 5 mm in diameter, were observed in sections passing through the left periprostatic bladder base. A transrectal ultrasound-guided prostate biopsy was performed.

Our pathological findings revealed a malignant tumor negative for several immunohistochemical (IHC) markers, including NKX3.1, androgen receptor (AR), prostate-specific membrane antigen (PSMA), and prostatic acid phosphatase (PSAP) (Figure 1A-D). Additionally, the tumor had positive staining for mucin with PAS-AB and, the tumor was positive for Villin, CK-7, (Figures 1E, F, 2B, D, F). On the previous biopsy, five months

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ago, the patient had been diagnosed with small focus prostate carcinoma Gleason score of 3+3 and a high-grade prostatic intraepithelial neoplasia (HGPIN) on his three cores was given. No signet ring cell-like morphology was found in the stroma outside this area. In the new biopsy, no significant HGPIN or prostate carcinoma was observed. In addition, serum prostate-specific antigen (PSA) levels were 8.3 and 6 in the previous and current biopsy, respectively. Based on these findings, we have diagnosed our patient with prostate metastasis of gastric SRRC. Informed consent was obtained from the patient.

Discussion

In this case, we initially identified the prostatic adenocarcinoma as Gleason pattern 5. However, based on the patient's medical history, the immune panel we did (NKX3.1, AR, PSMA, PSAP) did not show any prostate-specific markers (Figure 1 A-D). The presence of extracellular mucin in the PAS-AB stain (Figure 1E) made us think it might be SRCC from somewhere else, since SRCC in the prostate usually doesn't have a lot of mucin droplets in the tumor cells (11). We looked at the immunostaining panel of the previous tumor and that of the current one to see if the carcinoma was a primary tumor of the prostate or came from the gastrointestinal system. The villin and CK7 staining patterns were similar (Figure 1F, Figure 2B,D,F). Compared to the literature cases in Table 1, which include patients primarily in their 50s and 60s with a history of gastric adenocarcinoma and presenting with urinary-related symptoms, the correct diagnosis was made by differential diagnosis with more immune markers. The patients underwent various surgical procedures, such as transuretral resection, transrectal ultrasound guided prostate biopsy (Bx), and transperineal ultrasound guided prostate Bx, with generally low PSA levels at diagnosis. Treatments ranged from chemotherapy and radiotherapy to conservative management, with mixed survival outcomes. IHC and histochemical staining revealed positive PAS results (2-4,8-9) and consistently negative PSA results (2,10) (Table 1). Despite the fact that PSMA, PSAP, and NKX3.1 were conducted in a limited number of cases (2-4,8) (Table 1), their negative results substantiated our diagnosis, as their positive results were prostate specific. Additionally, the patient's prostate biopsy and previous gastric tumor showed positive CK7 staining, which was unexpected in the prostate (4,10) (Table 1). Furthermore, we added a new marker to support

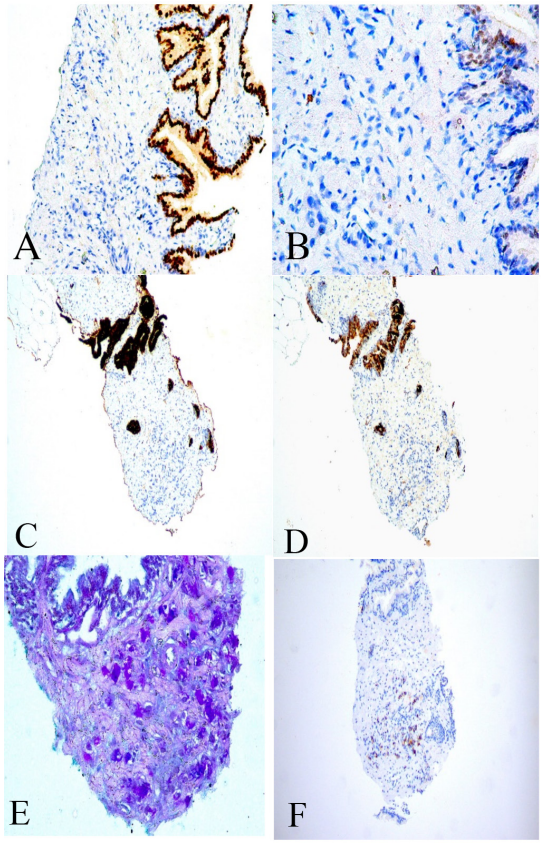

Figure 1. (A) Prostate needle biopsy stained negative for NKX3.1 in the same area with Figure 2C (B) Prostate needle biopsy stained negative for AR adjacent to slightly positive normal prostate glands in the same area as well. (C) Tumor cells stain negative for PSMA in the same area with Fig.2A, (D) Tumor cells stain negative for PSAP in the same area, (E) PAS-positive mucins in the same area, (F) Villin positivity in the same tumor cells as well. Magnifications: A: 400x; B:200x; C, D, E, F: 100x

AR: Androgen receptor, PSMA: Prostate-specific membrane antigen, PSAP: Prostate specific acid phosphatas, PAS: Prostate adenocarcinomas

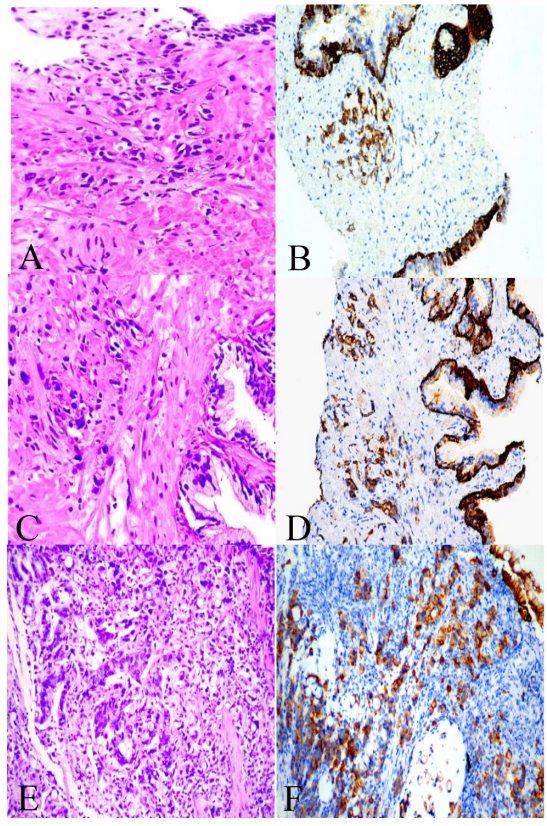

Figure 2. (A) Prostate needle biopsy had atypical signet ring-like tumor cells like the previous gastric biopsy, (B) Prostate needle biopsy stained positive for CK7 in the same area with A, (C) Prostate needle biopsy poorly cohesive signet ring cell like tumor infiltration, (D) Prostate needle biopsy shows CK7 positivity in the tumor cells in the same area, (E) Patient's previous gastric biopsy had atypical cells like in our case, (F) Patient's previous gastric biopsy stains positive for CK7 as well, Stains: A, C, E: Hematoxylin-Eosin; B, D, F: CK7; All pictures 200x Magnifications

Table 1. The summary of clinical information, special and immunohistochemical staining of cases in the literature

Case reports	Borum and Chen (2)	Roshni et al. (5)	Lin et al. (6)	Zhang et al. (3)	Plancke et al. (8)	Cobo Dols et al. (7)	Cimino et al. (4)	Ni et al. (9)	Presenting case
Age	80	56	70	51	60	60	52	60	61
Presentation	Urinary retention	Dysphagia and abdominal pain	Ureteral stone	Urinary retention	Urinary retention	Micturition	Lower urinary tract symptoms	Lower urinary tract symptoms	Lower urinary tract symptoms
Surgical procedures	TUR	Tru-cut biopsy	TRUS Bx.	TRUS Bx.	TUR	TRUS Bx.	TPUS Bx.	TUR	TRUS Bx.
PSA level at diagnosis	Not mentioned	1.94 (ng/dL)	9.7 (ng/dL)	Not mentioned	2 (ng/dL)	0.84 (ng/mL)	0.2 (ng/dL)	1.959 (ng/mL)	6 (ng/dL)
Treatment	Not mentioned	Palliative chemotherapy (EOX)	Conservatively	Not mentioned	Chemotherapy	Radiotherapy	Chemotherapy (5-FU, cisplatin, epirubicin+radiotherapy	Chemotherapy	Will get 3 courses of chemotherapy after that get prostatectomy
History	RCC,Prostate Ca.,Gastric A.Ca.	Gastric Adeno Ca.	Gastric Adeno Ca.	Gastric Adeno Ca.	Gastric Adeno Ca.	Gastric Adeno Ca.	Gastric Adeno Ca.	Gastric Adeno Ca.	GastricAdeno Ca., Prostate A.Ca.
Survival	Unknown	Lost after 3-course chemo.	Unknown	Unknown	A.t.m.l. (1994)	Absence recurrent	A.t.m.l. (2012)	Lost after 2 years	A.t.m.l. (2023)
PAS	+	NA	NA	+	+	NA	+	+	+
PSA	-	-	-	-	-	-	-	-	-
PSMA	NA	NA	NA	NA	NA	NA	NA	NA	-
PSAP	-	NA	NA	-	-	NA	-	NA	-
NKX3.1	NA	NA	NA	NA	-	NA	-	NA	-
CK7	NA	-	NA	NA	NA	NA	+	-	+
CK20	NA	NA	NA	NA	NA	+	+/-	-	+/-
VILLIN	NA	NA	NA	NA	NA	NA	+/-	NA	+

TUR: Transuretral resection, TRUS: Transrectal ultrasound guided prostate biopsy, TPUS: Transperineal ultrasound guided prostate biopsy, EOX: Epirubicin, Oxaliplatin, Capecitabine, 5-FU: 5-Fluorourasil, A.t.m.l.: At the moment live, PSA: Prostate-specific antigen, PAS: Prostate adenocarcinomas, PSMA: Prostate-specific membrane antigen, PSAP: Prostate specific acid phosphatas

our diagnosis. We decided to make an immun stain that showed that the patient's previous gastrointestinal carcinoma was positive, such as Villin. A study by Dum et al. (12) found that 63.4% of diffuse-type gastric adenocarcinomas were positive, and 36.6% were negative for Villin. In PACa, 1.3% were positive, and 98.7% were negative. On the other hand, there is an absence of acinar prostatic adenocarcinoma and HGPIN. The decrease in the serum PSA level compared to the patient's previous results, along with the presence of multiple new nodules in the lungs and suspicious wall thickening between the bladder and prostate on radiological imaging, strongly supported the diagnosis of metastasis. Also, another pathology center interpreted the case as we did, and the diagnosis of gastric adenocarcinoma with metastasis to the prostate was confirmed.

Conclusion

In conclusion, this case underscores the significance of a thorough histopathological evaluation and IHC analysis in diagnosing rare metastatic events. Awareness of unusual metastatic patterns, such as gastric adenocarcinoma metastasizing to the prostate, is crucial for timely and accurate diagnosis. We believe that our detailed analysis will provide valuable insights on similar cases in the future.

Footnote

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