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The Bulletin publishes basic and clinical research original articles, reviews, editorials, case reports, and letters to the editor relevant to urooncology (prostate cancer, urothelial cancers, testis and kidney cancer, benign prostatic hyperplasia, and any aspect of urologic oncology). The Bulletin of Urooncology is indexed by several international databases and is committed to rigorous peer review.

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Use only standard abbreviations. Avoid abbreviations in the title and abstract. The full term for an abbreviation should precede its first use in the text, unless it is a standard abbreviation. Abbreviations that are used should be defined in parenthesis where the full word is first mentioned.

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Measurements should be reported using the metric system, according to the International System of Units (SI).

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All retrospective, prospective, and experimental research articles must be evaluated in terms of biostatics and should be stated together with an appropriate plan, analysis, and report. P values must be given clearly in the manuscripts (e.g., p=0.033). It is the authors' responsibility to prepare a manuscript that meets biostatistical rules.

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3) Main text,

4) Acknowledgements (optional),

5) References,

6) Tables/figures (each table should be written with the titles and footnotes in a separate page) and figure legends.

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- Title

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Introduction

- Materials and Methods/Patients and Methods
- Results
- Discussion
- Study Limitations
- Conclusion
- Acknowledgements
- References
- Tables/Figures

Preparation of research articles, systematic reviews, and meta-analyses must comply with study design guidelines: CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consortstatement.org/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

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Case reports should include cases which are rarely seen and distinctive in diagnosis and treatment. These can include brief descriptions of

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Case Presentation

Discussion

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Content:

- Title

Abstract (maximum 250 words; without structural divisions;

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Introduction

Main Text

Conclusions

Tables/Figures

Figure Legends

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These are solicited by the editor, will go through the peer review process, and will cover recently published selected articles in the field of urologic oncology. It is a mini-review article that highlights the importance of a particular topic and provides recently published supporting data. The guidelines stated above for Review articles are applicable. Word count should not exceed 1500 and references are limited to 10.

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Abstracts should be prepared in accordance with the specific instructions for the different article types. For original articles, a structured abstract should be provided using the following headings: Objective, Materials and Methods, Results, and Conclusions. Provide 3-5 keywords. English keywords should be provided from Medical Subject Headings (http://www.nlm.nih.gov/mesh).

C. Main Text

Introduction: Should include brief explanation of the topic, the objective of the study, and supporting information from the literature.

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Discussion: The positive and negative aspects of the study data should be discussed and compared with literature.

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Conclusion: The conclusion of the study should be highlighted.

D. Acknowledgements

Acknowledgments are given for contributors who may not be listed as authors, or for grant support of the research. Any technical or financial support or editorial contributions (statistical analysis, English/Turkish evaluation) to the study should appear at the end of the article.

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The author is responsible for the accuracy of references. Cite references in the text with numbers in parentheses. All authors should be listed if four or fewer, otherwise list the first three authors and add et al. Number references consecutively according to the order in which they first appear in the text. Journal titles should be abbreviated according to the style used in Index Medicus (consult List of Journals Indexed in Index Medicus).

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Journal: Soukup V, Dušková J, Pešl M, et al. The prognostic value of t1 bladder cancer substaging: a single institution retrospective study. Urol Int 2014;92:150-156.

Format for books: initials of author's names and surnames. chapter title. In: editor's name, Eds. Book title. Edition, City: Publisher; Year. p. pages.

Example:

Book Chapters: Lang TF, Duryea J. Peripheral Bone Mineral Assessment of the Axial Skeleton: Technical Aspects. In: Orwoll ES, Bliziotes M, eds. Osteoporosis: Pathophysiology and Clinical Management. New Jersey, Humana Pres Inc, 2003;83-104.

Books: Greenspan A. Orthopaedic Radiology a Practical Approach. 3rd ed. Philadelphia: Lippincott Williams Wilkins; 2000. p. 295-330.

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Contents

Original Article
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Risk Factors for Adrenal Invasion in Renal Cell Carcinoma

Kaan Çömez MD[1], Serdar Çelik MD[1], Ozan Bozkurt MD[1], Ömer Demir MD[1], Güven Aslan MD[1], Kutsal Yörükoğlu MD[2], İlhan Çelebi MD[1]

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Abstract

Objective: In this study, we aimed to describe the risk factors associated with adrenal invasion in patients who were diagnosed with renal cell carcinoma (RCC) after radical nephrectomy and identify which risk factors are indications for ipsilateral adrenalectomy (IA).

Materials and Methods: Preoperative (age, gender, tumor side and location, presence of lung metastasis), intraoperative (thrombectomy rate, IA and additional surgery rate), and histopathological data of 298 patients with RCC were reviewed. The patients were divided into 2 groups, those with adrenal invasion and those without, and patient data were compared between these groups. Subsequently, rates of renal sinus invasion, perinephric invasion, and renal vein invasion were evaluated in the T3-4 and T3a patient group and the relationship between these rates and adrenal invasion was investigated.

Results: Adrenal invasion was detected in 8 (2.7%) of the patients. There were no significant relationships between adrenal invasion and age, gender, tumor side, tumor location, surgery duration, thrombectomy rate, disease stage, sarcomatoid features, microvascular invasion, collecting system invasion, tumor necrosis, or renal vein invasion. The presence of adrenal invasion was associated with a higher rate of additional intraoperative interventions. Adrenal invasion was also significantly associated with greater tumor size, higher pathologic T (pT) stage, and rates of lung metastasis, perinephric invasion, and renal sinus invasion. When stage pT3-4 and pT3a patients were evaluated separately, no significant relation was found between adrenal invasion and renal sinus invasion, perinephric invasion, or renal venous invasion.

Conclusion: pT stage, presence of pulmonary metastasis, and renal sinus invasion were important risk factors for adrenal invasion.

Keywords: Renal cell carcinoma, adrenal invasion, adrenalectomy, radical nephrectomy

Introduction

Renal cell carcinoma (RCC), which accounts for 2-3% of all cancer cases, is the most common malignant tumor of the kidney (1). Ipsilateral adrenalectomy (IA) with radical nephrectomy was first described by Robson et al. (2) in 1969 to correctly determine the size and spread of the tumor and to improve oncological outcomes in RCC. Later, IA continued to be practiced with radical nephrectomy in order to achieve a wide, intact surgical margin (3). In response to this practice, Lane et al. (4) demonstrated in their study that IA did not significantly impact 5- and 10-year disease-specific or overall survival. In subsequent studies it was reported that the rate of adrenal invasion in patients who undergo nephrectomy with IA is 1-4% (5,6,7). Therefore, routine IA during nephrectomy is not recommended in these studies, but IA is recommended for patients whose radiological images suggest a large tumor, an upper pole tumor, or adrenal invasion (5,6,7,8). These recommendations indicate that the practice of IA has changed over the years based on the risk-benefit ratio for the patient. However, even if the rate of adrenal invasion is 1-4%, we believe that predicting adrenal invasion provides information that is important for correctly staging patients, gaining insight into prognosis, and creating adjunct therapy and follow-up protocols. Because reducing tumor burden is a facet of RCC treatment, resecting an adrenal gland that has invasion/

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metastasis becomes even more important. Therefore, in this study we aimed to identify patient risk factors associated with adrenal invasion and to determine which risk factors constitute indications for IA.

Materials and Methods

Patients who underwent radical nephrectomy between 1995 and 2013 were retrospectively evaluated. Those with a histopathological diagnosis of RCC were included in the study. A total of 298 patients with RCC were evaluated based on preoperative data (age, sex, tumor side, tumor location, presence of lung metastasis), intraoperative data (thrombectomy, IA, and other procedures), and histopathological data [pathological T (pT) stage, Fuhrman grade, sarcomatoid features, adrenal invasion, microvascular invasion, renal sinus invasion, perinephric invasion, collecting system invasion, tumor necrosis, renal vein and/or vena cava invasion]. The patients were divided into groups based on presence or absence of adrenal invasion and patient data were compared between the groups. The same comparisons were done within the group of patients who underwent IA. We then evaluated rates of renal sinus invasion, perinephric invasion, and renal vein invasion in the T3-4 and T3a patient groups and examined the relationship between these rates and adrenal invasion.

Statistical Analysis

First, patient data were evaluated by comparing those with and without adrenal invasion using the Mann-Whitney U test for continuous variables and a chi-square test for categorical variables. Kaplan-Meier survival analysis and chi-square test were used to evaluate mortality and survival between groups. Chi-square test was used to compare presence of adrenal invasion and rates of renal sinus invasion, perinephric invasion, and renal vein invasion rates in the T3-4 and T3a patient groups. The Statistical Package for the Social Sciences (SPSS version 20.0; SPSS, Chicago, Illinois, USA) was used for statistical analysis. The data were expressed as mean and standard deviation, and statistical analysis was based on median values. Results with p values ≤ 0.05 were considered significant.

Results

The 298 patients who underwent radical nephrectomy had a mean age of 59.2±11.6 (26.5-86.4) years. Of these, 85 patients underwent IA, and 8 (2.7%) of those patients had adrenal invasion. There were no cases of adrenal metastasis. The mean follow-up period was 52.3±35.9 (1-185.1) months and mean overall survival was 114.4±5.6 months. No significant relationship was found between adrenal invasion and sex, tumor side, tumor location, operative time, thrombectomy rate, Fuhrman grade, sarcomatoid features, microvascular invasion, collecting system invasion, tumor necrosis, renal vein invasion, and vena cava invasion (Tables 1 and 2). Additional intraoperative interventions were more common in the presence of adrenal invasion. Presence of adrenal invasion was also associated with significantly greater tumor size (whole group only), pT stage, presence of lung metastasis, and rates of perinephric invasion and renal sinus invasion (Tables 1 and 2). When pT3-4 and pT3a patients were evaluated separately, no significant relationship was observed between adrenal invasion and renal sinus invasion, perinephric invasion, or renal vein invasion (Table 3).

Discussion

Performing IA at the time of radical nephrectomy has been a topic of debate for over 25 years (9). The rate of ipsilateral adrenal invasion in patients who undergo radical nephrectomy for RCC is reported to be <4% (5,6,7). The rate of adrenal invasion in our study was 2.7%. Current guidelines state that IA during radical nephrectomy does not confer a survival advantage in patients without radiological or intraoperative signs of adrenal invasion and is therefore not recommended for these patients (10).

In a randomized study of 40 patients investigating the perioperative complications of IA in radical nephrectomy, no significant difference was seen in operative time or postoperative complications (11). In our study, the presence of adrenal invasion did not significantly affect operative time.

Many risk factors for predicting adrenal invasion have been identified. It was reported that upper-pole renal tumors >7 cm in size may be associated with adrenal invasion (5). On the other hand, Kutikov et al. (12) pathologically examined IA specimens from 91 patients with >7 cm upper-pole renal tumors and found adrenal invasion in only 4 patients (4.4%). They concluded based on their findings that upper-pole localization is not a predictive factor in RCC (12). There was no significant relationship between adrenal invasion and tumor side or location in our study. However, we observed that adrenal invasion was present in a significant proportion of patients with distant metastasis (lung). This suggests that lung metastasis rates are higher in patients with adrenal invasion due to the advanced tumor stage.

Previous studies examining whether adrenal invasion by RCC occurs via direct extension or through the renal/adrenal veins have emphasized that hematogenous spread may be more common that direct invasion. In a review evaluating this observation, it was reported that left sided primary renal tumors were predominant (62-100%) among patients with adrenal invasion (5). It was suggested the risk of retrograde tumor embolization was higher on the left side because the adrenal vein drains into the renal vein on that side. However, the multivariate analysis results of other studies within the same review did not support the association between left-sided RCC and adrenal invasion. Due to these contradictory results, it was concluded that RCC laterality cannot be considered an independent risk factor (5). There was also no significant relationship between adrenal invasion and tumor side in our study.

pT stage has also been investigated as a risk factor for adrenal invasion. In a study by Moudouni et al. (13) involving 210 patients, adrenal invasion was detected in 15 patients, 13 of whom were stage T3-4. Similarly, 70% of the patients with adrenal invasion in our study had at least stage pT3a tumors. When pT3-4 and pT3a patients with renal sinus invasion, renal vein invasion, and perinephric invasion were evaluated

Table 1. Analysis of possible risk factors in patients with and without adrenal invasion				
		Adrenal invasion (-) (n=290)	**Adrenal invasion (+) (n=8)**	**p**
Age (years)		59.2±11.6	59.6±10.1	0.924
Gender	Female	95	3	0.721
	Male	195	5	
Operative time (minutes)		165.2±61.4	183.8±43.7	0.219
Tumor size (mm)		67.2±32	98.1±39.4	0.014
Tumor side	Right	143	3	0.510
	Left	147	5	
Tumor location	Upper pole	102	3	0.412
	Mid-pole	95	1	
	Lower pole	93	4	
Lung metastasis	(-)	274	5	0.000
	(+)	16	3	
Thrombectomy	(+)	12	1	0.253
	(-)	278	7	
Additional intraoperative procedure	(+)	18	3	0.01
	(-)	272	5	
Pathological stage	T1a	70	0	0.012
	T1b	75	0	
	T2a	52	1	
	T2b	21	1	
	T3a	47	2	
	T3b	15	1	
	T3c	1	0	
	T4	9	3	
Fuhrman grade	1	45	0	0.077
	2	131	2	
	3	60	4	
	4	28	1	
Sarcomatoid features	(+)	19	1	0.507
	(-)	271	7	
Microvascular invasion	(+)	43	2	0.428
	(-)	247	6	
Renal sinus invasion	(+)	23	4	0.003
	(-)	267	4	
Collecting system invasion	(+)	8	1	0.112
	(-)	282	7	
Tumor necrosis	(+)	14	1	0.342
	(-)	276	7	
Pathologic renal vein invasion	(+)	25	1	0.701
	(-)	265	7	
Pathologic vena cava invasion	(+)	4	0	0.738
	(-)	286	8	
Perinephric invasion	(+)	48	5	0.001
	(-)	242	3	
Overall mortality		70 (24.1%)	5 (62.5%)	0.014
Overall survival (months)		116.1±5.7	30.1±9.2	<0.001

Table 2. Possible risk factors for adrenal invasion in patients who underwent adrenalectomy				
		Adrenal invasion (-) (n=77)	**Adrenal invasion (+) (n=8)**	**p**
Age (years)		58.4±12	59.6±10.1	0.741
Gender	Female	27	3	0.891
	Male	50	5	
Operative time (minutes)		178±61.4	183.8±43.7	0.556
Tumor size (mm)		82±35.6	98.1±39.4	0.197
Tumor side	Right kidney	34	3	0.718
	Left kidney	43	5	
Tumor location	Upper pole	34	3	0.519
	Mid-pole	19	1	
	Lower pole	24	4	
Lung metastasis	(-)	74	5	**<0.001**
	(+)	3	3	
Thrombectomy	(+)	8	1	0.854
	(-)	69	7	
Additional intraoperative procedures	(+)	8	3	**0.030**
	(-)	69	5	
Pathological stage	T1a	5	0	**0.012**
	T1b	15	0	
	T2a	21	1	
	T2b	10	1	
	T3a	17	2	
	T3b	6	1	
	T3c	1	0	
	T4	2	3	
Fuhrman grade	1	11	0	0.268
	2	34	2	
	3	18	4	
	4	9	1	
Sarcomatoid features	(+)	8	1	0.854
	(-)	69	7	
Microvascular invasion	(+)	19	2	0.984
	(-)	58	6	
Renal sinus invasion	(+)	11	4	**0.012**
	(-)	66	4	
Collecting system invasion	(+)	3	1	0.274
	(-)	74	7	
Tumor necrosis	(+)	5	1	0.528
	(-)	72	7	
Pathologic renal vein invasion	(+)	12	1	0.818
	(-)	65	7	
Pathologic vena cava invasion	(+)	4	0	0.509
	(-)	73	8	
Perinephric invasion	(+)	17	5	**0.013**
	(-)	60	3	
Overall mortality		16 (20.8%)	5 (62.5%)	**0.009**
Overall survival (months)		131±11.8	30.1±9.2	**<0.001**

Table 3. Analysis of pathologic T3-4 patients in terms of perinephric, renal sinus, and renal vein invasion				
T3a patients (n=49)		**Adrenal invasion (-) (n=47)**	**Adrenal invasion (+) (n=2)**	**p**
Perinephric invasion	(+)	34	1	0.493
	(-)	13	1	
Renal sinus invasion	(+)	18	2	0.082
	(-)	29	0	
Renal vein invasion	(+)	10	0	0.465
	(-)	37	2	
T3-4 patients (n=78)		**Adrenal invasion (-) (n=72)**	**Adrenal invasion (+) (n=6)**	**p**
Perinephric invasion	(+)	48	5	0.401
	(-)	24	1	
Renal sinus invasion	(+)	23	3	0.367
	(-)	49	3	
Renal vein invasion	(+)	24	0	0.089
	(-)	48	6	

in separate subgroups, all groups had similar rates of adrenal invasion. These results suggest that pT3-4 is a risk factor for adrenal invasion, whereas renal sinus, renal vein, and perinephric invasion do not effectively discriminate adrenal invasion on their own. However, the nonsignificance of our findings may be due to the small numbers of patients with adrenal invasion and in the subgroups, which is one of the limitations of this study. When we examined pathological data other than T stage, we observed no significant association between adrenal invasion and Fuhrman grade, sarcomatoid features, microvascular invasion, collecting system invasion, tumor necrosis, renal vein invasion, or vena cava invasion. Our findings indicate that adrenal invasion is more common only in the presence of perinephric and renal sinus invasion. The possible pathophysiology of this may be related to the higher risk of metastasis in RCC due to the presence of ample venous and lymphatic drainage in the renal sinus (14). However, our review of the literature yielded no study that shows a direct association between adrenal invasion and pathological data other than T stage, especially renal sinus invasion. Perinephric invasion and renal sinus invasion may be signs of advanced disease, which could explain their significant relationship with adrenal invasion. Other than this, overall survival times were lower and mortality rates were higher in patients with adrenal invasion compared to the other patients. This finding is also related to advanced T stage.

Study Limitations

Cancer-specific survival and metastasis-free survival were not assessed in this study. Due to the adrenal preserving approach developed over the years, the long-term, retrospective nature of the study and the small patient population (especially in the group with adrenal invasion) constitute limitations of this research.

Conclusion

In summary, the findings of this study indicate that pT stage and the presence of lung metastasis and renal sinus invasion constitute important risk factors for adrenal invasion. However, the necessity of IA in patients with risk factors for adrenal involvement is debatable. It is clear that more extensive prospective studies are needed to bring clarity to this issue.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.B., Ö.D., G.A., İ.Ç., Concept: K.Ç., S.Ç., Design: K.Ç., S.Ç., K.Y., Data Collection or Processing: K.Ç., S.Ç., Analysis or Interpretation: K.Ç., S.Ç., K.Y., Literature Search: K.Ç., S.Ç., Writing: K.Ç.

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Analysis of Factors Affecting Functional Outcomes in Robotic-assisted Laparoscopic Radical Prostatectomy

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Abstract

Objective: In addition to ensuring cancer control, prevention of incontinence and erectile dysfunction, which significantly impact patients' quality of life, is also an important issue in robot-assisted laparoscopic radical prostatectomy (RALRP) operations. In this study, we aimed to evaluate the factors affecting postoperative urinary continence and erectile function in patients who underwent RALRP due to localized prostate cancer in our clinic.

Materials and Methods: Our study included 439 patients who were diagnosed with stage 1 prostate cancer and underwent RALRP. Patients' age, preoperative prostate-specific antigen (PSA) value, prostate volume, radical prostatectomy material Gleason score, operative time, transperitoneal surgical approach (posterior or anterior), and surgical margin and extraprostatic extension statuses were recorded. Postoperative continence and erectile function status of the patients were questioned and recorded via telephone interviews and in outpatient clinic follow-up. Patients were divided into groups according to postoperative incontinence and erectile dysfunction status and the variables were compared between the groups.

Results: There was no statistically significant difference between the continent and incontinent groups in terms of age, preoperative PSA, prostate volume, operative time, postoperative Gleason score, surgical margin status, extraprostatic extension status, or anterior or posterior approach ($p>0.05$). There was no statistically significant difference between the groups with and without erectile dysfunction in terms of prostate volume, operative time, postoperative Gleason score, surgical margin status, or extraprostatic extension status ($p>0.05$), while there were statistically significant differences between the 2 groups in terms of age ($p<0.001$), preoperative PSA value ($p=0.042$), and surgical technique ($p<0.001$).

Conclusion: We concluded that patient- and disease-related factors did not significantly affect postoperative urinary continence in patients undergoing RALRP due to prostate cancer, while patient age, preoperative PSA value, and operative technique had a significant effect on erectile function.

Keywords: Robot-assisted laparoscopic radical prostatectomy, prostate cancer, erectile dysfunction, incontinence, quality of life

Introduction

Globally, prostate cancer (PCa) is the 4th most common type of cancer among both genders and second most common among males (1). PCa is often diagnosed in young and healthy men, and in addition to providing long-term cancer control, preserving patients' quality of life is also an important goal. Radical prostatectomy (RP) is considered the gold standard for surgical treatment of localized PCa (2). RP outcomes are generally assessed in terms of urinary continence, potency, and cancer control, referred to as the "trifecta" (3). After Walsh and Donker (4) developed the anatomic nerve-sparing technique for retropubic RP (RRP), RRP became the gold standard, most widely used surgical method that provides excellent cancer control for clinically localized PCa (5).

A minimally invasive method for PCa treatment aiming to reduce the morbidity of RRP was first described in 1992 by Schuessler et al. (6). The authors concluded that laparoscopic RP (LRP) was

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a difficult technique with a long learning curve and offered no advantages over RRP. Larger series published later showed the technique to be feasible with similar outcomes to open surgery (7,8). However, its technical difficulty and long learning curve prevented it from being widely accepted among surgeons.

Bringing technological advances such as 3-dimensional (3D) imaging, 7 degrees of freedom, surgical comfort, and extension of surgical field, the introduction of the Da Vinci Robotic Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA) offered a groundbreaking minimally invasive method for RP. About a decade after robot-assisted LRP (RALRP) was introduced, many modifications were made and the technique was standardized (8,9). Data from large series indicate that RALRP yields similar oncological results as other large RRP and LRP series. The introduction of this technique resulted in greater patient expectations, and complications and surgical margin status were added to the trifecta to create a pentafecta.

The aim of the present study was to analyze parameters that affect urinary continence and erectile function, the main factors determining postoperative quality of life, in patients who underwent RALRP in our clinic for localized PCa.

Materials and Methods

Patient Selection and Data Collection

Data from 439 patients who were diagnosed with stage 1 PCa and treated with RALRP in our clinic between March 2012 and January 2017 were retrospectively analyzed. The patients' age, preoperative prostate-specific antigen (PSA) level, prostate volume, Gleason score of RP material, surgery duration, transperitoneal RALRP technique (posterior or anterior approach), surgical margin positivity, and extraprostatic spread were noted. Written consent was obtained from the patients prior to the operation. The patients were invited for follow-up visits by telephone and were assessed for postoperative continence and erectile function. Those who did not use pads or those who used a single pad for protection per 24 hours were considered continent. Erectile function was evaluated using the International Index of Erectile Function (IIEF) and patients with an IEFF scores below 10 were accepted as having erectile dysfunction. Patients with at least 12 months of postoperative follow-up were included in the study.

Inclusion criteria for the study were being diagnosed with PCa by transrectal ultrasound-guided biopsy or transurethral prostate resection, and having prostate-limited disease (stage 1). Exclusion criteria were presence of preoperative erectile dysfunction, preoperative urinary incontinence, or locally advanced or advanced PCa.

Statistical Analysis

Statistical analysis of the data were done using SPSS 17.0 software package. Study data were expressed as mean ± standard deviation or number (percent). Student's t-test and chi-square tests were used for statistical analyses. P value <0.05 was considered statistically significant.

Robot-Assisted Laparoscopic Radical Prostatectomy Procedure

A 12 mm trocar was placed superior to the umbilicus. A point approximately 15 cm superior to the symphysis pubis and about 7-8 cm left lateral was marked and a second 8 mm trocar was placed 7-8 mm lateral to the first one. These trocars were used for robotic arms 2 and 3, respectively. An 8 mm trocar was then inserted 7-8 cm lateral to the reference mark. This included robotic arm 1. A 12 mm trocar was inserted 3-4 cm superomedial to the iliac crest on the axis directly connecting the iliac crest and the camera port. Finally, the 5 mm assistant port was inserted between the 2 previously placed right ports, about 3 cm superior to the line connecting the 2 trocars. An incision was made in the peritoneum above the symphysis pubis level. The median umbilical ligaments and urachus were cut. After cutting the endopelvic facia, sutures were made around the dorsal vein complex with 0-PDS or Vicryl on a CT-1 needle. The Foley catheter was deflated and withdrawn to the urethra to visualize the vesical trigone. When the posterior bladder and the trigone were clearly visible, the incision was continued along the length of the bladder neck.

Two approaches have been described for the dissection of seminal vesicles in transperitoneal RALRP: posterior (Montsouris technique) and anterior (Menon technique). In the anterior approach (Menon technique), seminal vesicles are located and dissected after the prostate and the posterior bladder neck incision. The posterior approach is essentially the dissection of the vas deferens and seminal vesicles before developing the Retzius space. In this approach, retrovesical antegrade dissection of the vas deferens and seminal vesicles was done first. A U-shaped incision was made in the peritoneum 1-1.5 cm above the rectum over the vasa deferentia. The areolar tissue in the region was dissected in order to locate and dissect the vasa deferentia. The seminal vesicles posterior to the vasa deferentia were also located and separated from the surrounding tissues by blunt and sharp dissection. The fascial sheath around the prostate was dissected. The lateral pelvic fascia was sharply incised along the anterolateral prostate. It was temporarily occluded using Weck clips and sutured after removal of the prostate. The ipsilateral seminal vesicle was grasped with arm 4 and suspended to clearly expose the pedicle. After cutting the pedicle, the posterolateral connections between the neurovascular bundle and the prostate were sharply incised with scissors. The catheter was withdrawn and the posterior urethra was cut. The surgical specimen was then removed and placed into a laparoscopy bag or left in the pelvis. A secure, mucosa-to-mucosa, vesicorurethral anastomosis was formed using continuous suture. After the anastomosis was created, a Foley catheter was inserted and the bladder was filled to check for anastomotic leakage. The stages of RALRP are summarized in Figure 1.

The patients were discharged on postoperative day 3 or 4. Foley catheters were removed on postoperative day 7.

Results

The patients' mean age was 64.29±6.69 years, mean PSA value was 9.52±10.25 ng/mL, mean prostate volume was 48.28±19.86 mL, and mean surgery duration was 146.18±25.90

min. Postoperatively, 273 (62.2%) of the 439 patients did not experience incontinence while 166 (37.8%) patients did. Sixty-seven patients with preoperative erectile dysfunction were excluded from the study, leaving 372 patients included in the study for analysis of postoperative erectile dysfunction. Postoperatively, 173 (46.5%) of the 372 patients had no erectile dysfunction while 199 (53.5%) patients experienced erectile dysfunction.

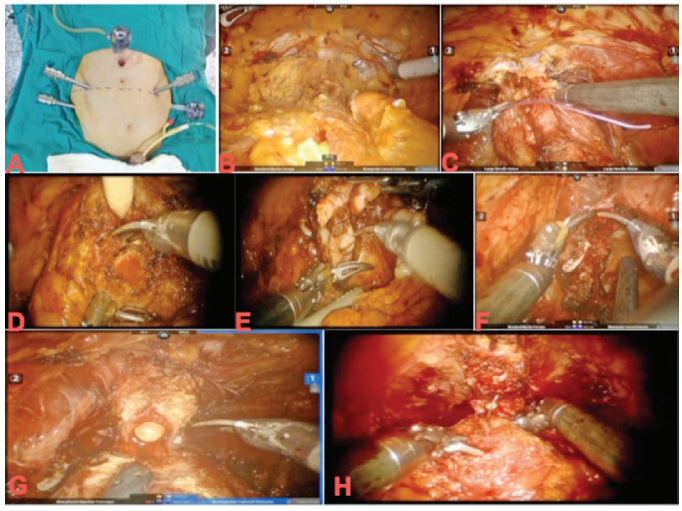

Figure 1. Stages of robot-assisted laparoscopic radical prostatectomy: A) placement of ports for robot-assisted radical prostatectomy, B) development of the Retzius space to expose the prostate, C) tying the deep dorsal vein plexus, D) dissection of the bladder neck, E) dissection of the vasa deferentia and seminal vesicles, F) dissection of the neurovascular bundle, G) dissection of the urethra, H) creation of vesicourethral anastomosis

Table 1. Comparison of age, prostate-specific antigen, prostate volume, surgery duration, surgical technique, surgical margin, extraprostatic extension, and Gleason score of prostatectomy material in patients with and without postoperative incontinence

	Incontinence		p
	No	Yes	
Age (years)	63.84±6.51	65.05±6.93	0.067[1]
PSA (ng/mL)	8.97±9.10	10.42±11.8	0.152[1]
Prostate weight (g)	47.60±18.7	49.43±21.3	0.347[1]
Operative time (minutes)	148.22±24.9	142.83±24.8	0.028[1]
Postoperative Gleason score	7.03±0.60	6.98±0.68	0.413[1]
Anterior approach	173 (64.3%)	96 (35.7%)	0.248[2]
Posterior approach	100 (58.8%)	70 (41.2%)	
Negative surgical margin	179 (63.3%)	104 (36.7%)	0.539[2]
Positive surgical margin	94 (60.3%)	62 (39.7%)	
Extraprostatic spread (-)	175 (65.8%)	91 (34.2%)	0.056[2]
Extraprostatic spread (+)	98 (56.6%)	75 (43.4%)	

PSA: Prostate-specific antigen
[1]Student's t-test
[2]Chi-square test
Values are given as mean ± standard deviation or number (percent)

There were no statistical differences between patients with and without postoperative incontinence in terms of demographical data, surgery duration, perioperative data, or postoperative histopathological data. The findings are summarized in Table 1.

Age ($p<0.001$), preoperative PSA value ($p=0.042$), and anterior or posterior approach in RALRP operation ($p<0.001$) were significant factors influencing the incidence of postoperative erectile dysfunction. However, the other demographic data, prostate characteristics, and histopathological parameters did not have a significant impact on erectile function. The correlations between the variables and postoperative erectile function are shown in Table 2.

Discussion

RALRP is one of the surgical techniques that developed rapidly and became widespread in the field of urology following the worldwide introduction of robotic systems. Various factors have made robotic methods feasible and appealing for RP, including the ability to have a closer, 3D view of the surgical site, make a sharper apical dissection, have a greater urethral length and more effective nerve sparing, reduced incisional morbidity, reduced need for blood transfusion and analgesic, and shorter hospital stay and recovery time.

While surgical treatment of PCa primarily targets oncological control, ensuring continued continence and erectile function is also important for the patient's quality of life.

Urinary incontinence is certainly one of the most important post-RALRP complications that impacts patients' daily lives. Full continence is defined in the literature as patients not using incontinence pads at all or only using a pad for security.

Many studies have investigated the effect of prostate volume on post-RP continence. Choo et al. (10) found that the likelihood of regaining continence in patients with a prostate larger than 40 g was lower in the RALRP group than in the group that had

Table 2. Relationship between demographic, surgical, and histopathological data and postoperative erectile dysfunction

	Erectile dysfunction		p
	No	Yes	
Age (years)	61.44±6.00	64.59±6.05	<0.001[1]
PSA (ng/mL)	8.28±7.44	10.18±10.5	0.042[1]
Prostate weight (g)	47±18.8	49±20.3	0.328[1]
Surgery duration (minutes)	143±24.9	147±24.2	0.061[1]
Postoperative Gleason score	7.05	6.98	0.330[1]
Anterior approach	73 (34.4%)	139 (65.6%)	<0.001[2]
Posterior approach	100 (62.5%)	60 (37.5%)	
Negative surgical margin	110 (44%)	140 (56%)	0.248[2]
Positive surgical margin	63 (51.6%)	59 (48.4%)	
Extraprostatic spread (-)	111 (48.1%)	120 (51.9%)	0.455[2]
Extraprostatic spread (+)	62 (44%)	79 (56%)	

PSA: Prostate-specific antigen
[1]Student's t-test
[2]Chi-square test
Values are given as mean ± standard deviation or number (percent)

open RP (97% vs 88%, p=0.025). The group with small prostate volume also had better outcomes with regard to potency (56% vs 50%, p=0.614) (10). Similarly, in a study evaluating the effects of prostate volume on functional outcomes, Boczko et al. (11) separated 355 patients who underwent RALRP into 2 groups, those with prostate volume greater than 75 g (n=36) and less than 75 g (n=319), for comparison. At 6 months, the continence rate was 97% in the group with lower prostate volume and 84% in the group with higher volume (p<0.05) (11). In addition to studies showing that smaller prostate volume has a favorable impact on post-RALRP urinary continence, the literature also includes studies in which prostate volume was not a significant factor in continence (12,13,14). Similar to the work of Labanaris et al. (13) and Yasui et al. (14) the results of our study suggest that prostate volume is not a determining factor in postoperative continence. Prostate volume was not a determinant of potency either.

Another factor investigated for its effect on post-RALRP continence is patient age. Kumar et al. (15) followed patients below and above the age of 70 with similar clinicopathologic characteristics (400 in each group) for 2 years and found similar continence rates (p=0.06) and time to regain continence. As for potency, both postoperative potency rates and time to regain potency were better in the younger group (15). Greco et al. (16) also divided patients into those younger and older than 70 and found that older males had significantly lower continence rates at postoperative 6 months but improved to a level comparable to that of the younger males by postoperative 12 months. However, it should be noted that the study included a significantly smaller number of older males compared to younger ones (23 vs 180). Similarly, Novara et al. (17) and Kim et al. (18) found that patient age was an independent prognostic factor for postoperative recovery of continence. Zorn et al. (19) divided patients into those older and younger than 60 and reported that continence rates were not different at 1-year follow-up after RALRP, but the younger patients had better results in terms of potency. Similar to their study, we also observed no significant association between mean age and continence in the present study, whereas the group exhibiting postoperative potency was younger. Advanced age was determined to be an important parameter in the development of postoperative erectile dysfunction. Another study investigated the effects of prostate volume and age on early post-RALRP recovery of erectile function. Of the 139 patients in the study, 53 showed subjective potency recovery at 3 months. In univariate analysis, prostate weight (43.3 vs 51.4 g, p=0.038) and age (55 vs 57 years, p=0.03) were significant. In multivariate analysis, only prostate weight was significantly correlated with potency (p=0.03) (20). Mendiola et al. (21) reported that younger males were more likely to regain potency in the early period than older males. In their study, patients were divided into 3 age groups: <50 years, 50-59 years, and ≥60 years. Young males (below 50) regained subjective potency earlier than the older patients (p=0.01). Potency rates were significantly higher among the young males at 3 and 6 months (p=0.04 for both) and this trend continued until 12 months (21).

There are various studies in the literature concerning the effects of PSA level on post-RALRP functional outcomes. Xylinas et al. (22) examined postoperative continence and erectile function in 500 patients who underwent RALRP. The patients' median PSA level was 9.7 ng/mL and median age was 62.2, and rates of continence and potency at 1 and 2 years were 44% and 53%, respectively. The authors reported that PSA below 10 ng/mL and age younger than 60 were correlated with favorable early functional outcomes (22). On the other hand, Torer et al. (23) found that preoperative serum PSA and Gleason score did not affect continence in 385 patients operated for RALRP. In our study, we found no significant difference in PSA level between patients with and without postoperative urinary incontinence. Our patients exhibited a higher rate of erectile dysfunction with higher PSA values (p=0.042). These data are consistent with the literature.

Another subject of analysis is the effect of the RALRP technique on functional results. In a study by Ko et al. (24), patients who underwent anterior (n=172) and posterior (n=172) RALRP were analyzed in separate groups. The potency ratios at 3, 6, and 9 months were 80.8%, 90.1%, and 92.9% respectively in the posterior group and 65%, 72.1%, and 85.3% respectively in the anterior group. At 12 months, there was no difference in potency rates between the groups, though it was noted that the posterior method resulted in significantly higher rates of early potency recovery. No significant difference was found between the methods with regard to continence rates or time to continence recovery (24). We also observed no significant difference between patients operated via the anterior and posterior approach with regard to incontinence. However, the posterior group exhibited less erectile dysfunction. Based on our findings, the effect of surgical technique on RALRP functional outcomes were similar to that reported by Ko et al. (24). On the other hand, Maddox et al. (25) had different results due to the shorter follow-up period.

Study Limitations

Limitations of this study include that it is retrospective, the RALRP procedures were performed by different surgeons, and there was no control group.

Conclusion

Technological advances and innovations in RALRP surgery have occurred in parallel with the ongoing development of robotic systems from their first incarnations, accumulation of knowledge regarding the anatomic and pathological characteristics of PCa, and experience gained through the widespread use of the technique. Our findings in this study indicate that patient- and disease-related factors are not associated with post-RALRP urinary continence, while erectile function is mainly influenced by the patient's age, preoperative PSA value, and the surgical technique. Conflicting functional outcomes reported after RALRP may be attributable to differences in patient populations, the questionnaire forms used, and the lack of standardization of the surgical techniques.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Written consent was obtained from the patients prior to the operation.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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The Effect of Transrectal Ultrasound-guided Prostate Needle Biopsy on Lower Urinary Tract Symptoms

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Abstract

Objective: To evaluate the effect of transrectal ultrasound-guided prostate biopsy on lower urinary system symptoms.

Materials and Methods: The study included 123 patients who underwent ultrasound-guided prostate biopsy between March 2013 and December 2013. Before and at 2, 4, and 8 weeks after the procedure, the patients completed the International Prostate Symptom Score (IPSS) questionnaire. Storage symptoms (questions 2, 4, 7) and voiding/postvoiding symptoms (questions 1, 3, 5, 6) were separately evaluated. The patients with cancer diagnosis were excluded after the week 4. The cancer-free patients were divided into subgroups based on education level and complication status and followed for 8 weeks to assess changes in IPSS and quality of life.

Results: IPSS increased significantly at week 2 follow-up of both the cancerous and cancer-free patients ($p=0.041$ and $p<0.01$); however, there was no statistically significant difference between the pre-biopsy scores and week 4 scores ($p=0.07$ and $p=0.09$). Voiding/postvoiding symptoms also increased significantly at week 2 for both groups ($p=0.04$ and $p<0.01$, respectively). IPSS was significantly higher in all subgroups of cancer-free patients at week 2, in correlation with voiding/postvoiding symptoms. In patients with low education level, there was a significant decrease in IPSS at 4 and 8 weeks compared to pre-biopsy ($p=0.031$ and $p=0.035$, respectively). IPSS changes were not associated with prostate volume. Quality of life was significantly reduced in the early period ($p<0.01$).

Conclusion: Lower urinary system symptoms are affected negatively in the early post-biopsy period in correlation with the increase of voiding/postvoiding symptoms. The time required for remission is 15-30 days. The procedure may decrease symptoms in patients with low education level due to the placebo effect.

Keywords: Lower urinary system symptoms, transrectal ultrasound, prostate biopsy

Introduction

Since it was first practiced by Hodge et al. (1) in 1989, transrectal ultrasound-guided prostate biopsy (TRUS-Bx) has been accepted as the standard diagnostic method for prostate cancer. Over 900,000 men worldwide are diagnosed with prostate cancer each year. Approximately 75% of diagnosed cases are reported from developed countries where prostate-specific antigen (PSA) testing is widely used and followed by prostate biopsy (2). Currently performed on more than 1 million patients per year in the United States of America and Europe, TRUS-Bx has become one of the most common procedures in urology practice (3).

Although TRUS-Bx is the standard method for the diagnosis of the disease, it can lead to various postoperative complications such as hematospermia, hematuria, rectal bleeding, urinary retention, urinary tract infections, and urosepsis (4,5,6,7). There are opposing views in the literature about the effects of TRUS-Bx on postoperative lower urinary tract symptoms (LUTS) (8,9,10,11).

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Our aim in this study was to evaluate patients undergoing TRUS-Bx preoperatively and postoperatively to determine the effects of the procedure on LUTS.

Materials and Methods

The study included 123 patients who underwent TRUS-Bx for the first time between March 2013 and December 2013. LUTS were assessed based on the International Prostate Symptom Score (IPSS) before and at 2, 4, and 8 weeks after the procedure. Approval for the study was obtained from the Ethics Committee of University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital (ethics committee date: 25/09/2013 and approval number: 2013/9/25). All patients included in the study signed an informed consent form.

Indications for prostate biopsy used in this study were abnormal rectal examination findings and/or serum PSA levels above 2.5 ng/mL.

Patients with urinary catheters prior to the procedure and those receiving medical treatment due to LUTS were excluded. In addition, medical treatment was initiated for patients whose IPSS was 20 or above before the procedure, and this group was also excluded from the study. None of the patients were given medical treatment due to LUTS after the procedure. Complications that developed after the procedure were classified according to the Clavien grading system. Patients who developed Clavien grade 2 or higher complications (urinary retention, infection symptoms, macroscopic clotted hematuria) were excluded from the study.

Urine cultures from all patients were studied prior to the procedure. Patients with growth in urine culture were treated with appropriate antibiotherapy; after achieving sterile urination, PSA level was measured again and the need for biopsy was reevaluated.

The IPSS, one of the most commonly used questionnaires in urology, was used to determine the effects of the TRUS-Bx procedure on LUTS. The patients' IPSS questionnaires were analyzed in 3 different ways to obtain an IPSS total score, storage symptom score (SSS) (questions 2, 4, and 7), and a voiding symptom score (VSS) (questions 1, 3, 5, and 6).

The IPSS item regarding quality of life, scored between 0 and 6 points, was used to assess whether possible changes in IPSS after TRUS-Bx affected the patients' lives.

Patients' ages, PSA levels, and prostate volumes were recorded and their association with postoperative LUTS were evaluated.

After pathology results returned, patients with benign pathology were divided into subgroups based on their education level (primary school and below, high school and above) and whether they had complications. Scores for all subgroups at each time point were calculated and changes were evaluated. Patients diagnosed with cancer were evaluated as a separate group and only in terms of the IPSS total and subscores.

All patients were prescribed oral ciprofloxacin 500 mg twice daily starting the day before TRUS-Bx and continuing for 3 days afterwards. All patients underwent bowel cleansing by intrarectal enema on the morning of the procedure. Oral analgesics were also prescribed for use within the first 3 days after the procedure.

For the TRUS-Bx procedure, patients were placed in the left lateral decubitus position, with the hip and knees flexed. Intrarectal 2% lidocaine gel was applied to all patients for local anesthesia. A 6.5 MHz rectal probe with a maximum diameter of 23 mm was used with a General Electric LOGIQ 100 PRO® series ultrasound device for TRUS imaging. Twelve-core biopsy specimens were taken from each patient using a 30 cm 18-gauge fully automatic biopsy needle.

Statistical Analysis

Nonparametric statistical tests were used because the variables did not conform to normal distribution. The Mann-Whitney U and Kruskal-Wallis tests were used for between-group comparisons, the Wilcoxon test was used for dependent samples, and chi-square and Fisher tests were used for categorical data. A p value of <0.05 was accepted as statistically significant.

Results

One hundred twenty-three patients who presented to our outpatient clinic and underwent TRUS-Bx for suspected prostate cancer were prospectively evaluated in this study. The mean age of the patients was 61.9 (38-75) years, mean PSA value was 12.73 (2.1-75.3) ng/dL, and mean prostate volume was 65.4 (20-310) cc.

Pathologic diagnosis was benign in 81 patients (65.8%) and malignant in 42 patients (34.2%). Patients diagnosed with cancer could not be evaluated at 8 weeks because they were referred for definitive treatment after week 4 of follow-up. Table 1 summarizes the first 4 weeks of evaluations of the patients diagnosed with cancer. Analysis of IPSS subscores showed that total scores and VSS increased significantly at week 2, while at later time points there were no statistically significant differences compared to preoperative values in any category.

IPSS subscores of the patients with benign pathology and their subgroups over the 8-week follow-up period are shown in Table 2.

When all patients were assessed, there was a statistically significant increase in total scores at week 2 ($p<0.001$). When the patients were evaluated in terms of SSS and VSS, it was seen that the higher scores during initial follow-up were primarily due to a statistically significant increase in VSS ($p<0.001$). At 4 weeks and 8 weeks after the procedure, total scores were not significantly different from preoperative values.

When analyzed based education level, there was a significant increase in IPSS total and VSS in both groups at 2 weeks. At 4

Table 1. International Prostate Symptom Score total and subscores of patients diagnosed with prostate cancer before and in the first 4 weeks after biopsy

PCa patients (n=42)	Pre-biopsy (week 0)	Week 2	p (week 2-0)	Week 4	p (week 4-0)
IPSS	10.90	11.85	**	11	*
VSS	6.96	7.6	**	6.90	*
SSS	3.90	4.20	*	4.10	*

PCa: Prostate cancer, IPPS: International Prostate Symptom Score, VSS: Voiding symptom score, SSS: Storage symptom score
*Nonsignificant, **significant ($p<0.05$), ***significant ($p<0.01$)

and 8 weeks, a statistically significant drop in IPSS total score compared to preoperative values was noted among patients with an education level of primary school or lower, while no significant difference was found in patients with high school or higher education.

The patients were divided into two groups based on the development of complications after the procedure, which were graded according to the Clavien classification. Thirty-two patients developed complications: 10 patients had hematospermia, 9 had hematuria, and 13 patients had 2 or more complications (Table 3). IPSS total and VSS increased significantly at week 2 follow-up both in patients with and without complications. At week 4, IPSS total and VSS fell significantly in the group without complications, and by week 8 there was no statistically significant difference in IPSS compared to preoperative values in either group.

The quality of life item revealed a significant decrease among patients with benign pathology and their subgroups at week 2, but it returned to preoperative values in later time points (Table 4).

No correlations were found between the patients' ages and prostate volumes and their score differences at the follow-up time points.

Discussion

Abnormal findings on digital rectal examination and elevated PSA values suggest the possibility of prostate cancer. Prostate needle biopsy is the most commonly used diagnostic method for the definitive diagnosis of these patients, and a pathological diagnosis of prostate cancer is established by TRUS-Bx in most cases (12). In the current American Urological Association guidelines, TRUS-guided 12-core biopsy that includes the distal lateral regions and the apex is recommended as the optimal initial biopsy method (13). A recent meta-analysis shows that multiparametric magnetic resonance imaging-guided biopsy is superior in the diagnosis of clinically significant prostate cancer (14). However, due economic factors and the fact that this procedure both takes longer and is not very widespread, TRUS-guided systematic biopsy is still accepted as the standard diagnostic method for prostate cancer.

The invasive nature of TRUS-Bx and especially the transrectal approach make certain complications possible. The patient and the physician should be prepared in the postoperative period, because the procedure can affect an individual's activities of daily living.

Klein et al. (8) evaluated postoperative LUTS in 198 patients who underwent TRUS-Bx for suspected prostate cancer. They divided the patients into 3 groups and used intrarectal lidocaine gel alone in the first group (71 patients), periprostatic nerve block in addition to intrarectal lidocaine gel in the second group (74 patients), and periprostatic nerve block alone prior to saturation biopsy to the third group (53 patients) who had previous negative biopsies and persistent elevated PSA. The patients were evaluated using the IPSS before and at 1, 4, and 12 weeks after the procedure. Each group showed an increase in IPSS at week 1. At weeks 4 and 12, this increase disappeared in the first group, persisted but was statistically nonsignificant in the second group, and persisted significantly in the group that

Table 2. Evaluation of International Prostate Symptom Score total and subscores of patients with benign pathology before and for 8 weeks after biopsy

	Pre-biopsy (week 0)	Week 2	p (week 2-0)	Week 4	p (week 4-0)	Week 8	p (week 8-0)
Mean IPSS							
All patients (n=81)	11.52	12.51	**<0.01**	11.28	0.088	11.32	0.09
Low education level (n=42)	12.31	13.19	**<0.01**	11.79	**0.021**	11.85	**0.029**
High education level (n=39)	10.67	11.77	**<0.01**	10.74	0.94	10.71	0.98
Complications (-) (n=49)	10.49	11.24	**<0.01**	10.06	**0.03**	10.30	0.8
Complications (+) (n=32)	13.09	14.44	**<0.01**	13.16	0.919	12.87	0.6
Mean VSS							
All patients	6.74	7.54	**<0.01**	6.74	0.9	6.85	0.8
Low education level	7.21	7.88	**<0.01**	7.02	0.15	7.26	0.09
High education level	6.23	7.18	**<0.01**	6.46	0.25	6.41	0.2
Complications (-)	6.49	7	**<0.01**	6.22	**0.02**	6.42	0.9
Complications (+)	7.13	8.38	**<0.01**	7.56	0.09	7.53	0.06
Mean SSS							
All patients	4.78	4.96	0.16	4.53	0.08	4.46	**0.04**
Low education level	5.10	5.31	0.28	4.76	0.12	4.59	**0.04**
High education level	4.44	4.59	0.36	4.28	0.37	4.30	0.4
Complications (-)	4	4.24	0.16	3.84	0.23	3.88	0.29
Complications (+)	5.97	6.06	0.59	5.59	0.2	5.34	**0.03**

IPSS: International Prostate Symptom Score, VSS: Voiding symptom score, SSS: Storage symptom score

underwent saturation biopsy (8). The changes in IPSS observed in our study are consistent with the study by Klein et al. (8). While patients' LUTS increased in the early post-biopsy follow-up, in subsequent follow-ups they did not differ significantly compared to pre-biopsy levels.

To the best of our knowledge, there are no studies in the literature which evaluate IPSS subscores. As a step further from the study by Klein et al. (8), in our study we separately categorized and evaluated the IPSS items regarding voiding symptoms and storage symptoms. The statistically significant increase in voiding symptoms in the early period was thought to be due to inflammation and edema in the prostate tissue due to the biopsy procedure. Our findings indicate that a period of 15-30 days is required after the procedure for the prostate edema to subside.

In another study, Helfand et al. (9) used pre- and post-biopsy American Urological Association Benign Prostatic Hyperplasia Symptom Score data to assess the LUTS of 85 patients who underwent 12-core TRUS-Bx for suspected prostate cancer. No statistically significant difference in LUTS was found when the lower urinary tract functions of all patients and those diagnosed with prostate cancer were analyzed before and after the procedure (9). Although our study is similar in that the tissue diagnosis was not associated with post-biopsy course, our findings differ from those of Helfand et al. (9) in terms of the effects of the procedure on LUTS.

In a study by Fujita et al. (10) published in 2009, 231 patients diagnosed with prostate cancer and under active surveillance were followed to assess the effects of serial biopsies on erectile function and LUTS. There were no statistically significant differences between IPSS values before and at 1 week after the procedure (10). Unlike the study by Fujita et al. (10), in our study we evaluated patients undergoing biopsy for the first time and were able to follow patients with cancer for only 4 weeks.

Table 3. Complications observed in patients after prostate biopsy

Complication	Number	%
Hematospermia (Clavien 1)	22	27.2
Hematuria (Clavien 1)	21	25.9
Rectal bleeding (Clavien 1)	4	4.9

Although the patients were not assessed with a questionnaire measuring anxiety, we observed changes in the emotional state of patients during the interviews. Similar to the patients in the benign group, the IPSS results of patients diagnosed with cancer did not differ significantly at week 4 follow-up compared to their pre-biopsy scores. This indicates that a cancer diagnosis and the resulting anxiety are not associated with any additional changes in LUTS after biopsy.

To the best of our knowledge, there are no studies in the literature showing the relationship between patients' education level and changes in LUTS after prostate biopsy. In our study, there was an increase in LUTS at week 2 in both the higher and lower educated patient groups. Subsequent follow-ups revealed a statistically significant drop in the IPSS of the lower education level group compared to pre-biopsy values. We believe this was due to the procedure being perceived as a treatment and creating a placebo effect, and while this effect can also be observed in patients with high education levels, it is more common among patients with a low level of education.

In the present study, we graded the complications developed after TRUS-Bx according to the Clavien classification. As in some other studies, hematuria lasting more than 3 days, hematospermia lasting more than 3 days, and rectal bleeding lasting more than 24 hours were graded as Clavien grade 1 complications (15). Predicting that high-grade complications such as macroscopic clotted hematuria and infectious conditions would definitely result in higher scores, we considered it appropriate to exclude these patients from the study. The relationship between pre-biopsy and post-biopsy week 2 and 8 scores of the patients with complications was similar to that seen in the assessment of all patients in our study. According to our results, low-grade complications that develop after the procedure do not influence LUTS. In light of our findings, we believe that low-grade complications should be regarded as a natural component of the post-biopsy period.

Studies examining the effect of prostate volume on post-biopsy IPSS present differing views. In a 2001 study conducted by Zisman et al. (11), 211 patients were prospectively evaluated before biopsy and at 7 and 30 days after biopsy using IPSS. The procedure was shown to cause temporary difficulty voiding, and a transitional zone volume of 42 mL or more was associated

Table 4. Assessment of quality of life scores of patients with benign pathology and subgroups before and for 8 weeks after prostate biopsy

QoL		QoL pre-biopsy (week 0)	QoL week 2	p (week 2-0)	QoL week 4	p (week 4-0)	QoL week 8	p (week 8-0)
All patients (n=81)		2 (0-6) 2.04	2 (0-6) 2.27	**<0.01**	2 (0-6) 2.09	0.346	2 (0-6) 2.02	0.467
Education level	Low	2 (0-6) 2.21	2 (0-6) 2.45	**<0.01**	2 (0-6) 2.21	1.00	2 (0-6) 2.13	0.157
	High	2 (0-6) 1.85	2 (0-6) 2.08	**<0.01**	2 (0-6) 1.95	0.216	2 (0-6) 1.90	0.739
Presence of complications	No	2 (0-6) 1.84	2 (0-6) 2.04	**<0.01**	2 (0-6) 1.82	0.763	1 (0-6) 1.57	0.166
	Yes	3 (0-6) 2.34	3 (0-6) 2.63	**0.014**	3 (0-6) 2.50	0.059	3 (0-6) 2.62	0.317

QoL: Quality of life

with greater difficulty voiding and the possibility of developing urinary retention (11). However, similar to the study by Klein et al. (8), no correlation was seen between prostate volume and IPSS changes in our study. These findings suggest that prostate volume prior to biopsy is not an effective predictor of the extent of LUTS increase following the procedure.

In addition, each patient in our study was assessed based on the quality of life score at the end of the IPSS questionnaire. As TRUS-Bx is an invasive and painful procedure, there was a significant deterioration in quality of life in the first 2 weeks in all groups. Subsequent questionnaires did not reveal any statistically significant differences compared to pre-biopsy values in any patient group. In a study conducted in 2003, Bozlu et al. (16) studied the effects of tamsulosin use on post-biopsy IPSS, peak flow rate, and quality of life. Sixty-six patients were prospectively evaluated and divided into a tamsulosin group and a control group. A reduction in quality of life was noted in the control group, although the change was not statistically significant. The most noteworthy finding was the statistically nonsignificant improvement in quality of life among patients using tamsulosin (16). We believe that the routine use of alpha blocker therapy will be beneficial in preventing the temporary increase in IPSS and deterioration of quality of life that were correlated with an increase in VSS in our study.

Study Limitations

The main limitations of this study are that was based on a questionnaire and included a small number of patients.

Conclusion

TRUX-Bx causes increased LUTS in the early postoperative period, especially associated with increased voiding symptoms. The increase in LUTS is independent of patient age and prostate volume.

Although we stated that we believe the placebo effect may be responsible for the earlier reduction in symptoms in the low education level group, it should be explained to patients that TRUS-Bx is not therapeutic so that patients do not neglect follow-up due to an unrealistic sense of healing after the procedure. Because the procedure is painful and may cause anxiety in the patient, quality of life was observed to drop in the early post-biopsy period. Adequately informing patients and providing effective symptomatic treatment will make the healing period more comfortable.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Ethics Committee of University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital (ethics committee date: 25/09/2013 and approval number: 2013/9/25).

Informed Consent: All patients included in the study signed an informed consent.

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Authorship Contributions

Surgical and Medical Practices: V.Ç., S.Ö., Concept: S.A., E.Ö., M.M.A., Design: M.M.A., M.D., Data Collection or Processing: V.Ç., Analysis or Interpretation: E.Ö., V.Ç., Literature Search: S.A., M.D., V.Ç., Writing: V.Ç., S.Ö.

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Socioeconomic Predictors and Patient Perspectives of Prostate-specific Antigen Testing

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Abstract

Objective: To identify important factors affecting men's decision to undergo prostate-specific antigen (PSA) testing and to determine who is at risk for prostate cancer based on age-specific PSA values.

Materials and Methods: We retrospectively analyzed data obtained from 4963 men aged between 40-80 years. Between 2010 and 2017, participants from rural districts of İzmir, Turkey were invited to join a free public health screening program including brief health history assessment, anthropometric measurements, and blood and urine analyses. Participants completed a questionnaire regarding educational level, marital status, economic status, and previous PSA tests, and venous blood samples were obtained for PSA testing.

Results: All 4963 men were included in the study. The majority of the participants had low education level and low or very low socioeconomic status. Nearly all of the subjects stated that their main reason for participating in the screening program was it was a free, regular health check-up program and was easily accessible in their hometown. Urinary complaints were present in 28% of the participants. Of the screened men, PSA level was ≥2 ng/mL in 21.1% and ≥4 ng/mL in 7.7%. Of the subjects with previous PSA tests, 77.5% were referred for either biopsy or further testing, but due to financial and transportation difficulties, only 7% of them followed-up at a hospital or urology department.

Conclusion: Economic factors determine men's attitude towards PSA testing. Specific measures should be taken to overcome factors that hinder the early detection of prostate cancer.

Keywords: Prostate cancer, prostate-specific antigen, screening, early detection

Introduction

Prostate cancer is the second commonest cause of cancer-related death in men worldwide (1,2). Enhanced detection through prostate-specific antigen (PSA) testing mostly explains the increased incidence of prostate cancer over the last 2 decades in many countries (3,4,5). Although PSA testing is not currently recommended as a routine screening tool for prostate cancer (6,7,8), in many countries it is widely performed in primary care, either as a frontline test for men presenting with urinary symptoms or as a free test for men over 40 years at the request of the patient.

PSA testing may be influenced by several factors, resulting in a high degree of variability. Healthcare policies, accessibility to healthcare providers, reimbursement, screening policies, and education can be potential barriers to participation in PSA testing and early prostate cancer detection.

To date, little is known about the value of PSA and its applicability and practicability for screening in different male populations. Normal and age-specific PSA ranges have not been determined for many different cultures and countries. There are also limited published data on the prevailing knowledge, attitudes, and practices regarding PSA testing in different countries (9,10). More data are needed to identify factors associated with PSA

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testing in elderly men and estimate the size of the population at risk of prostate cancer who are not tested.

The present study aimed to identify the salient factors that influenced men's decision to undergo PSA testing and to determine who are at risk of prostate cancer based on age-specific PSA. Our findings may offer insight into the factors influencing these men's decision to participate in screening and as a result, may help guide the design of effective, culturally sensitive, and relevant interventions aimed at increasing participation in screening, as well as further studies aimed at improving treatment options.

Materials and Methods

Our study is a descriptive cross-sectional population-based study. We analyzed data obtained from 4963 men aged 40-80 years from rural districts within the province of İzmir, Turkey who volunteered to participate in a health screening program. The study was designed to assess the health and socioeconomic status of elderly individuals in those districts through the İzmir Metropolitan Municipality public health screening program conducted from 2010 to 2017. Invitations were sent via the news media and local authorities. A free health screening, including for non-communicable diseases like diabetes and hypertension, was performed. The health screening was based primarily on a standardized questionnaire with elements of a brief health history assessment, blood pressure and anthropometric measurements, and analysis of selected blood and urine parameters. Prostate screening was done on-site using a venous blood sample and qualitative screening kits using a cut-off value of 4 ng/mL. Patients with PSA >4 ng/mL and urinary symptoms were referred to the hospital for follow-up. The study questionnaire included items such as previous PSA testing, lower urinary tract symptoms, and past medical history. Factors that may be potential determinants of PSA testing (education level, marital status, and economic status) were also noted. Further information was obtained on the basis of hospital medical records held by the participants. The data were subjected to simple statistical analysis.

Because the study was designed as a retrospective chart review, ethics committee approval and informed consent were not obtained. However, the participants provided informed consent during the health screening.

Results

All 4963 men who consented to the health screening were included in the study. PSA testing was carried out in all of them. Table 1 shows demographic characteristics of the study participants.

The majority of the respondents were married (70.6%) and had a secondary or lower level of education (78%). Most of the screening population invited for the free health screening program had low or very low socioeconomic status.

The participants were asked about factors that motivated them to participate in this health program. Nearly all reported that their main reason was that it was a free, regular health check-up program and was easily accessible in their own hometown. Twenty-eight percent of the participants had urinary complaints. Other less common reasons for participation were aging and growing concerns about general health and the prostate.

Serum PSA had been previously tested in 544 of the participants. Of these, 77.5% were referred for either biopsy or further testing, but only 7% of them presented to a hospital or urology department for follow-up due to reasons such as cost and lack of access to healthcare. Respondents over 50 years old who had never been tested for prostate cancer cited various reasons for this, including not knowing about PSA testing, never being advised by their physicians to have PSA testing, not being able to afford testing, and lack of interest.

Of the 4963 men, 1403 stated that symptoms such as frequent urination, incontinence, and pain had prompted them to visit their doctor. Of these, 522 reported that a physician had advised them to undergo a detailed prostate examination. However, most of them had not been examined by urologist.

PSA distribution by age groups is shown in Table 2. Of the screened men, 21.1% had PSA ≥2 ng/mL. Only 2.2% of the men aged 40-50 years had PSA over 2 ng/mL. As expected, mean PSA was higher after the age of 60.

PSA levels were elevated (>4 ng/mL) in 382 of the total 4963 men tested (7.7%), which included 90% of patients over 60 years old. This finding was also evident when using a threshold of PSA >3, which showed a dramatic rise after 60 years old.

Table 1. Demographic features of the subjects involved in the study

Age in years	60.5±9.3
Age groups, n (%)	
All	4963
40-49	721
50-59	1488
60-69	1671
70-79	1083
Marital status, n (%)	
Married	3506 (70.6)
Single	211 (4.3)
Other	1246 (25.1)
Education	
Middle school	3879 (78.2)
High school or higher	1084 (21.8)
Urinary complaints	
Yes	1403 (28.2)
No	3560 (71.8)
Ever had a prostate-specific antigen before	
Yes	544 (10.9)
No	4419 (89.1)

Table 2. Prostate-specific antigen level distribution by age group					
	Age groups				
	All	40-49	50-59	60-69	70-79
PSA ng/mL (mean ± SD)	1.81±4.6	0.94±3.0	1.2±2.3	1.9±4.3	3.1±7.2
PSA ng/mL, n (%)					
0.0-1.0	2538 (51.1)	540 (21.3)	930 (36.6)	719 (28.3)	349 (13.8)
1.01-2.0	1380 (27.8)	152 (11.0)	389 (28.2)	522 (37.8)	317 (23.0)
≥2	1045 (21.1)	29 (2.8)	169 (16.2)	430 (41.1)	417 (39.9)
≥3	620 (12.5)	9 (1.5)	70 (11.3)	259 (41.8)	282 (45.5)
≥4	382 (7.7)	4 (1)	38 (9.9)	147 (38.5)	193 (50.5)
PSA: Prostate-specific antigen, SD: Standard deviation					

Discussion

The results of our general population healthcare screening initiative including 4963 Turkish males demonstrated a 7.7% prevalence of PSA levels ≥4 ng/mL, which is comparable to that reported in other previously unscreened low-incidence community-based populations (11,12). When the European Association of Urology guideline recommendation of PSA <2 ng/mL is considered, by the age 60 the prevalence of high PSA levels increased to 19% (8). Our results clearly show the need for prostate cancer awareness and education programs for the male population. As we have determined that a high percentage of the population is at risk for prostate cancer, more measures to increase screening and access to healthcare should be considered.

The present study identified a number of factors that influence men's decision to undergo prostate cancer screening. Our study shows that some of the participants acted on their doctors' instructions after they had presented with urinary complaints. A finding which was evident in our study was that symptoms experienced by participants influenced their decision to seek a PSA test. Over a quarter of the participants reported that their symptoms had prompted them to visit their physician, who then referred them to undergo PSA testing. Some of these men stated that they had no previous knowledge of the PSA test and only acted upon their physician's advice because they sought a solution to their problem. Because most of the participants were undereducated with low economic status, few expressed any views regarding individually requested PSA test. Knowledge about prostate cancer, its risk factors, and PSA testing were all identified as factors influencing men's motivation to be tested. This suggests that knowledge is very important to the issue of PSA testing because, as with other health issues, when men are informed they can make better decisions.

In our study, 89% of the participants had never been tested previously, although they were in the age group recommended for prostate cancer screening. Furthermore, very few of the men who had been tested later presented to a urologist for further testing. The accessibility of testing services also appeared to influence men's decisions to get tested. Some of the patients said that access to PSA testing was not difficult, which made it easier for them to undergo testing. Most participants indicated that their main reason for undergoing testing was that the health screening program was provided free of charge by the Municipal Public Hospital. Free and easy access as an incentive for early testing indicates lower overall socioeconomic status. Lack of information on where to go for testing also delayed some participants from utilizing testing services, and limited resources to pay for testing was cited as a barrier to early testing. These points were supported by Odedina et al. (13), who argued that access to health care, free screening, and transportation were facilitators of prostate cancer screening. Therefore, our findings underline the need to establish free or affordable testing centers which are accessible to all age groups of men in the community. Interventions for targeted PSA screening among these patients should be considered by those in the health policy field.

Study Limitations

Limitations of this study are the characteristics of the study sample, which consisted primarily of men who were undereducated and at low socioeconomic status. Hence, the results may not represent men of all socioeconomic groups, and might not include the views of men with better access to testing service and treatment facilities. Nevertheless, this study has provided useful information on important factors influencing men to undergo testing and therefore, highlighted areas to direct health promotional activities in order to increase testing rates.

Conclusion

Our study supported much of the existing knowledge on the factors which influence men to undergo testing. Based on the results of this study, economic factors are a major determinant of men's attitudes towards prostate cancer screening and testing. Several measures should be taken to overcome the barriers hindering participation in early prostate cancer screening.

Ethics

Ethics Committee Approval: Because the study was designed as a retrospective chart review, ethics committee approval was not obtained.

Informed Consent: Because the study was designed as a retrospective chart review, ethics committee approval was not obtained, but the participants provided informed consent during the health screening.

Peer-review: Internally peer-reviewed.

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Review
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Contemporary Trends in Adjuvant and Neoadjuvant Treatment for Renal Cell Carcinoma

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Abstract

Renal cell carcinoma is an increasingly significant cancer in which surgical resection is still the sole curative approach. There is a risk of recurrence in one-third of patients after surgery. Successful experiences with some solid organ cancers and effective treatment response to targeted agents in metastatic cases have suggested a similar adjuvant approach for renal cell carcinoma. Consequently, placebo-controlled adjuvant trials have been reported and the Food and Drug Administration approved sunutinib as an adjuvant treatment after nephrectomy in high-risk patients, with the risk of treatment-related side effects. Several clinical series have indicated that neoadjuvant application can provide significant downsizing of the cancer mass in complex cases and enable radical surgery. Similarly, neoadjuvant therapy could enable nephron-sparing surgery for certain patients. Both adjuvant and neoadjuvant approaches for renal cell carcinoma require further trials with larger patient numbers. This review presents contemporary experience on adjuvant and neoadjuvant treatment for renal cell carcinoma.
Keywords: Renal cell carcinoma, adjuvant, neoadjuvant, targeted therapy

Adjuvant Therapy

Renal cell carcinoma has an important place among adult cancers. Although its overall incidence is reported as 2-3%, significant differences have been observed between countries (1). It is also important to note that its incidence is showing an upward trend. Its incidence has risen by more than 30% over the past 15 years (2). This clearly indicates that the significance of renal cell carcinoma will continue to grow. Early incidental diagnosis increases the rate of local disease and enables curative surgical treatment. However, a substantial proportion of patients, about 1 in 3, may develop metastatic disease within 5 years of curative surgery (3,4). Recurrence after curative surgery can involve metastatic disease, and mortality may be unavoidable (5). This shows that a significant proportion of patients who receive curative treatment will experience recurrence during follow-up, and raises the need to prevent recurrence by detecting patients at risk and providing adjuvant therapy in advance. Indeed, favorable results of adjuvant systemic therapies in breast and gastrointestinal tract cancers suggest a similar approach may be applicable in renal cell carcinoma (6). This gives rise to the need to at least identify and provide adjuvant systemic therapy to high-risk patients, and there is a growing body of research in pursuit of these ends.

For many years, it was accepted as a general rule that adjuvant therapy had no place in the treatment of renal cell carcinomas (7). However, this appears to be changing due to recent developments. This section discusses the current state of postoperative adjuvant systemic therapies in renal cell carcinomas.

Early Adjuvant Therapy Studies

Renal cell carcinoma is generally a chemoresistant cancer. Therefore, before the availability of agents targeting the vascular endothelial growth factor receptor (VEGF-R) system, two classic immunotherapy molecules widely used in metastatic disease,

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interferon (IFN-α) and interleukin (IL)-2, were tried as adjuvant therapy. In particular, IFN-α and IL-2 alone, in combination, and even combined with various chemotherapeutics were tried as adjuvant therapy, but none provided a significant advantage in terms of disease-free or overall survival (8,9,10,11). Despite being an old and costly study, the data demonstrating a significant extension of disease-free survival in renal cell carcinoma were reported in a trial of a vaccine obtained from autologous tumor cells in a series of 558 patients (12). However, the study faced serious criticism due to the high risk of bias, poor explanation of the criteria used in patient selection, the significant number of non-clear cell cancer cases included, the nonhomogeneity of the groups (even in numbers), and the drop-out rate. Besides these concerns, commercial production of the vaccine also proved impossible.

In a meta-analysis done in 2013, data from 14 clinical trials were examined and a detailed evaluation of 3380 patients treated with various agents (mostly IFN and IL, but 1 trial included adjuvant radiotherapy) revealed no survival advantage (13). Conversely, an unfavorable effect on 5-year disease-free survival was observed in patients who received adjuvant cytokines. It light of these data, it can be concluded that there is no evidence supporting the adjuvant use of non-targeted therapeutic agents and that clinical trials evaluating them ended at this stage.

Recent Adjuvant Therapy Studies

Identifying the von Hippel-Lindau gene mutation in the molecular pathogenesis of renal cell carcinoma and understanding its role in angiogenesis gave rise to the concept of "targeted" therapy. Similarly, the role of the phosphatidylinositol-3-kinase-Akt-mammalian target of rapamycin (mTOR) system in renal cell carcinoma was determined. Thus, angiogenesis (VEGF-R system) and mTOR inhibitors soon began to be used effectively for metastatic renal cell carcinoma and were clearly shown to confer advantages in both disease-free and overall survival. They are currently in standard use as first-line and even second-line therapies for systemic disease. Therefore, it is imperative to evaluate the use of these agents in the adjuvant setting.

This section focuses on targeted agents that are used in metastatic disease and shown to induce an objective clinical response in recent adjuvant therapy trials (i.e. agents with proven efficacy). Accordingly, sorafenib and sunitinib, which target the VEGF-R system, were the first targeted molecules to be investigated for adjuvant use. The studies for which results have been published to date and their findings can be summarized as follows.

ASSURE: A randomized prospective trial including a large number of patients (14). The study initially included 1943 nephrectomy cases and pathological stages ranging from T1b (high grade) to T4 (all grades). Both lymph node positive and negative patients were included. Patients were stratified based on parameters such as intermediate/high or very high risk, clear or non-clear cell type, performance status, and type of resection. They were then randomly assigned to receive sunitinib daily for 4 weeks/no treatment for 2 weeks (n=647), sorafenib daily (n=649), or placebo (n=647). One year of treatment was planned. An increase in disease-free survival from 5.8 years to 7.7 years was initially anticipated. However, dose adjustments were necessary due to adverse events. The report of an initial interim analysis stated that neither arm of the study yielded significant differences in disease-free survival or overall survival compared to the placebo group (14). It was noted that dose adjustments increased treatment adherence. Nevertheless, severe adverse effects were reported in the treatment arms. These preliminary results laid the foundation for a strong opinion against adjuvant therapy.

STRAC: The second prospective, randomized, placebo-controlled trial investigating adjuvant therapy (15). This study included 615 high-risk patients with clear-cell renal carcinoma who underwent nephrectomy. Treatment with sunitinib 50 mg daily (4 weeks treatment/2 weeks off) versus placebo for 1 year was planned. According to the results of an initial evaluation, median disease-free survival was 6.8 years in the treatment group and 5.6 years in the placebo group. Disease-free survival rates were also significantly higher in the treatment arm based on 3- and 5-year data (59.5% for placebo versus 64.9% for sunitinib at 3 years, 51.3% for placebo versus 59.3% for sunitinib at 5 years). Dosage titration was required in approximately one-third of patients in the treatment arm due to adverse events. Treatment discontinuation was reported at a rate of 28% in the treatment arm versus 5.6% in the placebo arm. Preliminary data indicated a disease-free survival advantage despite the high incidence of adverse events. According to these data, adjuvant sunitinib provided a 14-month disease-free survival advantage and a 24% risk reduction. Thus, contrary to the first study, a significant disease-free survival advantage was reported. It is noteworthy that despite the potential patient overlap with ASSURE, STRAC included relatively higher risk patients and involved a central radiological evaluation. However, STRAC had a shorter follow-up period and included fewer patients. Considering these possible limitations, a "small" meta-analysis including the STRAC data challenged the statistical significance of the increase in disease-free survival (7). Although patients treated with sunitinib were evaluated as a meta-analysis, it deserves mention that the patients were heterogeneous and the majority comprised ASSURE patients. Essentially, the results of the STRAC trial are striking and support the view that adjuvant therapy is necessary at least for high-risk patients, but it is clear that there is a significant adverse event profile. It was recently published that adjuvant sunitinib therapy also showed a disease-free survival advantage in subgroup analyses of the STRAC trial (16). Based on STRAC data demonstrating this survival advantage, sunitinib was recently approved by the Food and Drug Administration (FDA) for adjuvant use in high-risk patients (17).

Comparison of ASSURE and STRAC: The discrepancy in disease-free survival reported in these two studies may be attributed to various factors. We believe the most important of these, which was mentioned briefly above, was that STRAC included more homogenous and, more importantly, relatively higher risk patients; in other words, patients with the greatest need for adjuvant therapy. Another noteworthy issue is the heterogeneous group included in the ASSURE trial. At least one-fifth of the patients in ASSURE had non-clear cell renal cancer and approximately 10% of those had sarcomatoid changes. In contrast, all of the patients in STRAC had clear cell carcinoma.

Approximately 10% of the patients in ASSURE had stage T1 disease, while all patients in STRAC were stage T3 and/or lymph node-positive. Furthermore, the trials included very different patient numbers. The sunitinib arms of ASSURE and STRAC included 647 and 309 patients, respectively. Dose titrations due to adverse events resulted in 25 mg and 37.5 mg doses in ASSURE and STRAC, respectively. Thus, higher doses of the drug were administered in the STRAC trial. Central radiological evaluation in the STRAC trial is another important difference. Both of these studies suggest that adjuvant sunitinib may be effective, at least in a well selected and high-risk patient group. Therefore, because STRAC included a more homogenous, higher risk patient group and the probability of micrometastasis is higher in these patients, it seems valid to believe that it conferred a disease-free survival advantage (18). In fact, even within the STRAC trial, it was reported that adjuvant therapy provided a significant disease-free survival advantage of 6.2 years versus 4 years in the "very high risk" subgroup. However, the fact that overall survival data have not been released fuels continued debate regarding adjuvant therapy. Due to both the lack of overall survival data and the high incidence of adverse events, adjuvant therapy is not recommended in the latest version of the European Urology Guidelines (7). It was stated that available evidence regarding adjuvant therapy is inadequate for various reasons such as the need for longer follow-up, the potential presence of radiologically undetectable micrometastases in high-risk patients, and the possibility that in the STRAC study, sunitinib stabilized these micrometastases, resulting in the extended time to detectable recurrence (i.e. disease-free survival). Adverse effects and the importance of quality of life were emphasized. One of the major arguments presented was that guidelines should be based on evaluation of the results of meta-analyses, as has been done with other cancers, rather than data from a single study. For example, a definitive conclusion regarding adjuvant therapy for rectal cancer and the subsequent creation of guidelines could only be achieved with meta-analysis data (19). The same must be done for renal cancer. Currently, a "small" and limited meta-analysis including the ASSURE and STRAC trials, with their limited patient numbers and follow-up periods, reports a conclusion against adjuvant therapy (7).

PROTECT: This is the latest phase 3 placebo-controlled randomized trial to publish results. A total of 1538 patients with high-grade stage T2 and T3 clear cell renal cancer were randomized to receive pazopanib or placebo for 1 year after nephrectomy. The initial dose of 800 mg administered to 403 patients was lowered to 600 mg, and disease-free survival was evaluated. A one-third reduction in hazard ratio for disease-free survival was reported in patients who started at 800 mg, while no statistically significant improvement in disease-free survival was detected in those treated with 600 mg (20). In a subanalysis supporting these findings, early (3 or 5 weeks) drug concentrations of 311 patients and late (16 or 20 weeks) drug concentrations of 250 patients were compared with disease-free survival and adverse event profile (21). The study showed that an early high drug dose prolonged disease-free survival with no change in the incidence of adverse events (except hypertension). Similarly, it was reported that those with a pazopanib concentration above 20.5 µg/mL in the early or late period had a significant disease-free survival advantage. However, it is clear that long-term follow-up of this study is needed.

Ongoing studies: Results from phase 3 placebo-controlled trials of other adjuvant targeted agents are being awaited. Of these, the results of studies of sorafenib (SORCE), axitinib (ATLAS), and everolimus (EVEREST) will be of interest.

The Future

In relation to STRAC in particular, there are no other large series/long follow-up data that show a disease-free survival advantage in favor of adjuvant therapy (22). Only an autologous vaccine trial which included a limited number of patients and was determined unfeasible due to cost reported an increase in survival (12). Long-term follow-up results are also expected for pazopanib. As results from trials of new targeted agents become available, adjuvant therapy approaches will continue to increase.

On the other hand, the optimal duration of adjuvant therapy with targeted agents is also unknown. In current studies, treatment usually continues for 1 year. It is known that in metastatic disease, resistance is acquired after response to targeted agents. Unnecessarily prolonged adjuvant therapy can lead to recurrence with a more resistant tumor population. Therefore, studies should also focus on determining optimal adjuvant treatment durations. It has yet to be determined whether adjuvant therapy should continue for 1 year, 5 years, or a lifetime. Adverse events and high cost are other barriers.

Essentially, treating micrometastases with targeted agents that suppress angiogenesis (at least in theory) may also be considered suspect. This is because the degree to which micrometastases are associated with angiogenesis must be further elucidated and investigated. New molecules are also needed in this respect. However, recent studies have demonstrated the efficacy of several new immunotherapeutics in advanced bladder and renal cancers. The most recent of these is nivolumab, a monoclonal antibody targeting the programmed death 1 receptor. Nivolumab and everolimus were compared in a study of 821 patients who had previously received systemic therapy with standard primary targeted agents, and nivolumab was reported to provide a survival advantage (21.8 months versus 19.6 months) with a milder adverse event profile (23). These findings in metastatic disease also suggested the possibility of its use in the adjuvant setting. Indeed, there is an example of favorable outcomes after the postoperative adjuvant use of these agents in melanoma (24). However, a major drawback to approaches using these agents is the theory that since the primary focus is removed with surgery, treatment targeting the immune checkpoints in question may fail in the absence of antigens (25). Therefore, prospective studies have also been designed to investigate the perioperative (neoadjuvant/adjuvant) use of such immune agents. For example, the PROSPER trial is evaluating nivolumab (2 cycles preoperatively + postoperatively until toxicity or progression) versus a placebo in 766 high-risk renal cell carcinoma patients. The IMmotion010 trial is investigating the adjuvant use of atezolizumab after

surgery. The results of these and similar studies will open new horizons for adjuvant therapy.

The need for risk evaluation in the planning of adjuvant therapy and its suitability for high-risk patients are apparent even in light of data from available studies. Different classification methods have also been described for this purpose. These methods aim to classify patients according to clinical stage and pathological features. The University of California, Los Angeles integrated staging system divided patients into 5 classes based on their T and N stages, Fuhrman grade, and Eastern Cooperative Oncology Group performance status (26). On the other hand, in an evaluation of 1671 patients using the Leibovich score or stage, size, grade, and necrosis (SSIGN), stage, tumor size, nuclear grade, and necrosis were used to predict "low, moderate, and high risk of recurrence" (27). For example, progression risk of 42% and 63% were reported at 1 year and 3 years, respectively, in the high-risk group. Therefore, patients in this at-risk group can be considered candidates for adjuvant treatment. There is also a striking recent publication recommending the use of the SSIGN classification (28). In fact, it was stated that the calculated SSIGN score can be used to predict recurrence during 20-year follow-up after surgery. High scores were found to correlate with disease-related mortality. However, it should be kept in mind that classifications based on such clinical and pathological criteria may show significant intra- and inter-observer variations for reasons such as standardization differences in pathological evaluation.

As in other cancers, an individualized or tumor-specific risk estimation and treatment plan based on various genetic and molecular properties will be the most realistic approach both in theory and practice. This type of approach is currently used in clinical practice for breast cancer (29). There is no reason this cannot be done in renal cell carcinoma. Indeed, a study reported that analysis of 16 genes is valuable in prediction of recurrence in renal cell carcinoma (30). The patients in STRAC were evaluated based on data from this 16-gene assay and a "16-gene recurrence score" was developed for clinical use (31). As in breast cancer, providing personalized treatment using such genetic risk calculations also seems possible for renal cell carcinoma in the future.

Neoadjuvant Therapy

The most effective curative treatment currently available for renal cell carcinoma is surgery. Therefore, surgical treatment is initially considered for all eligible patients. This is also the case for patients with tumor thrombosis or locally advanced disease, and even metastatic patients with a single focus. In some patients, however, the excision of large masses invading surrounding tissues may not be surgically possible or may be highly risky. These cases may require an alternative to extensive surgery requiring adjacent organ resection or vascular graft, or a mass-reducing approach to make surgery more feasible. Similarly, alternative approaches that enable patients with a mass in their only kidney or patients with bilateral renal masses to avoid dialysis must also be considered. For example, a nephron-sparing approach may be possible for these patients if the mass can be reduced. Considering the fact that renal cell carcinoma is a radioresistant disease, effective systemic therapy is also needed for this purpose. Essentially, neoadjuvant systemic therapy is needed for two important reasons: to enable the removal of difficult and complex masses, and for mass reduction in order to facilitate nephron-sparing surgery.

Although questionable for angiogenesis inhibitors, one of the potential benefits of neoadjuvant therapy is the possibility of early control of micrometastases. Another potential benefit, however, is that it may offer the possibility of safe surgery for high-risk patients and reduce the likelihood of recurrence with systemic therapy. In addition, it may be possible to prevent disease progression while the patient is awaiting surgery, at least in theory.

For all of these reasons, targeted agents that are proven effective and have become standard in metastatic disease are being increasingly used in the neoadjuvant setting. Neoadjuvant applications, especially with targeted agents, appear in the literature first as case reports, then as small series. A review was also published recently (32).

On the other hand, the potential unfavorable consequences of neoadjuvant therapy should not be ignored. Targeted agents are known to cause serious adverse events. Developing some of these adverse events, such as cardiac toxicity, during the course of neoadjuvant therapy may result in a patient becoming ineligible for surgery, which offers a real chance at curative treatment. There may be progression while under neoadjuvant therapy and the patient may, for example, jump to the metastatic stage. Another drawback is the increased risk of perioperative morbidity after neoadjuvant therapy (33).

One of the possible theoretical benefits of neoadjuvant therapy is for metastatic patients. Although this application in metastatic patients is actually considered "pseudo-neoadjuvant", such an approach may become widespread in the future as a more rational method. Cytoreductive nephrectomy may be more meaningful for patients who respond to this type of (pseudo-) neoadjuvant therapy, and an unnecessary and risky surgical treatment with nephrectomy, for instance in a metastatic patient not responding to systemic therapy, can be avoided (34).

Which drug to use and for what duration have yet to be determined for neoadjuvant therapy. This section summarizes the current state of neoadjuvant applications.

Pre-nephrectomy Systemic Therapy Studies

In the first study to demonstrate the downsizing effect of sunitinib on primary tumors, treatment responses were reported for 17 patients with available abdominal tomography scans from a series of 22 patients (35). The Response Evaluation Criteria in Solid Tumors were used to measure treatment efficacy. According to these criteria, only 1 patient showed progression, 12 patients (71%) had stable disease, and 4 patients (24%) showed partial response. The authors reported a median tumor volume reduction of 31% and a median increase in mass necrosis volume of 39%. A total of 3 patients underwent nephrectomy and extensive necrosis was reported. Soon after, a more definitive series regarding the neoadjuvant use of sunitinib was published (36). In a series of 19 patients

who were initially ineligible for nephrectomy due to locally advanced disease or metastatic load, 9 patients (47%) had progression, 7 patients (37%) had stable disease, and 3 patients (16%) showed partial response. Reduction in primary tumor volume was seen in 8 patients (42%), with an average decrease of 24%. However, nephrectomy was possible in 4 of the 19 patients. No perioperative morbidity was reported. In a series of 28 patients in the same center, it was reported that neoadjuvant sunitinib resulted in a median tumor reduction of 28%, and nearly half of the patients were able to undergo nephrectomy (37). Similarly, another study reported decreased tumor diameter (mean reduction of 12%) in 17 (85%) of 20 patients treated with neoadjuvant sunitinib (38).

In a phase 2 trial on the neoadjuvant use of sorafenib, a mean reduction in tumor size of 10% was observed in 77% of patients (39). In a prospective, randomized, placebo-controlled trial of the same agent, a tumor volume reduction of 29% was reported in stage T1-3 patients in the sorafenib arm (40). There was no difference in survival during the 2-year follow-up period, and it was suggested that the tumor gained heterogeneity during treatment and that resistance to treatment may develop.

Different results have been reported for neoadjuvant targeted therapy in patients with inferior vena cava thrombosis. In a series of 5 patients with vena cava thrombosis who received sorafenib, tumor downsizing/downstaging was observed in 4 patients (41). On the other hand, in another series of 25 patients, regression of the thrombosis level was reported in only 3 patients treated with sunitinib (42). Similarly, in 14 patients with tumor thrombosis, neoadjuvant therapy resulted in thrombosis regression in only 1 patient (43). Therefore, there is not enough scientific evidence on the efficacy of neoadjuvant therapy in those with vena cava thrombosis.

Studies on Systemic Therapy for Nephron-sparing Surgery

One of the main reasons neoadjuvant therapy is needed is that it may enable the downsizing of large masses and thus facilitate nephron-sparing surgery. This approach may be necessary to allow patients with a mass in their only kidney or with bilateral renal masses to avoid hemodialysis.

On this topic, a 12-patient experience with sunitinib was reported in the first series presenting nephron-sparing surgery after neoadjuvant therapy (44). All of the patients had large or central masses. A mean reduction in tumor volume of 21% was observed and all of the patients were able to undergo nephron-sparing surgery. Surgical margins were tumor-negative in all cases. In another study, nephron-sparing surgery was planned after pazopanib therapy in 25 patients with large and central masses, 92% of the patients showed a reduction in tumor volume, and 20 were able to undergo nephron-preserving surgery (45). In addition, it was reported that neoadjuvant therapy enabled the preservation of a significant amount of renal parenchymal tissue. In a multicenter retrospective analysis, neoadjuvant sunitinib in 72 patients (78 kidneys) reduced tumor size by a mean of 32% and enabled nephron-preserving surgery in 63% of the kidneys (46).

These data show that neoadjuvant therapy has a place in the treatment of complex/central masses, especially if nephron-sparing surgery is needed.

Adverse Events and Complications

One of the main problems with neoadjuvant therapy is the side effects of the agents used. As mentioned in the previous section, large adjuvant therapy trials have demonstrated that patients can develop serious adverse events which can result in discontinuation of treatment. Hypertension and cardiac adverse effects are the most important. The ASSURE trial reported a potential adverse effect on left ventricular ejection fraction (47). Therefore, patients with limited cardiac reserve, for example, require a more cautious approach; the risk of being ineligible for surgery due to cardiac reasons after neoadjuvant therapy must be weighed, and it may even be necessary to perform surgery first.

It is also argued that the anti-angiogenic effect of targeted agents that suppress the VEGF system increase surgical morbidity (48). Due to the role of angiogenesis in wound healing, it has been claimed that there may be an increased risk of surgical site infection or urinary tract leakage due to neoadjuvant agents, but that the rate of serious complications (Clavien ≥3) remains unchanged (49). However, a significant increase (up to 25%) in the incidence of urinary leakage has also been reported (45).

Studies are needed to determine the necessary duration of neoadjuvant therapy. Available data suggest that tumor shrinkage usually occurs within the first 3-5 months. In this case, a presurgical 3-course treatment may be adequate for sunitinib, for example (33). The timing of treatment discontinuation prior to surgery is also important to ensure a minimum impact on wound healing. Authors stating that such complications do not change with neoadjuvant therapy suggest that discontinuation 24 hours before surgery is sufficient for sunitinib, although agents with a long half-life, such as bevacizumab, should undoubtedly be discontinued earlier (50). Some authors state that it is safer to discontinue treatment at least 2 weeks preoperatively (51). Based on the half-life of the drug being used, it may also be safe to discontinue therapy 2-3 times the half-life before surgery (52). This may in theory enable a low-risk approach in terms of disease progression by avoiding a long drug-free period. According to this, since the half-life of sorafenib is 1-2 days and the half-life of the active metabolite of sunitinib is about 4 days, it may be safer and more reasonable to discontinue sorafenib 3-4 days before surgery and discontinue sunitinib at least 1 week before surgery. This problem will be solved as agents with short half-lives become available.

Conclusion

Considering the FDA approval for high-risk patients based on STRAC data, an appropriate approach in current practice is to present adjuvant therapy to the patient as an alternative in light of clinical and pathological evaluations but also taking into account the possibility of adverse events. In the meantime, patients should definitely be informed about the high risk of adverse events and impaired quality of life. However, it should also be noted that the drug in question is not licensed for

adjuvant use in our country and is therefore not covered by social security reimbursement for this indication.

Neoadjuvant therapy utilizing more effective agents with safer adverse event profiles and short half-lives may be used more widely in the future. On the other hand, recent developments have prompted the initiation of clinical trials evaluating the neoadjuvant use of immunomodulatory agents in renal cell carcinoma. There is still a need for prospective, randomized, large-scale series to elucidate this topic.

Questions

1. Which targeted therapy agent has been approved by the Food and Drug Administration for adjuvant therapy following nephrectomy in renal cell carcinoma?

Sunitinib.

2. Which trial resulted in Food and Drug Administration approval of adjuvant therapy after nephrectomy in renal cell carcinoma?

STRAC.

3. Adjuvant therapy with which targeted agent was shown to confer an overall survival advantage in renal cell carcinoma?

There is no agent with a demonstrated overall survival advantage, prolonged disease-free survival was observed with sunitinib and pazopanib.

4. Neoadjuvant angiogenesis inhibitors may be associated with which surgical complications in particular?

Surgical site infection, impaired wound healing, and urinary leakage.

5. Considering the half-life of neoadjuvant sunitinib, discontinuing treatment at least how long before surgery may be safer in terms of surgical side effects?

One week.

Ethics

Peer-review: Externally peer-reviewed.

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Current Status of Oligometastatic Prostate Cancer: Risk Factors and Treatment Approaches

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Abstract

Prostate cancer (PCa) is a common disease that causes significant mortality rates. The widespread use of more sophisticated imaging methods has led to the identification of oligometastatic PCa, which has a limited number of metastases. Local therapy (radical prostatectomy and/or radiotherapy) for the primary tumor and metastasis-directed therapies have been proposed. A number of retrospective analyses have been conducted in this patient group to determine the place of systemic treatment, which is still the recommended standard treatment for metastatic disease. These studies were based on the aims of improving survival, protecting the patient from the potential side effects of systemic therapy, and eliminating local prostate-related symptoms. Although the studies were retrospective in nature, a survival advantage has been demonstrated in patients receiving local treatment or metastasis-directed treatments. It has been also shown in these studies that local treatment has no effect, at least no detrimental effect, on non-oncologic outcomes. However, these studies have significant limitations, primarily their retrospective design, differences in definitions and end-points used, and patient selection biases. Nevertheless, these results are clinically valuable and can be utilized in practice in some special cases. This patient group needs comprehensive standardization and risk stratification. Determining the definition, staging, treatment, and which patients will benefit from local treatment is essential. With ongoing prospective studies, it is expected that these uncertainties will be resolved and there will be revolutionary changes in the treatment of oligometastatic PCa in the near future.
Keywords: Metastatic prostate cancer, oligometastatic, radiotherapy, radical prostatectomy, survival

Introduction

Prostate cancer (PCa) is the second most common cancer in men worldwide with about 1.1 million new cases per year, and almost all patients have metastatic disease at time of PCa-related death (more than 300,000 deaths annually) (1). Current urology guidelines recommend treatment with androgen ablation alone or with chemotherapy as standard treatment for newly diagnosed metastatic PCa (mPCa) (2). There is ample evidence in the literature that mPCa is highly heterogeneous. Systemic disease may be less aggressive in nature with low metastatic burden, or it may be a highly aggressive form with diffuse metastases (3,4,5). For this reason, although there is no high-level evidence of a survival benefit with primary tumor debulking in oligometastatic PCa (oligo-mPCa), there is growing interest in surgical treatment for primary tumors in these cases.

Rational for the Treatment of Primary Tumor and Metastases in Oligometastatic Disease

Oligometastatic disease theory was first proposed by Hellman and Weichselbaum (5) in 1995. The authors suggested that progression is a step-by-step process, and that some tumors are at an intermediate level between localized disease and diffuse metastatic disease. This stepwise progression prediction has shown that a group of tumors with low metastatic burden may benefit from local and/or systemic treatment, and some may even

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be cured. The concept of oligometastatic disease and treatment of the primary tumor has been put forward and implemented in colon, lung, breast, and kidney tumors. For example, some colon tumors with a limited number of liver metastases may be cured by surgical treatment of the lesions and adjuvant therapy (6). It is also a well-known fact that cytoreductive nephrectomy in metastatic renal tumors prolongs overall survival and is performed in appropriate patients (7). European Organisation for Research and Treatment of Cancer and the Southwest Oncology Group have shown that nephrectomy prolongs survival by 13-36% in addition to systemic treatment (8,9). A meta-analysis of 6885 women with advanced-stage ovarian cancer revealed that mean survival was 33.9 months in patient groups with >75% maximal cytoreduction and 22.7 months in groups with <25% maximal cytoreduction (10).

History and Definition of Oligometastatic Prostate Cancer

Over the past 20 years, our knowledge of oligometastatic disease has increased (11). Improved imaging modalities and closer follow-up protocols have resulted in a greater number of patients diagnosed with limited metastatic disease (12,13). Many recent genetic and biological studies have shown that primary cancers, limited metastatic cancers, and widespread metastatic cancers actually have different biological behaviors (14,15,16). These findings suggest that not all tumors with limited metastatic lesions will become common metastatic disease, and may have a unique oligometastatic biology. Therefore, distinguishing these tumors from others is very important before planning an aggressive treatment (17).

Definitions of oligo-mPCa have been established based on lesion number by some authors and depending on their location by others. Most of the studies which defined it according to number accepted less than 3, 4, or 5 metastases, and only 1 study accepted less than 10 metastases as oligo-mPCa (18,19,20,21). The majority of the studies that defined it according to the metastatic location are based on bone or lymph node involvement, but in some prospective studies the classification was made according to extrapelvic involvement (22,23,24). On the other hand, Tabata et al. (25) accepted isolated bone metastases less than half the size of a vertebral body as the metastatic dimension in their definition of oligometastatic disease. The studies defining oligometastatic PCa according to the number, location, and size of the lesions are summarized in Table 1.

Specifically, the effect of a primary tumor-debulking surgery in oligo-mPCa was first described in 2015 by Heidenreich et al. (26). Patients had less than 3 skeletal metastases and prostate-specific antigen (PSA) levels were less than 1.0 ng/mL after neoadjuvant androgen deprivation therapy (ADT). Patients were divided into 2 groups: those who underwent radical prostatectomy (RP) and those who received only ADT. Median time to castration-resistant PCa was longer in the RP group (40 vs 29 months). In addition, patients treated with RP had longer progression-free (38.6 vs 26.5 months) and cancer-specific survival (CSS) rate (95.6 vs 84.2%). The authors concluded that cytoreduction was a feasible and safe treatment method with 39% overall complication rate and 56.5% urinary continence recovery rate.

There is a growing interest in local treatment for patients with mPCa, with the hope that local treatment can alter the course of metastatic disease and provide local tumor control, and with the expectation to give the patient the chance of curative treatment by reducing the need for palliative treatment. Patients with mPCa have a median survival of about 3-4 years, and like all oncology patients, deserve more effective treatments that may contribute to their survival (27).

Current Status of Oligometastatic Prostate Cancer Treatment

There is a large body of data showing the benefits of radical treatment in oligo-mPCa. However, studies in this area are largely retrospective analyses, and ongoing prospective, randomized trials are expected to provide higher quality evidence on this topic. Although the common opinion is that local treatment is feasible in these patients, we are confronted with the fact that the patients in these studies were better candidates for surgical treatment, which is an important factor leading to significant selection bias.

In the majority of these studies, oncologic outcomes such as cancer-specific mortality (CSM) and overall mortality rates and non-oncologic outcomes such as complications, blood loss, and length of hospital stay were evaluated and favorable results achieved. Local treatment in oligo-mPCa patients is an important issue for the surgical treatment of these patients, since the prostate has more local-invasive features and predisposes to more complications. This concern has been the subject of many studies and will also be mentioned below.

Culp et al. (28) first evaluated the oncologic outcomes of local treatment in mPCa patients. Patients were divided into 3 groups: those who did not receive local treatment, those who underwent RP, and those who received brachytherapy. Overall 5-year survival and predicted CSS rates were significantly higher in the local treatment groups ($p<0.001$). In addition, CSM was significantly lower in those who received local treatment ($p<0.01$). Leyh-Bannurah et al. (29) analyzed CSM in 13,692 patients in the Surveillance, Epidemiology, and End Results Program database. Both radiotherapy (RT) and RP provided lower CSM rates compared to those who did not receive local therapy ($p<0.001$). In addition, the authors also showed that RP provides lower CSM rates than RT ($p=0.048$). In a study by Satkunasivam et al. (30), 4069 patients with mPCa were retrospectively analyzed. CSM rate decreased by 52% with RP and by 62% with intensity-modulated RT. However, no favorable contribution of conformal RT to oncologic outcomes was observed (30). Another study by Rusthoven et al. (31) in which 538 of 6382 newly diagnosed mPCa patients received prostate RT showed that adding RT to ADT provided an overall survival advantage in both univariate and multivariate analyses. In a second analysis, no significant difference in survival was found between patients with RP added to ADT and patients with RT added to ADT (31). Similarly, Löppenberg et al. (32) classified 15,501 mPCa patients as local treatment and non-local treatment groups, with 9.5% of the patients receiving local treatment. Similar to other studies, they found that 3-year overall survival rates were better in those who received local treatment (69% vs 54%, $p<0.001$).

Although there have been numerous studies showing the benefit of local treatment, all were retrospective series and had selection bias. This limitation is mentioned by Parikh et al. (33), who noted that local treatment was often used in younger (<70 years) patients and patients with fewer comorbidities, lower T stage, lower Gleason score (<8), and lymph node-negative mPCa. In addition, the authors found that patients who received local treatment had a 50% lower risk of overall mortality than those who did not.

Oncologic outcomes as well as non-oncologic functional results of local oligo-mPCa treatment, particularly RP, are also a matter of curiosity. In these patients, there is a concern that the prostate may be more invasive and the planned surgical treatment may be more complicated, while on the other hand, there is also an emerging opinion that prostate removal may improve patients' quality of life by preventing local symptoms. Significant complications that may cause adverse consequences in advanced PCa are urinary retention that may require catheterization and transurethral resection, ureteral obstruction, hematuria that may require palliative RT, urinary diversion, and pelvic exenteration. The first single-center, single-surgeon study for mPCa patients receiving local treatment in the literature was published by Moschini et al. (34). Although the authors demonstrated favorable complication rates and functional results, they were not able to demonstrate a survival benefit compared to those who did not undergo RP. However, no information was given about the number of metastases in this study (34). In a study by Frazier et al. (35), the rate of symptomatic local progression was 24.6% in patients diagnosed with node positivity in frozen section analysis after pelvic lymph node dissection who did not undergo RP, and 9.5% in those who underwent surgery. Moreover, complication rates were 32.6% and 54.6%, respectively, when local treatment was applied in patients who developed castration-resistant PCa. The results of RP were better than RT (35). The morbidity and mortality associated with local treatment of multimodality therapy in metastatic disease is an important factor for clinicians as well as for patients. The studies evaluating oncologic outcomes of local treatment in oligo-mPCa are summarized in Table 2.

Table 1. Published and ongoing studies defining the number, location, and size of the lesions in oligometastatic prostate cancer

Study name	Author	Publication or initiation year	Maximum lesion number accepted as oligometastases	Metastatic lesion location
Radiotherapy for oligometastases and oligo-recurrence of bone in prostate cancer (25)	Tabata et al. (25)	2012	5	Bone, smaller than 50% of the vertebral body
Stereotactic body radiation therapy in the treatment of oligometastatic prostate cancer (60)	Ahmed et al. (60)	2012	5	NSM
Androgen deprivation and high-dose radiotherapy for oligometastatic prostate cancer patients with less than 5 regional and/or distant metastases (61)	Schick et al. (61)	2013	4	NSM
Salvage stereotactic body radiotherapy for patients with limited prostate cancer metastases: deferring androgen deprivation therapy (22)	Berkovic et al. (22)	2013	3	Bone or lymph node
Repeated stereotactic body radiotherapy for oligometastatic prostate cancer recurrence (23)	Decaestecker et al. (23)	2014	3	Bone or lymph node
Progression-free survival following stereotactic body radiotherapy for oligometastatic prostate cancer treatment-naive recurrence: a multiinstitutional analysis (58)	Ost et al. (58)	2016	3	NSM
NCT02563691	NA	2015	5	Outside the prostate and pelvic lymph nodes
NCT01859221	NA	2016	NSM	Any location other than the brain
NCT01777802	NA	2016	3	NSM
NCT02489357	NA	2015	4	Extrapelvic
NCT01558427	NA	2016	3	NSM
NCT02192788	NA	2017	4	Bone or lymph node
NCT00544830	NA	2016	5	NSM
NCT02264379	NA	2016	5	NSM
NCT02680587	NA	2016	3	Bone or lymph node
NCT02020070	NA	2016	10	Bone or lymph node

NSM: Not specifically mentioned, NA: Not available

Heidenreich et al. (26) found similar complication rates to those with high-risk localized disease in 23 patients who underwent RP in metastatic disease. The researchers also emphasized that local progression symptoms developed in 28.9% of 38 patients who did not undergo surgery, and none of the patients who underwent surgery developed these symptoms (26). Similarly, Sooriakumaran et al. (36) showed that cytoreductive surgery was safe in 106 mPCa patients, with 20.8% of the patients complication-free after surgery. Steuber et al. (37) compared complication rates in patients with and without RP. Interestingly, the local complication rate was 7% in the RP-treated group and 35% in the supportive care group (37). The studies evaluating the functional outcomes of local treatment in mPCa patients are summarized in Table 3. There are limited data on functional outcomes due to incomplete information in the databases of multicenter studies. It is inevitable that potency rates will be lower in this patient group because none of the mPCa patients are treated with nerve-sparing surgery and these patients may require ADT (26,36). Hormonal therapy may adversely affect postoperative continence rates as well as potency rates (38).

Risk Stratifications That Predict Treatment Success in Oligometastatic Prostate Cancer

There has been growing interest over the last 20 years in the curing effect of local treatment in oligometastatic disease. The oligometastatic status of these patients should be validated in detail and a stratification system based on clinical and genetic factors is required. First, a definite consensus on the definition of oligometastatic disease should be established, optimal imaging modalities should be identified, clinical and molecular factors predicting disease progression in hormone-sensitive metastatic disease should be identified, and treatment approaches should be optimized. There is a strong need for risk prediction systems, and a risk stratification of these patients is expected with the completion of ongoing prospective clinical trials.

For clinical use, a useful risk stratification system requires molecular classification of genetic, genomic, epigenetic, and microenvironmental factors that affect disease outcomes. An important issue for the definition of oligometastatic disease is the standardization of the imaging methods utilized for diagnosis. The most commonly used imaging modalities for advanced PCa staging are cross-sectional imaging with computed tomography (CT) and magnetic resonance imaging or functional imaging with 99m-Tc-methylene diphosphonate planar scintigraphy or single-photon emission CT. The low sensitivity of these imaging modalities is an obstacle to their acceptance as a gold standard for routine use in risk classification. Gallium-68-prostate-specific membrane antigen (PSMA)-11 is one of the most sensitive radiotracers and may identify metastatic disease in 54% of

Table 2. Summary of studies evaluating oncologic outcomes in oligometastatic prostate cancer

Author	Journal, publication year	Intervention	Accepted oncologic outcome	Result
Culp et al. (28)	Eur Urol, 2014	RP, BT, NLT	5-year OS and CSS	Survival rates were higher in local treatments, in most RP group
Antwi and Everson (62)	Cancer Epidemiol, 2014	RP, BT, NLT	OS and CSS	Survival rates were higher in local treatments, in most RP group
Fossati et al. (63)	Eur Urol, 2014	RP, BT, NLT	CSS and CSM	LT provided a survival benefit if predicted 3-year CSM risk <40%
Leyh-Bannurah et al. (29)	Eur Urol, 2017	RP, BT, NLT	CSM	LT provided a better CSM ratio, LT was most beneficial in patients <1 risk factor
Rusthoven et al. (31)	JCO, 2016	RP, NLT	OS and OM	RP provided better OS and OM
Löppenberg et al. (32)	Eur Urol, 2016	RP, BT, NLT	OS and OM	In the LT group, the survival rate was higher and the mortality rate was lower
Parikh et al. (33)	The Prostate, 2017	RP, IMRT, NLT	OS and OM	5-year survival rate favored LT (RP > IMRT > NLT). The 3-year OM risk was similar in LT and NLT groups
Gratzke et al. (54)	Eur Urol, 2014	RP, NS	OS	5-year survival rate favored RP
Heidenreich et al. (26)	J Urol, 2015	RP, NLT	OS, CSS, PFS	All 3 factors were in favor of RP
Sooriakumaran et al. (36)	Eur Urol, 2015	RP	OM	OM rate was 11.3%
Gandaglia et al. (4)	Eur Urol, 2016	RP + ePLND	CSS, PFS	The 7-year CSS and PFS rates were 82% and 45%, respectively
Steuber et al. (37)	Eur Urol Focus, 2017	RP, BST	OS	No significant difference
Bianchini et al. (64)	Clin Genitiurin Cancer, 2017	LRT, NLT	OS, OM	Median OS and OM rates were in favor of LRT
Cho et al. (65)	PloS One, 2016	RT, NLT	OS, OM	3-year survival rate favored RT, OM ratio was lower in RT group
Jang et al. (66)	BJU Int, 2017	RALP, ADT	CSS, CSM	Both factors were in favor of RALP

RT: Radiotherapy, RP: Radical prostatectomy, BT: Brachytherapy, NLT: No local treatment, OS: Overall survival, CSS: Cancer-specific survival, CSM: Cancer spesific mortality, LT: Local treatment, OM: Overall mortality, IMRT: Intensity-modulated radiation therapy, NS: No surgery, PFS: Progression-free survival, ePLND: Extensive pelvic lymph node dissection, BST: Best supportive care, LRT: Locoregional treatment, RALP: Robot-assisted laparoscopic prostatectomy

patients with a PSA value below 1.0 ng/mL, but is currently not widely available (39).

Thompson et al. (40) published the first prospective evidence that treatment of primary PCa in metastatic disease may reduce mortality. Factors associated with shorter overall survival were widespread disease (appendicular skeletal and/or visceral involvement), bone pain, Gleason score >8, and black race. Testosterone at castration level prior to treatment was also associated with poor survival.

Many studies have emphasized the genomic heterogeneity of PCa. It has been shown that every tumor does not respond to systemic treatment in the same way and that genomic differences result in a potentially high- or low-risk phenotype (41). Unpublished data of an ongoing study indicated that a group of metastatic hormone-sensitive mPCa patients with a distinct biological phenotype had a 10-year survival rate of 17%. In many studies, molecular characterization of primary PCas has been used to assess disease aggressiveness and response rates, but none have specifically evaluated oligometastatic disease (42,43).

Zhao et al. (42) utilized a molecular marker called PAM50, routinely used in breast cancer, in patients undergoing RP. Luminal A subtype had the best prognosis, but only the luminal B subtype benefited from ADT after prostatectomy (42). Nguyen et al. (43) used a molecular marker called Decipher in 235 patients undergoing RP or RT, and reported that biopsy Decipher score was associated with metastatic disease development and PCa-specific mortality. Spratt et al. (44) reported that metastatic risk and PCa-specific mortality could be better predicted by combining the National Comprehensive Cancer Network clinical risk factors and Decipher score. Although none of these genomic tests have been validated in oligometastatic disease, the development of a clinically beneficial risk stratification system is anticipated with the completion of ongoing studies.

Treatment Approaches in Oligometastatic Prostate Cancer

Whether oligo- or widely metastatic, standard treatment for PCa is long-term palliative ADT with or without chemotherapy. There is a growing body of data about whether primary tumor treatment with stereotactic body RT (SBRT) or RP in oligometastatic disease will improve survival, slow symptomatic disease progression, and reduce the need for palliative surgery (3,45). The 3 main treatment modalities for oligo-mPCa are systemic therapy, primary tumor therapy, and metastasis-directed therapy (MDT).

ADT is still the standard recommended treatment in metastatic disease. Recently, the STAMPEDE, CHARTEED, and GETUG-15 studies have revealed data that support the use of docetaxel with ADT. The outcomes of these studies have shown improved survival and prolonged time to castration-resistant disease (46). However, there is insufficient evidence for a specific recommendation for the oligometastatic patient subgroup. Patients with diffuse metastases have a much higher risk of catastrophic complications such as pathological fractures, spinal compression, and renal insufficiency. Therefore, the application of early ADT in these patients reduces these risks (47). The risk of these complications is much lower in oligometastatic disease. Considering the adverse effects of ADT on morbidity and quality of life, it seems logical to pursue alternative treatments in this group of patients. Despite continuing research for new treatments in oligometastatic patients, docetaxel therapy with ADT is still the standard treatment approach in many urological centers.

It has been shown that cytoreductive or radical surgery to reduce primary tumor burden and RT improve survival in colon, breast, ovarian, and kidney cancers (10,48,49). It has also been shown that radical surgery improves survival in metastatic disease in glioblastoma, renal cell carcinoma, and colorectal cancer (8,50,51). The exact reason underlying these consequences is not fully understood, but the "soil and seed" hypothesis is a logical theory. According to this theory, the tumor cell needs a suitable micro-environment to settle in the metastasis zone. In some studies, it has been shown that primary tumor foci release membrane vesicles, proteins, and nucleic acids that feed the metastatic nest in the locations where circulating tumor cells are located (52,53). In addition, the genetic pathway between primary foci and metastatic foci may also contribute to disease progression. Severing this link by removing the primary tumor may alter the tumor physiology and contribute to the regression or downsizing of metastatic foci.

Table 3. The summary of studies evaluating the functional outcomes of local treatment in metastatic prostate cancer patients

Author	Journal, publication year	Intervention	Summary of complication comparison
Sooriakumaran et al. (36)	Eur Urol, 2015	RP	Overall complication rate was 20.8%
Steuber et al. (37)	Eur Urol Focus, 2017	RP, BST	Severe local complications were 7% and 35% in RP group and BST group, respectively
Jang et al. (66)	BJU Int, 2017	RALP, ADT	There were no urinary tract complications in the RALP group, while complication rate was between the range 2.4-14.6% in the ADT group
Heidenreich et al. (26)	J Urol, 2015	RP, NLT	Complication rates were similar in both groups
Gandaglia et al. (4)	Eur Urol, 2016	RP + ePLND	18% Clavien 1 and 2, and 0% Clavien 4 and 5 complications
Cho et al. (65)	PloS One, 2016	RT, NLT	While no complications were seen in the NLT group, none of the complications in the RT group were more than grade 3

RT: Radiotherapy, RP: Radical prostatectomy, NLT: No local treatment, ePLND: Extensive pelvic lymph node dissection, BST: Best supportive care, RALP: Robot-assisted laparoscopic prostatectomy, ADT: Androgen deprivation therapy, PloS: Public Library of Science

Although there is currently no prospective study showing that primary tumor treatment improves survival in mPCa, there are retrospective studies demonstrating this aforementioned benefit. The Southwest Oncology Group 8894 study in which 1286 mPCa patients were analyzed showed that the risk of death was lower in those who previously underwent RP than those who did not (40). Recent analyses from large databases have shown that 5-year survival in mPCa patients treated with radical therapy is higher than those who received systemic treatment alone (28,54). Clinicians are concerned that RP will be more complicated in these patients and will cause more morbidity and mortality. However, this does not seem to be the case. For example, Sooriakumaran et al. (55) showed in a large number of mPCa patients that cancer-related mortality rate was 3 times higher among those who did not undergo radical treatment compared to those who did. Similarly, in a Swedish study, radical treatment in very high-risk PCa patients was shown to reduce overall mortality (56). In the literature, there is growing evidence that radical or cytoreductive local treatment will contribute to survival in metastatic disease, as long as patients are selected appropriately and the intervention is performed in an adequately experienced center.

The concept of MDT emerged from the concern that metastatic foci could also act as primary foci and lead to other distant metastases. MDT is considered for cases of true oligo-mPCa with a few metastases (3 to 5). The main purpose is to control cancer progression, prevent the development of other metastases, and improve quality of life by reducing the need for systemic treatment (5). MDT is routinely recommended in colorectal, sarcoma, and renal cell carcinomas. Studies are usually based on retrospective series and MDT is usually performed in metachronous oligometastases. In a systematic review of 7 studies reporting the outcome of patients receiving MDT for metachronous metastases following primary PCa treatment, 51% of patients were progression-free at 1-3 years after MDT (57). In these studies, MDT was performed as surgical metastasectomy or RT. In a study including 119 metachronous oligo-mPCa patients from different centers, a dose-dependent survival advantage with SBRT was detected; higher doses of radiation provided better survival outcomes (58). The results of all these studies indicate that MDT may be a useful treatment modality for metastatic recurrence of PCa and that the implementation of appropriate local therapies may allow systemic therapy to be delayed in patients with limited metastases (59). However, there is uncertainty regarding the application of these treatments in synchronous metastases. Prospective, randomized trials are likely to answer the question of whether SBRT should be performed alone or in conjunction with RP or RT in synchronous disease. These results are needed before offering these treatments as standard therapy.

Future Expectations and Recommendations Regarding Local Treatments for Oligometastatic Prostate Cancer

Current data in the literature suggest that local treatments and MDT in mPCa patients are safe and effective. However, using aggressive treatments such as radical surgery in metastatic disease is still a controversial issue. Existing studies are based on retrospective series and only a few studies include an appropriate control group. The design, endpoints, disease definitions, and analysis quality of these studies are highly heterogeneous. Important information such as comorbidities, performance status, baseline PSA information, and the number of metastases that play an important role in survival are missing in some studies. Although a few studies have used propensity score adjustment, the patients treated with local treatment are usually meticulously selected patients and this constitutes an important selection bias.

For now, this treatment modality is in its infancy and a definitive judgment must await the results of ongoing prospective studies. Currently, many randomized controlled trials (e.g. NCT00268476, NCT02454543) are seeking an answer to whether local treatment offers a survival benefit over systemic treatment in mPCa. Currently, aggressive treatment in mPCa can be recommended only in prospective studies approved by an ethics committee or in the context of a prospective registry of patients having severe morbidity due to the disease. Patients should be informed in detail about the possible benefits and risks of treatment, and their treatment and follow-up should be planned by a multidisciplinary team including a urologist, oncologist, and radiation oncologist.

The optimal treatment of oligo-mPCa will likely become clear in the next few years and clinicians will be able to offer their patients evidence-based therapy. There are advances in diagnostic methods as well as treatment methods; for example, the staging of patients with novel methods such as PSMA-positron emission tomography has emerged, which will influence the number of patients diagnosed with mPCa. Undoubtedly, diagnosis and treatment are 2 closely related modalities and will continue to coevolve.

Conclusion

Low-volume mPCa is a very heterogeneous disease subgroup within PCa. There is no consensus on the definition, classification, or treatment of the disease. Currently, the widely accepted definition of oligometastatic PCa is the presence of fewer than 5 metastatic lesions that can be detected by imaging modalities. Current data suggest that RP or RT may be safely administered to these patients and may reduce the need for future palliative care. MDTs such as SBRT may also contribute to local cancer control and have low morbidity. At the moment, there is insufficient evidence to make a definitive judgment regarding the impact of aggressive treatments on overall survival or CSS rates. However, at present, the most appropriate approach seems to be the rational use of local treatments as well as systemic treatments after appropriate patient selection and comprehensive clinical evaluation. The genetic and biological characteristics of cancers are also being investigated and this information is expected to contribute to treatment approaches. With the results of prospective, randomized controlled trials, significant changes in disease management are expected in the near future.

Questions

1. Currently, what is the most commonly accepted definition for oligometastatic prostate cancer?

2. What is the physiological mechanism of local treatment in oligometastatic prostate cancer and what is the expected benefit from this treatment?

3. What are the recommended treatment options and the recommended indications for oligometastatic prostate cancer?

4. What are the common endpoints of ongoing prospective studies regarding oligometastatic prostate cancer treatment?

Ethics

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Case Report

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A Rare Tumor: Small Cell Prostate Carcinoma Case Report

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Abstract

Prostate small cell carcinoma is a rare and aggressive tumor. They can be distinguished from classic prostate adenocarcinoma by features such as lack of prostate-specific antigen secretion, failure to respond to androgen suppression therapy, osteolytic bone lesions, and visceral metastasis. Herein, we present a case of previously diagnosed prostate adenocarcinoma that transformed to prostate small cell carcinoma, together with a discussion of the current literature.

Keywords: Prostate cancer, small cell carcinoma, prostate-specific antigen, survival

Introduction

Prostate cancer is the second most common cancer in men (1). Prostatic small cell carcinoma (PSCC) is a rare and aggressive tumor. It accounts for 0.5-2% of all prostate cancers (2) and the mean age at detection is 65 years (3).

Although Wenk et al. (4) first described PSCC in 1977, their biological behavior remains unclear (5). PSCC has features unlike prostate adenocarcinoma such as lack of prostate-specific antigen (PSA) secretion, nonresponse to androgen suppression therapy, and formation of osteolytic bone lesions and visceral metastases, and follows an aggressive course (6).

Due to the absence of androgen receptors in PSCC cells, it is hormone-resistant and is currently treated similarly to small cell lung cancer (5). Prognosis is poor, with only a few cases of complete remission reported in the literature (7).

In this article, we describe the development of PSCC in a patient who was diagnosed with prostate adenocarcinoma but could not be followed regularly, and discuss the case in light of the literature.

Case Presentation

An 87-year-old male patient was referred to our clinic in May 2017 due to bladder perforation that occurred during passive transurethral resection of the prostate (TURP) at another center. According to the patient's history, TURP performed in 2013 due to PSA level of 84 ng/mL resulted in a diagnosis of prostate adenocarcinoma (Gleason score: 4+3) and hormone therapy was recommended, but his treatment adherence was poor.

The discharge report from the other medical center indicated that prior to TURP, the patient's prostate was grade-3 in size, hard and fixed on rectal examination, PSA was >100 ng/mL, and urinary system ultrasound (US) showed grade-2 dilation in the collecting systems of both kidneys and a 40x21 mm mass in the bladder base that was evaluated as a prostatic invasion of the bladder.

Abdominal US performed during TURP due to the development of abdominal distension showed free fluid in the abdomen. A peroperative drain was placed in the abdomen and the patient was referred to our clinic for further examination and treatment. On physical examination, the abdomen was painless

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with no distention or rebound. Laboratory results showed creatinine level of 3.4 mg/dL, leukocyte count of 10,310/mm^3, hemoglobin level of 12.9 g/dL, and the other laboratory values were within normal range. Under local anesthesia, the patient underwent bilateral US-guided percutaneous nephrostomy. The patient's leukocyte and creatinine values returned to normal range during follow-up. The abdominal fluid resolved and the drain was removed, followed by the urethral catheter.

The pathology report for the TURP indicated 90% small cell carcinoma and 10% prostate adenocarcinoma (Gleason score: 4+3). The tumor showed occasional irregular cribriform pattern in the acinar cell carcinoma areas, while small cell carcinoma morphology showing solid layering was seen in the large areas. Tumor cells in these areas had relatively uniform, narrow cytoplasm and coarse chromatin pattern. In immunohistochemical staining, the small cell carcinoma areas were CD56, chromogranin, synaptophysin, thyroid and transcription factor-1 (TTF-1) positive; cytokeratin focal positive; PSA, prostate-specific acid phosphatase (PSAP), and alpha-methylacyl-coenzyme A racemase (AMACR) negative, and Ki67 index was 80% (Figures 1 and 2). No metastatic lesions were detected in contrast-enhanced thoracic and whole-body computed tomography scans conducted for staging purposes. Whole-body bone scintigraphy (WBBS) revealed multiple areas of increased uptake in the thoracic and lumbar vertebrae, the costa, and both acetabulums, and the patient was started on maximal androgen blockade (MAB) therapy and referred to the medical oncology department for chemotherapy. It was learned that the patient did not present to medical oncology and died 2 months later.

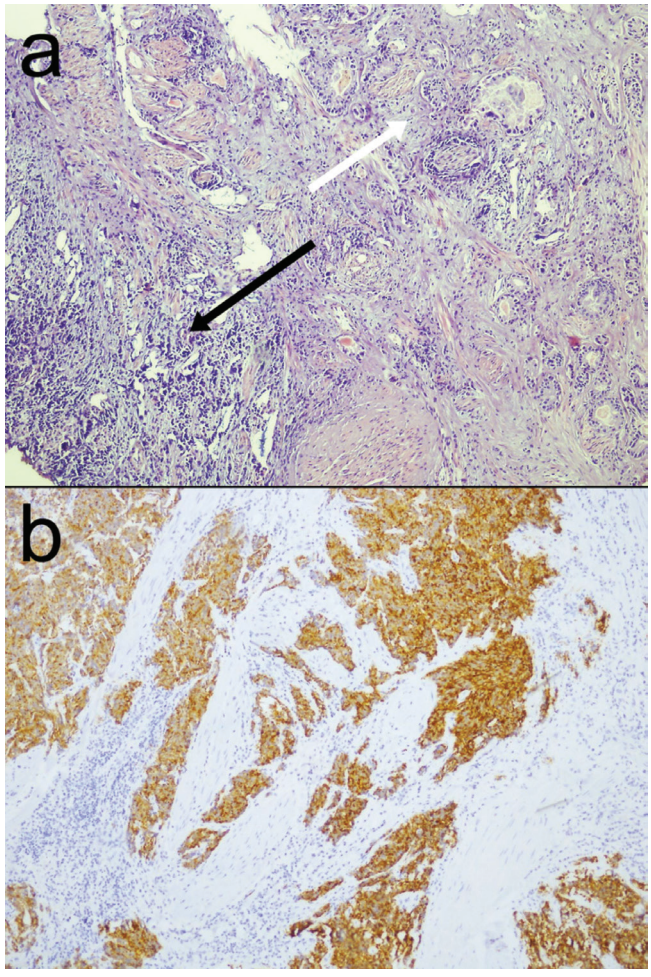

Figure 1. a) Prostate adenocarcinoma with perineural invasion in the upper right area, prostate small cell carcinoma in the lower left (hematoxylin and eosin; 100x); b) Cytoplasmic synaptophysin staining in tumor cells showing diffuse stratification (immunohistochemistry, synaptophysin; 100x)

Discussion

Histologically, most prostate cancers are adenocarcinomas originating from prostate glandular cells. PSCC is a rare and aggressive malignancy of the prostate, with a mean age at diagnosis of 65 (3).

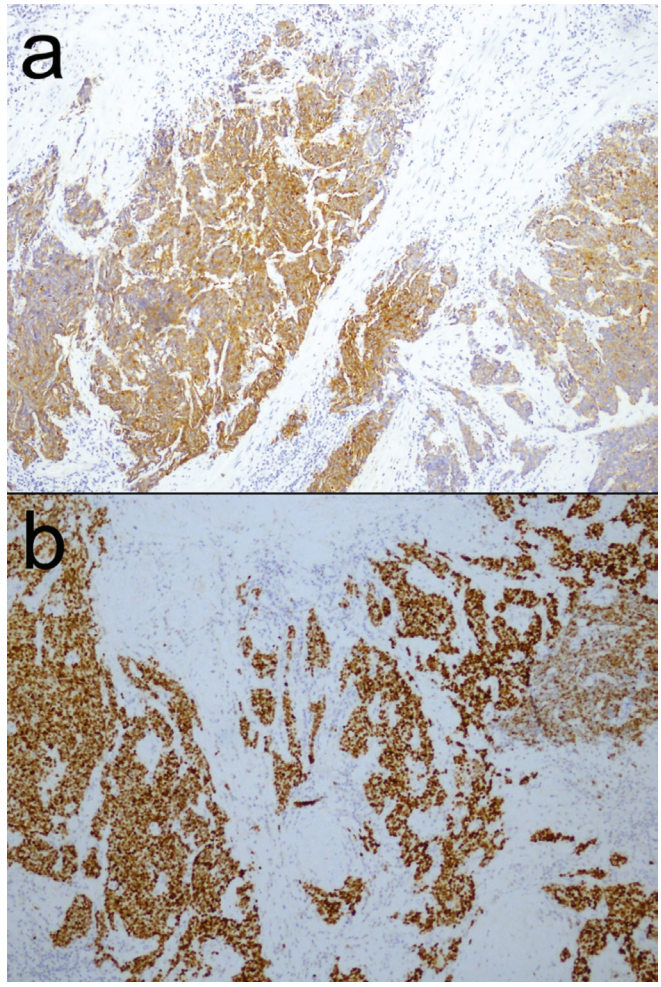

Figure 2. a) Cytoplasmic chromogranin staining in the prostatic small cell carcinoma component (immunohistochemistry, chromogranin; 100x); b) nuclear thyroid and transcription factor-1 staining in the prostatic small cell carcinoma component (immunohistochemistry, thyroid and transcription factor-1; 100x)

There are various theories regarding the origins of PSCC. In patients previously diagnosed with prostate adenocarcinoma, it is believed to arise due to adenocarcinoma cell transformation or to neuroendocrine cell proliferation induced by antiandrogen therapy, and due to neuroendocrine differentiation after radiotherapy in some patients (8). Another theory suggests that the neuroendocrine component originates from malignant transformation of normal prostate cells or pluripotent epithelial cells (5).

Approximately 50% of patients have pure small cell histology at time of diagnosis, while 25-50% have mixed prostate adenocarcinoma and small cell carcinoma. In about 25-40% of patients, initial diagnosis is adenocarcinoma only, but relapse occurs after hormone therapy as a combination of small cell carcinoma and adenocarcinoma (9). In the present case, the patient was initially diagnosed with prostate adenocarcinoma, underwent hormone therapy, and relapsed with PSCC and adenocarcinoma.

PSSC can be differentiated from classic adenocarcinomas through clinical behavior such as the formation of osteolytic bone and visceral organs metastasis and the presence of normal PSA level (5). In addition, staining of biopsy specimens is negative for androgen receptors (10). The most commonly used immunohistochemical markers for the tumor are neuron-specific enolase (NSE), chromogranin, synaptophysin, CD56, and TTF-1 (11).

Wang and Epstein (9) performed immunohistochemical studies on 95 patients with PSCC and showed that 92% stained positive for CD-56 and 85% were positive for synaptophysin. These features facilitate the differentiation of PSSC from poorly differentiated acinar adenocarcinoma. Moreover, PSA and NSE were not detected in 14 hormone-resistant prostate carcinomas, while high serum chromogranin A levels were detected in 10 cases. Early detection of high chromogranin A levels may be an indicator to switch to a more aggressive treatment (9).

In the biopsy specimen obtained from our patient, some areas other than the prostate adenocarcinoma areas stained positive for CD56, chromogranin, synaptophysin, and TTF-1 but were negative for PSA, PSAP, and AMACR, leading to a diagnosis of PSCC in addition to prostate adenocarcinoma (Figure 1, 2).

These patients do not exhibit the expected increase in PSA level based on their prostate enlargement and the presence of metastatic disease (12). We attributed the elevated PSA in our patient to the prostate adenocarcinoma component of the tumor.

There is still no specific treatment for PSCC. The lack of androgen receptors in the PSCC cells renders hormone therapy ineffective (6). Prostate-limited tumors can be removed by radical prostatectomy (7).

Approximately 75% of patients have metastatic disease at the time of diagnosis. Metastases are usually in lymph node, liver, bone, lung, and brain, but there have also been occasional cases reported with metastases in locations such as the omentum, adrenal gland, and facial bones (13).

PSCC has similar morphological features to small cell lung cancer. Although a standard chemotherapy regimen has not been established for the treatment of metastatic PSCC, platin-based chemotherapy is generally used. Even if there is an initial response, this chemotherapy regimen is not an effective standard treatment (14). Radiotherapy is used to control local disease or as a palliative treatment option for patients with disseminated disease. Prognosis is poor, with an average survival of 6-17 months after diagnosis (15). In a study including 30 patients, Stein et al. (16) reported a remission of 54 months after chemotherapy in only 1 patient. The patients' mean survival time was 13 months (16). In another study, Cohen et al. (17) reported a 2-year survival rate of 97% for patients with adenocarcinoma versus 35% for patients with PSCC, and noted that PSCC metastasizes rapidly.

In the present case, no visceral metastasis was detected in CT, while WBBS revealed multiple bone metastases, and the patient was started on MAB therapy and referred to medical oncology. The patient did not present to medical oncology and died a short time (2 months) after diagnosis.

PSCC is a rare and aggressive cancer and its clinical behavior differs from that of prostate adenocarcinoma. Although the treatment approach is similar to that used for small cell lung cancer, a standard treatment regimen not yet been established. PSCC becomes metastatic quickly and has a poor prognosis with short survival times, unlike classic prostate adenocarcinoma.

Ethics

Informed Consent: It wasn't taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.B., Concept: M.E.A., D.B., Design: T.D., Data Collection or Processing: F.T., Analysis or Interpretation: T.D., B.G., Literature Search: M.E.A., Writing: M.E.A.

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

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Case Report

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Granulomatous Prostatitis: Case Report and Review of the Literature

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Abstract

Granulomatous prostatitis, first described by Tanner and McDonald in 1943, is a histopathological diagnosis that includes mixed type inflammation with granulomas in the prostatic tissue. Granulomatous prostatitis comprises 0.8-1% of benign inflammatory conditions of the prostate. Prior surgery, intravesical bacillus Calmette-Guérin treatment, or systematic tuberculosis are some causes of granulomatous prostatitis. It mimics prostate cancer clinically, histologically, and biochemically. Granulomatous prostatitis has a specific and nonspecific type, with the nonspecific type being more common. In this study, we report a patient who had high prostate-specific antigen level and underwent transrectal ultrasound-guided prostate biopsy, and histologic examination revealed nonspecific granulomatous prostatitis.

Keywords: Granulomatous prostatitis, prostate-specific antigen, prostatitis

Introduction

Urinary tract infections, benign prostatic hyperplasia, and stone diseases are among the most common pathologies of the urinary system. Prostatitis accounts for 10-14% of urinary tract infections. Unlike the more common acute bacterial prostatitis (98-99%), chronic bacterial prostatitis, chronic pelvic pain syndrome, and asymptomatic prostatitis, granulomatous prostatitis (GP) accounts for less than 1% of all cases of prostatitis and its etiology is unknown. GP can often be seen after surgical interventions and intravesical bacillus Calmette-Guérin (BCG) therapy. In this study, we present a case of GP detected in a patient who underwent transrectal ultrasound (TRUS)-guided prostate biopsy for suspected prostate cancer after testing revealed elevated serum prostate-specific antigen (PSA) level.

Case Presentation

A 63-year-old male patient presented to our clinic with complaints of dysuria, pollakiuria, and nocturia. He had no history of treatment for prostate infection or prior prostate or bladder surgery. On physical examination, digital rectal examination was normal, there were no signs of suprapubic tenderness, and systemic examination was normal. Routine blood and urine analysis showed serum PSA level of 9.32 ng/mL and free PSA level of 0.907 ng/mL. Urinalysis was normal. Based on these findings, TRUS-guided prostate biopsy was performed due to suspected prostate cancer. Biopsy results indicated non-necrotizing GP. The patient was followed in our clinic to monitor his serum PSA level. Three months later, his serum PSA level was 8.4 ng/mL.

The patient provided informed consent for this case report.

Discussion

GP, which was first described by Tanner and McDonald (1) in 1943, is a histopathological diagnosis characterized by mixed-type inflammatory granulomas of the prostate. GP can be bacterial, fungal, parasitic, or viral and the mixed inflammation includes histiocytes, lymphocytes, and plasma cells. Pathologic examination in our case revealed well-defined granulomatous

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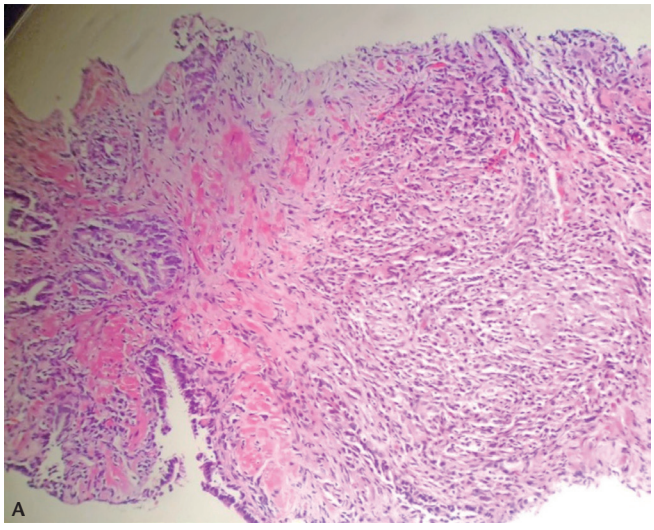
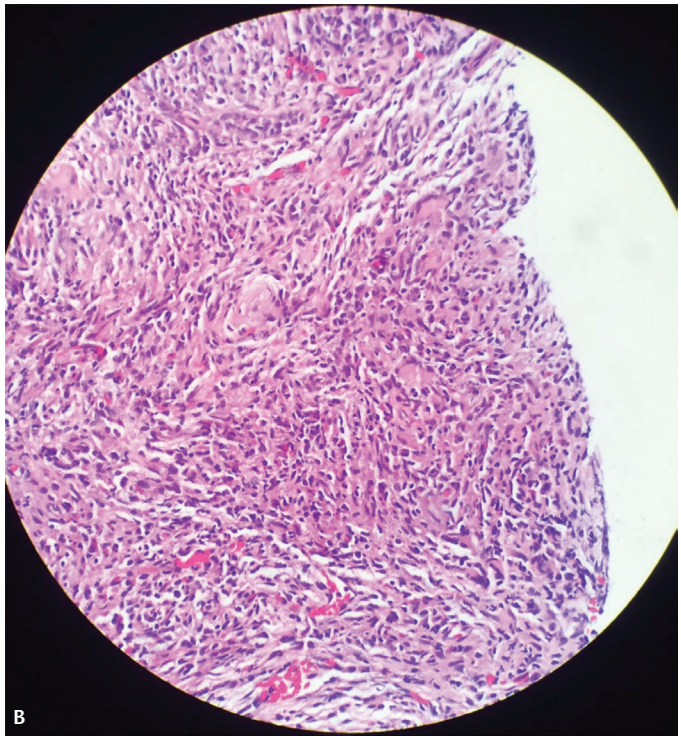
structures containing a central giant cell surrounded by lymphoplasmacytic cells (Figures 1A, B).

GP comprises 0.8-1% of benign inflammatory prostate disease. The nonspecific GP is the most common type, accounting for 77% all cases. Clinically, 59% of cases present with prostate lumps or hardness, mimicking prostate cancer (2). PSA levels may be normal or elevated. Histopathologically, 4% of nonspecific cases mimic prostate cancer with high Gleason grade (3).





Figures 1A, B. In the examined sections, giant glandular structures lined with 2 rows of epithelium and large and small granulomatous structures consisting of histiocyte clusters with multinuclear giant cells which in some areas replace the gland are observed in the fibromuscular stroma

Concomitant prostate cancer was not observed in our patient during follow-up. Although the etiopathogenesis of the disease remains unclear, urinary infections, surgical interventions involving the prostate, and intravesical BCG therapy have been implicated in the etiology. In 1981, Hedelin et al. (4) first described GP in 6 patients who underwent transurethral prostate resection (TURP). In 1986, Helpap and Vogel (5) reported that they detected GP in 7.1% of 2850 prostate specimens examined. They suggested that electrocautery was the causative factor of GP, as in previous experimental studies. While GP after TURP was reported as rheumatoid granulomas in pathologic examination, GP after BCG presents as tuberculous granulomas. Leibovici et al. (6) observed serum PSA levels in 75% of 36 patients after intravesical chemotherapy treatment and therefore associated it with GP.

GP can occur after both intravesical and systemic BCG administration. In a study evaluating radical prostatectomy specimens, the incidence of GP in BCG patients was 1-27% (7). Another cause of GP is the injection of Teflon material into the bladder neck as treatment for urinary incontinence. It has been reported that nonspecific GP develops as an autoimmune reaction via human leukocyte antigen-15-mediated T cell response to certain proteins, particularly those found in prostate secretions such as PSA (8). It is also proposed that GP may be an autoimmune disease. Rarely, GP can coexist with systemic granulomatous diseases such as Wegener's granulomatosis. Nonetheless, it is referred to as nonspecific GP because a specific cause cannot be determined in the majority of patients, similar to our case.

In various series, GP has been reported in 0.36-11% of patients after TRUS-guided biopsy for suspected prostate cancer. Herranz et al. (9) reported detecting GP at a rate of 1.5% after TRUS-guided biopsy in 1835 patients. It has been proposed that prostate secretions due to the biopsy procedure and substances secreted by various bacterial agents have a role in the etiology of GP in cases of nonspecific prostatitis after TRUS-guided biopsy. Patients with GP may present with storage and voiding symptoms or complaints of pelvic pain, or they may be asymptomatic. As in the present case, this pathology may also manifest with normal digital rectal examinations but elevated PSA levels. For this reason, GP can mimic prostate cancer clinically and histologically. However, this increase in PSA level is usually transient and associated with other factors such as infection, retention, and diagnostic interventions. Because most cases are nonspecific, they regress spontaneously without requiring treatment. In some studies, however, antibiotic and cortisone therapy was reported to dramatically improve symptoms and lower serum PSA to normal levels. Therefore, although rare, GP should be considered in patients with elevated serum PSA or who exhibit serum PSA elevation after TRUS-guided biopsy.

Ethics

Informed Consent: The patient provided informed consent for this case report.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.D.G., Concept: T.N.Y., E.Ö., Design: E.Ö., Data Collection or Processing: M.D.G., T.N.Y., Analysis or Interpretation: H.B., Literature Search: M.D.G., T.N.Y., Writing: M.D.G.

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

Financial Disclosure: The authors declared that this study received no financial support.

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