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# About Us

The Bulletin of Urooncology is the official journal of the Turkish Urooncology Association. The Bulletin is an independent, peer-reviewed, international journal published quarterly in March, June, September, and December.

The Bulletin accepts research articles in the basic and clinical sciences, reviews of current topics, relevant surgery videos and extraordinary case reports for publication.

The main aim of the journal is to enable all physicians-especially urologists to access research findings from the urooncology field quickly and effectively. It also contributes to physicians' vocational training with specific numbers of reviews, surgery videos and case reports.

The Bulletin accepts manuscripts through an online submission system. Free access to full text versions is provided to members through the website and mobile applications.

**SUBMISSION, PROCESSING AND PUBLICATION ARE FREE OF CHARGE. NO FEES ARE REQUESTED FROM THE AUTHORS INCLUDING ALL STEPS FROM SUBMISSION TO PUBLICATION.**

After online manuscript submission, leading reviewers from the relevant areas will evaluate the papers and send feedback to the authors within a short time mostly in one month duration.

The Bulletin is included in leading international indices. Currently, the Bulletin of Urooncology is indexed in **Emerging Sources Citation Index (ESCI), TUBITAK/ULAKBIM Turkish Medical Database, Directory of Open Access Journals (DOAJ), EBSCO, Embase, CINAHL Complete Database, Gale/Cengage Learning, ProQuest, Index Copernicus, British Library, Root Indexing, J-Gate, IdealOnline, ROOT INDEXING, Turk Medline, Hinari, GOALI, ARDI, OARE, AGORA, EuroPub and Turkiye Citation Index.**

The Bulletin of Urooncology is published in English since 2018 as an e-journal.

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# Instructions to Authors

## 1. General Information

The Bulletin of Urooncology is the official scientific publication of the Turkish Society of Urooncology. It is published quarterly (March, June, September, and December). Supplements are also published during the year if necessary. Accepted articles will be published in English online without a hard copy.

The Bulletin publishes basic and clinical research original articles, reviews, editorials, case reports, surgery videos (Video-urooncology) 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).

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approval by an ethics review committee and affirmation that informed consent was obtained from each participant.

All manuscripts dealing with animal subjects must contain a statement indicating that the study was performed in accordance with "The Guide for the Care and Use of Laboratory Animals" (<http://oacu.od.nih.gov/regs/guide/guide.pdf>) with the approval (including approval number) of the Institutional Ethic Review Board, in the "Materials and Methods" section.

Prospective clinical trials, surgery videos and case reports should be accompanied by informed consent and the identity of the patient should not be disclosed.

During the evaluation of the manuscript or even after publication, the research data and/or ethics committee approval form and/or patients' informed consent document can be requested from the authors if it is required by the editorial board.

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Bulletin consists of elected experts of the Bulletin and if necessary, selected from national and international authorities. The editorial board has the right to not publish a manuscript that does not comply with the Instructions for Authors, and to request revisions or re-editing from the authors. The review process will be managed and decisions made by the Editor-in-chief, who will act independently.

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THE EDITORS WILL QUICKLY MAKE A SCIENTIFIC EVALUATION OF YOUR ARTICLE AND MOSTLY REACH A FINAL DECISION ABOUT YOUR ARTICLE WITHIN 20 TO 30 DAYS. THUS, WE OFFER A QUICK SYSTEMATIC REVIEW PROCESS TO ALL AUTHORS.

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It is the authors' responsibility to prepare a manuscript that meets scientific criteria. All persons designated as authors should have made substantial contributions to the following:

- (1) conception and design of the study, acquisition of data, or analysis and interpretation of data,
- (2) drafting the article or revising it critically for intellectual content,
- (3) final approval of the version to be submitted.

If the article includes any direct or indirect commercial links or if any institution provided material support to the study, authors must state in the "Copyright Transfer and Author Declaration Statement Form". They must state that they have no relationship with the commercial product, drug, pharmaceutical company, etc. concerned; or specify the type of relationship (consultant, other agreements), if any. This information should also be included in the "Acknowledgements Form".

In case of any suspicion or allegation regarding scientific shortcomings or ethical infringement, the Bulletin reserves the right to submit the manuscript to the supporting institutions or other authorities for investigation. The Bulletin accepts the responsibility of initiating action but does not undertake any responsibility for an actual investigation or any power of decision.

#### -Abbreviations:

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.

#### -Units of Measurement:

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

#### -Statistical Evaluation:

All retrospective, prospective, and experimental research articles must be evaluated in terms of biostatistics 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.

#### -Language:

Accepted articles will be published in English online. It is the authors' responsibility to prepare a manuscript that meets spelling and grammar

rules. Authors who feel their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English are encouraged to consult an expert. All spelling and grammar mistakes in the submitted articles are corrected by our redaction committee without changing the data presented.

### 5. Article Types

The Bulletin of Urooncology publishes articles prepared in compliance with the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals published by International Committee for Medical Journal Editors (ICMJE). Manuscripts that do not meet these requirements will be returned to the author for necessary revision prior to review.

The Bulletin requires that all submissions be submitted according to these guidelines: Manuscripts should be prepared as a word document (\*.doc) or rich text format (\*.rtf). Text should be double-spaced with 2.5 cm margins on both sides using 12-point type double spaced in Times Roman.

All manuscripts submitted must be accompanied by the "Copyright Transfer and Author Declaration Statement Form" ([www.uroonkolojibulteni.com](http://www.uroonkolojibulteni.com)). The corresponding author must also provide a separate "Title Page" including full correspondence address including telephone, fax number, and e-mail address, list of all authors with The ORCID number. Contact information for the corresponding author is published in the Bulletin.

All manuscripts submitted must also be accompanied by an "Acknowledgements Form" ([www.uroonkolojibulteni.com](http://www.uroonkolojibulteni.com)). Acknowledgements are given for contributors who may not be listed as authors. Any grants or financial support received for the paper should be stated in the "Acknowledgements Form". If presented as an abstract; the name, date, and place of the meeting should also be stated in this form. A statement of financial, commercial or any other relationships of a declarable nature relevant to the manuscript being submitted, (i.e. a potential conflict of interest) must also be included in "Acknowledgements Form".

Each section of the "Main Text" mentioned below should be started on a new page and be organized according to the following sequence:

- 1) First page: Title, abstract and keywords (without authors' credentials)
- 2) Manuscript text structured based on the article type (without authors' credentials)
- 3) References
- 4) Figure legends
- 5) Short Quiz for review articles.

Tables and figures should be uploaded separately.

Also, "Acknowledgements Form" should be uploaded separately.

#### A. Original Research Articles

Original prospective or retrospective studies of basic or clinical investigations in areas relevant to urologic oncology.

Content (Main text): Each part should start on a new page.

- First page: Title - Abstract (structured abstract limited to 300 words, containing the following sections: Objective, Materials and Methods, Results, Conclusions) - Keywords (List 3-5 keywords using Medical Subjects Headings [MeSH])

-Introduction

- Materials and Methods

- Results

- Discussion

## Instructions to Authors

- Study Limitations
- Conclusions
- References
- Figure Legends: These should be included on separate page after the references.
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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).

A word count for the original articles (excluding title page, acknowledgements, references, figure and table legends) should be provided not exceed 3000 words. Number of references should not exceed 30. Number of figure/tables is restricted to five for original articles.

### B. Case Reports

Case reports should include cases which are rarely seen and distinctive in diagnosis and treatment. These can include brief descriptions of a previously undocumented disease process, a unique unreported manifestation or treatment of a known disease process, or unique unreported complications of treatment regimens, and should contribute to our present knowledge.

Content (Main text): Each part should start on a new page.

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- Introduction
- Case Presentation
- Discussion
- References
- **Figure Legends:** These should be included on separate page after the references.
- Tables and figures should be uploaded separately.
- Also, "Acknowledgements Form" should be uploaded separately.

A word count for the case reports (excluding title page, acknowledgements, references, figure and table legends) should be provided not exceeding 1500 words. Number of references should not exceed 15. Number of figure/tables is restricted to three for case reports.

### C. Review Article

These are manuscripts which are prepared on current subjects by experts who have extensive experience and knowledge of a certain subject and who have achieved a high number of publications and citations. Reviews are usually submitted directly or by invitation of the editorial board. Submitted reviews within the scope of the journal will be taken into consideration by the editors. The content of the manuscript should include the latest achievements in an area and information and comments that would lead to future studies in that area. Number of authors should be limited to three.

Content (Main text): Each part should start on a new page.

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- **Text:** This part should present detailed information based on current literature about the subject of the review. The author(s) should organize the manuscript into appropriate headings and subheadings to facilitate reading.
- Conclusions
- References

- **Figure Legends:** These should be included on separate page after the references.

-Short Quiz (a list of 3-5 questions about the context of article for CME credit). The editorial board and Urooncology Association of Turkey executive committee will evaluate the answers and members submitting correct answers may receive education grants).

-Tables and figures should be uploaded separately.

-Also, "Acknowledgements Form" should be uploaded separately.

Number of figure/tables is restricted to five for review articles. Number of references should not exceed 100.

### D. Literature Review

These short reviews 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.

### E. Editorial Commentary

These short comments are solicited by the editor and should not be submitted without prior invitation. An original research article is evaluated by specialists in the area (not including the authors of the research article) and this is published at the end of the related article. Word count should not exceed 500 words and number of references is limited to 5.

### F. Letters to the Editor

These are letters that include different views, experiments, and questions from readers about the manuscripts published in the Bulletin within the last year and should be no more that 500 words with maximum of 5 references. There should be no title or abstract. Submitted letters should indicate the article being referenced (with issue number and date) and the name, affiliation, and address of the author(s). If the authors of the original article or the editors respond to the letter, it will also be published in the Bulletin.

### G. Surgery Videos on Urooncology (Video-urooncology)

These videos are solicited by the editor. The videos are prepared on urooncological surgeries by experts who have extensive experience and knowledge of certain advanced surgical techniques. This section is also intended to enable urologists to learn, evaluate, and apply new or complex surgical principles in their surgical practice. The videos can describe current sophisticated or new surgical techniques or modification of current techniques. The surgery video must be high quality material.

Videos are only submitted by the invitation of the editorial board. Submitted videos are also evaluated based on double-blind peer-review principles.

The Bulletin of Urooncology publishes original videos containing material that has not been reported elsewhere as a video manuscript, except in the form of an abstract. The authors should describe prior abstract publications in the "Acknowledgements Form". Published videos become the sole property of The Bulletin of Urooncology.

Video-urooncology submission should include:

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- 6) "Acknowledgements Form" should be uploaded separately.

Videos should be up to 30 minutes in duration. The video must include audio narration explaining the procedure. All text and audio in the video must be in English. Audio must include narration in clear, grammatically correct English. Videos must be clear, in focus, and without excessive camera movement. Radiographs and other material must not contain any patient-identifiable information. Limited number of slides incorporated into video may be included to provide details of patient history, clinical and laboratory findings.

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# Adjuvant Intraluminal Therapies in Upper Urinary Tract Urothelial Tumors

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## Abstract

The gold standard treatment option for upper urinary tract urothelial tumors is radical nephroureterectomy and bladder cuff resection. On the other hand, with the development of surgical techniques, improvement in endoscopic instruments and better risk stratification in recent years, minimally invasive endoscopic procedures and renal-sparing surgical approaches such as segmental/total ureterectomy have begun to be applied. Metachronous tumor recurrences can be seen despite the use of renal-sparing approaches in selected patients. Adjuvant intraluminal treatments are applied in upper urinary tract tumors to reduce tumor recurrences. In this review, we discussed the role of adjuvant intraluminal therapies.

**Keywords:** Upper urinary tract urothelial tumor, renal-sparing approach, adjuvant intraluminal therapy

## Introduction

Urothelial tumors take the 4<sup>th</sup> place among cancers seen in developed countries (1). Upper urinary tract urothelial tumors (UUTUTs) are relatively rare and constitute 5-10% of all urothelial tumors (2). Although it is mostly diagnosed unilaterally, synchronous bilateral UUTUTs can be seen rarely (1.6%) (3). The incidence of contralateral UUTUTs has been reported as 1-6% in the literature (4). It is thought that environmental factors may be effective in the formation of UUTUTs. Smoking and aristolochic acid are scientifically proven environmental factors in etiology (5,6). In addition, there are strong findings that there is a relationship between hereditary UUTUTs and hereditary non-polyposis colorectal carcinoma (7).

The gold standard treatment option in UUTUTs is radical nephroureterectomy and resection around the bladder orifice (8). However, in recent years, the view that radical nephroureterectomy may be overtreatment in low-stage and high-risk UUTUTs has been accepted (9). On the other hand, the development in surgical techniques and endoscopic instruments used in recent years allows better risk stratification and the introduction of minimally invasive endoscopic procedures such as segmental/total ureterectomy and renal-sparing surgical approaches (10,11). On the other hand, metachronous tumor recurrences can be seen despite the use of renal-sparing approaches in selected patients. Adjuvant intraluminal treatments are applied in UUTUTs to reduce tumor

recurrences. In this review, we discussed the role of adjuvant intraluminal therapies.

## Renal-sparing Surgery Indications and Risk Stratification

European Urology Guidelines defined indications for renal-sparing surgery (12). Anatomical or functional solitary kidney, presence of bilateral tumors, detection of kidney failure, and poor performance of the patient for radical surgery are definite indications. However, low-risk tumor or selected patients with high-risk tumors (multifocal tumors, large, low-risk and superficial tumors) are relative indications (Table 1). In addition, the risk stratification of UUTUTs was defined in the 2019 European Urology Guideline to determine which patients were more suitable for a renal-sparing approach (12). According to the European Urology Guideline risk stratification; single focus, tumor size <2 cm, low-grade cytology or ureteroscopic biopsy results, and no invasive spread on computer tomography-urography are features of low-risk UUTUT. Presence of hydronephrosis, tumor size >2 cm, high-grade cytology or ureteroscopic biopsy result, multifocal tumor, variant histology, and a history of radical cystectomy are features of a high-risk UUTUT (Table 2).

## Renal-sparing Endoscopic Approach

In recent years, with the development of endoscopic instruments, retrograde or antegrade endoscopic approach has been started

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**Table 1. Indications for renal-sparing surgery in upper urinary tract urothelial tumors**

Strong Recommendations
Anatomical or functional solitary kidney Bilateral tumor Chronic renal failure Not suitable for radical nephroureterectomy
Weak Recommendations
Low risk upper urinary tract urothelial tumor Appropriate high-risk upper urinary tract urothelial tumor: Multifocal tumor, large tumor, tumor with low-risk features, superficial tumor

**Table 2. Risk stratification in upper urinary tract urothelial tumors**

High risk upper urinary tract urothelial tumor
<ul style="list-style-type: none"> <li>• Hydronephrosis</li> <li>• High grade (Ureteroscopic biopsy or cytology)</li> <li>• Tumor size &gt;2 cm</li> <li>• Multifocal disease</li> <li>• Variant histology</li> <li>• History of radical cystectomy</li> </ul>
Low risk upper urinary tract urothelial tumor
<ul style="list-style-type: none"> <li>• Single focus</li> <li>• Tumor size &lt;2 cm</li> <li>• Low grade (Ureteroscopic biopsy or cytology)</li> <li>• No invasive spread in computer tomography-urography</li> </ul>

to be used frequently in UUTUTs, especially in low-risk patient group. In a meta-analysis, Seisen T. showed that low-risk patients who underwent ureteroscopy or percutaneous renal-sparing surgical approach had similar survival compared to patients who underwent radical nephroureterectomy (13). Similar oncological outcomes, better renal function after renal-sparing surgery, and lower morbidity made the renal-sparing approach to be preferred more often than the radical approach in low-risk patients. The current European Urology Guideline states that endoscopic ablation can be applied in low-risk patients if there are suitable instruments for ablation and biopsy, if there is a flexible ureteroscope, if the patient is informed about the need for close follow-up, and if complete tumor resection can be performed (14). Although the percutaneous approach is applied in patients with low-risk renal pelvis or calyx tumors, it has been used less frequently in recent years due to the development of retrograde endoscopic instruments and the risk of tumor seeding in the percutaneous approach (15).

### Intraluminal Treatments

Although the indications for the use of intraluminal therapies in bladder cancer are stated in European and American Urology Guidelines, there is still insufficient evidence regarding the use of intraluminal therapies in UUTUTs. Although there are no randomized clinical studies conducted to date, most of the available data in the literature are based on retrospective studies.

Intraluminal treatments are applied antegrade or retrograde way in UUTUTs. In both methods, there is no standard approach in terms of duration, frequency, and the agent applied. For antegrade administration, a 10F percutaneous nephrostomy tube is inserted into the patient and it is waited for 2 weeks for the tract to form before starting the infusion. For antegrade

intraluminal immunotherapy [Bacillus Calmette-Guerin (BCG)], 360 mg Immune BCG Pasteur or 243 mg ImmuCyst is dissolved in 150 mL 0.9% saline and given as an infusion over 2 hours at 1 mL per minute over 20 cm above the patient's kidney level (16,17). Antegrade intraluminal chemotherapy (mitomycin C) is administered using a similar procedure by dissolving 40 mg of mitomycin in 20 mL of 0.9% saline. During the treatment, the nephrostomy tube is changed every 3 months (17). Although antegrade method with percutaneous nephrostomy tube is a more direct method, the nephrostomy tube should remain on the patient during the treatment process. This may adversely affect the patient's quality of life. On the other hand, in retrograde method, a 5F ureteral catheter is placed in the patient with cystoscopy. In patients who are infused through a ureteral catheter, the pressure of the manometer is kept below 20-30 mmHg, and the patient is told to change positions every 15-20 minutes for the infusion to affect the entire urinary tract (right side, left side, supine and prone positions) (18). The agent used, dose and duration of administration are similar to antegrade method. Retrograde method is seen as a more comfortable method by patients, especially since it can be performed under local anesthesia and there is no permanent catheter on the patient during the treatment process. Before both applications, urine cultures are taken from the patients and prophylactic antibiotics are given. The induction dose for intraluminal chemotherapy (mitomycin C) and immunotherapy (BCG) is given once a week for 6 weeks. Although the maintenance dose for intraluminal chemotherapy is not clear, it is given once a month for at least 3 months (18). The maintenance dose for intraluminal BCG is once a week for 3 weeks at the 3<sup>rd</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 18<sup>th</sup>, 24<sup>th</sup>, 30<sup>th</sup> and 36<sup>th</sup> months (19). One of the main problems in retrograde method is the time it takes for the applied agent to pass and act in the upper urinary tract tract. It should be ensured that the proximal end of the inserted catheter is in the renal pelvis and that there is no mucosal injury. Methods such as ureteral meatotomy and permanent ureteral stenting which causes retrograde reflux have been described. However, before induction therapy, it should be ensured that there is sufficient volume to activate the reflux (20).

It has been thought that intraluminal treatments would prevent recurrence after a renal-sparing approach, especially in low-risk patients, as in bladder cancer. Chemotherapeutic and immunotherapeutic agents have been applied for a short time in UUTUTs (21,22). The results of adjuvant intraluminal BCG administration after UUTUT resection or ablation are not promising. In a study by Giannarini et al. (16), recurrence-free survival and progression-free survival (PFS) were found 41% and 59%, respectively, in patients with T<sub>a</sub> or T<sub>1</sub> UUTUT treated with BCG antegrade perfusion as an induction regimen (16). In another study by Rastinehad et al. (23), no statistically significant difference was found in terms of recurrence in patients who received adjuvant intraluminal BCG in both high-grade and low-grade UUTUTs compared to those who did not (low grade 26%-33% vs high grade 38%-39%). On the other hand, it has been shown that adjuvant intraluminal BCG induction therapy gives better results in upper urinary tract carcinoma *in situ* (CIS) (24). Carmignani et al. (25) evaluated 12 studies involving a total of 185 patients and stated that the mean recurrence rate was 32%

in a mean follow-up period of 19-57 months after 6 weeks of BCG induction therapy in 165 patients with upper urinary tract CIS. On the other hand, Shapiro et al. (26) evaluated the role of BCG-interferon therapy in biopsy-confirmed upper urinary tract CIS in a study they conducted. In a study involving 11 patients, complete response was observed in 8 (73%) patients and only 1 patient had biopsy-proven recurrence. Based on the available data in the literature, it can be concluded that adjuvant intraluminal BCG therapy is effective and can be used as a primary treatment option in upper urinary tract CIS without papillary tumor. However, prospective randomized clinical studies with larger patient populations are needed.

Just as adjuvant chemotherapeutic agents are used to prevent progression and recurrence after transurethral resection in bladder tumors; adjuvant chemotherapeutic agents are used to reduce recurrence after resection in low-risk patients with UUTUTs. The recurrence rate in patients who have received adjuvant intraluminal mitomycin c after resection is between 29-54%, and the rate of nephroureterectomy is between 5-21% (27,28). In a study by Metcalfe et al. (18), 28 patients with low-grade Ta-T1 UUTUTs were given adjuvant induction and maintenance intraluminal mitomycin c after resection, and the 3-year recurrence-free, progression-free, and nephroureterectomy-free survival rates were 60%, [confidence interval (CI) (95% CI): 42, 86%], 80% (95% CI: 64, 100%), and 76% (95% CI: 60, 97%), respectively (18). On the other hand, postoperative single dose intravesical chemotherapy can be applied to prevent bladder recurrence after radical nephroureterectomy. The bladder recurrence rate after radical nephroureterectomy in UUTUTs is 22-47%. In a study by Alma et al. (29), bladder tumor recurrence was observed in 22.7% (5 patients) of 22 patients who underwent radical nephroureterectomy due to UUTUT during a mean follow-up period of 32 months. In a meta-analysis, it was shown that administration of a single dose of intravesical chemotherapy (mitomycin c, epirubicin) within 2-10 days after radical nephroureterectomy statistically significantly reduced the rate of bladder recurrence within 1 year (30). In the current European Urology Guideline, post-operative single-dose intravesical chemotherapy is recommended after radical nephroureterectomy.

## Conclusion

Although minimally invasive renal-sparing surgical methods have been used frequently with the development of endoscopic instruments in low-risk patients with UUTUTs, the role of adjuvant intraluminal therapies used to reduce recurrence and progression after renal-sparing surgery is still not clear according to current literature data. There are still no recommendations regarding adjuvant intraluminal therapies in the current European Urology Guidelines. Randomized clinical trials with larger populations and meta-analyses investigating the effectiveness of adjuvant intraluminal therapies in UUTUTs are needed.

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# Turkish Linguistic Validation of the Geriatric 8 Screening Tool

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## Abstract

**Objective:** To evaluate the Turkish linguistic validation of the Geriatric 8 (G8) screening tool.

**Materials and Methods:** Professional medical translators independently performed the translation and backtranslation of the original English G8 questionnaire. Patients aged 70 years or older were included in the study. The final Turkish version of the G8 screening tool was administered to all patients, and internal consistency was evaluated using Cronbach's alpha coefficient. The G8 screening tool was administered once more to the patients two weeks after the first administration to evaluate the test-retest reliability. Intraclass correlation coefficient test was used to evaluate the test-retest results. The construct validity of the scale was examined using the exploratory factor analysis.

**Results:** One hundred and nineteen patients were included in the study. Cronbach's alpha coefficient was 0.72, which indicated that the screening tool was internally consistent. According to the test-retest analysis, a strong correlation was noted between the test and retest results. When the answers to the same question in the test and retest were compared, they were similar, and this result was consistent with the correlation results.

**Conclusion:** The Turkish version of the G8 screening tool was established in this study.

**Keywords:** Aging, cancer, geriatrics, questionnaire

## Introduction

Worldwide, it has been noted that the geriatric population has increased and is continuously growing. According to the Turkish Statistical Institute data, the geriatric population (individuals aged 65 years and above) has increased by 17% between 2013 and 2017, accounting for 8.5% of the Turkish population (1). Life expectancy at birth has increased to 81 years in European countries and to 78 years in Turkey (1). Considering the growing older male population in industrialized countries and increasing cancer incidence with aging, the management of elderly patients with cancer has become an important public health problem. Several aspects of the aging process and health status widely vary in older patients. Hence, individual treatment choice is especially important to provide optimal efficacy and minimize toxicity in these patients. Therefore, screening tools have been established to distinguish fit geriatric patients (who can tolerate standard treatments) from frail patients with reversible or irreversible impairments [who need a comprehensive geriatric assessment (CGA)] (2,3). However, most tools have been

validated in patients without cancer and evaluated without the side effects of cancer therapy and had to be administered by clinicians (4,5,6,7,8). In 2012, Bellera et al. (9) created the geriatric 8 (G8) screening tool. They showed that G8 had good screening properties for identifying older patients who could benefit from CGA. The G8 screening tool is a self-administered tool consisting of eight items, which evaluate self-perception of health, psychological status, age, weight loss, body mass index, nutritional status of patients, number of medications, and mobility (9). Recently, the G8 screening tool has been used in the treatment of elderly patients with prostate cancer and recommended by the EAU-ESTRO-ESUR-SIOG guidelines on prostate cancer (2,10,11,12). This study aimed to study aimed to evaluate the Turkish linguistic validation of the G8 screening tool.

## Materials and Methods

We contacted the corresponding author and developer of the G8 screening tool, Carine A. Bellera, and obtained permission

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for a Turkish linguistic validation. The G8 screening tool includes eight items, and the total G8 score ranges from 0 (heavily impaired) to 17 (not at all impaired). It is emphasized that healthy patients with a G8 score greater than 14 and frail patients, who have reversible impairments after the resolution of their geriatric problems with a G8 score of 14 or less, should receive the same definitive treatment as young patients. Patients with a G8 score of 14 or less and who have irreversible geriatric problems should receive symptomatic or palliative treatment.

The Institutional Review Board of Dokuz Eylül University approved the study protocol (decision number: 2019/02-43). All patients provided written informed consent. A three-stage protocol was used to obtain the Turkish version of the G8 screening tool: translation, internal consistency and content validity, and stability (test-retest reliability).

**The First Stage:** Two certificated professional Turkish translators independently translated the original English G8 questionnaire (Table 1) into Turkish. The authors checked the translation for medical coherence. Afterwards, two professional medical translators, who did not have access to the original English version, performed a backtranslation of the final document. The original and backtranslated versions of the G8 questionnaire were compared, and a final Turkish version was agreed upon (Table 2).

**The Second Stage:** Patients who were admitted to our urology outpatient clinic and aged 70 years or older between March 2019 and June 2019 were included in the study. The final Turkish version of the G8 screening tool was administered to all patients, accompanied with a urologist, and internal consistency was evaluated using Cronbach’s alpha coefficient.

**The Third Stage:** The G8 screening tool was administered once more, accompanied with a urologist, to the patients two weeks after the first administration to evaluate the test-retest reliability. The test and retest results of each question in the G8 screening tool were compared.

**Statistical Analysis**

Data analysis was performed using IBM Statistical Package for Social Sciences version 25 (IBM Corp., Armonk, NY, USA), and a p-value less than 0.05 was considered statistically significant. In the evaluation of descriptive data, mean ± standard deviation, median, and 25<sup>th</sup> and 75<sup>th</sup> quartile values were used. Item total score correlation and internal consistency (Cronbach’s alpha) were used to assess the reliability of the scale, and intraclass correlation coefficient (ICC) was used to evaluate the test-retest results. In the concurrent criterion validity for content validity, the Pearson product-moment correlation coefficient was used. In the investigation of the sample size for the validity of the results obtained from the exploratory factor analysis, Kaiser-Meyer-Olkin (KMO) and Bartlett’s tests were used. Confirmatory factor analysis (CFA) was performed using STATISTICA-12. Root mean square error of approximation (RMSEA) and standard root mean square residual (SRMR) were given as model fit indices.

**Results**

One hundred and forty-one patients answered the G8 questionnaire on the first administration. However, 22 patients

did not return in the second week of outpatient management and did not complete the retest. Finally, 119 patients were included in the study. The mean age of the patients was 76.72±5.36 years. Of these patients, 88.2% were males and 11.8% were females. The most common comorbidities were hypertension (57.1%) and diabetes mellitus (21.0%). The majority of the patients had a surgical and smoking history (85.7% and 68.9%, respectively). Cronbach’s alpha coefficient was used to evaluate the internal consistency and was 0.72, which indicated that the screening tool was internally consistent.

The stability of the G8 screening tool was determined by calculating the test and retest reliability using ICC. According to the test-retest analysis, a strong correlation between the test and retest results for each question was noted. When the answers to the same question in the test and retest were compared, they were similar, and this result is consistent with the correlation

**Table 1. G8 questionnaire (adapted form)**

	Items	Possible responses (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake
		1 = moderate decrease in food intake
		2 = no decrease in food intake
B	Weight loss during the last 3 months?	0 = weight loss >3 kg
		1 = does not know
		2 = weight loss between 1 and 3 kg
		3 = no weight loss
C	Mobility?	0 = bed or chair bound
		1 = able to get out of bed/chair but does not go out
		2 = goes out
E	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems
F	BMI? (weight in kg)/ (height in m <sup>2</sup> )	0 = BMI <19
		1 = BMI 19 to <21
		2 = BMI 21 to <23
		3 = BMI ≥23
H	Takes more than three prescription drugs per day?	0 = yes
		1 = no
P	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better
	Age	0: >85
	1: 80-85	
	2: <80	
	Total score	0-17

BMI: Body mass index

results. The test-retest reliability results of the G8 screening tool are shown in Tables 3 and 4.

In the exploratory factor analysis, KMO technique is the most commonly used for the sample size's adequacy. The KMO value varies between 0 and 1, and this value is recommended to be greater than 0.60. Bartlett's test of sphericity tests whether the data are from a multivariate normal distribution. In this study, the KMO test result was 0.647, and Bartlett's test was 163.262 ( $p < 0.001$ ). According to these results, it was found that the data came from multiple normal distributions, and the sample size was sufficient and suitable for factor analysis. To validate the construct validity in the Turkish adaptation of the G8 screening tool, CFA was used because of the one-dimensional structure. CFA based on the theoretical background showed acceptable fit for the G8 screening tool [ $\chi^2(20)=37.209$ ,  $p=0.011$ ; RMSEA=0.084, 95% confidence interval (0.039-0.127); SRMR=0.082 (13)].

	Maddeler	Olası yanıtlar (puan)
A	İştahsızlık, sindirim problemleri, çiğneme veya yutma güçlüğünü nedeniyle gıda alımı son 3 ayda azaldı mı?	0 = besin alımında ciddi azalma
		1 = besin alımında orta düzeyde azalma
		2 = besin alımında azalma yok
B	Son 3 aydaki kilo kaybı?	0 = kilo kaybı >3 kg
		1 = bilmiyor
		2 = 1 ile 3 kg arasında kilo kaybı
		3 = kilo kaybı yok
C	Hareketlilik?	0 = yatağa ya da sandalyeye bağlı
		1 = yataktan/sandalyeden kalkabiliyor, ancak dışarı çıkmıyor
		2 = dışarı çıkıyor
E	Nöropsikolojik sorunlar?	0 = şiddetli demans ya da depresyon
		1 = hafif demans
		2 = psikolojik sorunları yok
F	VKİ? (kg cinsinden ağırlık)/(m <sup>2</sup> cinsinden boy)	0 = VKİ <19
		1 = VKİ 19 ile <21 arası
		2 = VKİ 21 ile <23 arası
		3 = VKİ ≥23
H	Günde üçten fazla reçeteli ilaç alıyor mu?	0 = evet
		1 = hayır
P	Aynı yaştaki diğer insanlarla karşılaştırıldığında hasta sağlık durumunu nasıl değerlendirir?	0.0 = diğerleri kadar iyi değil
		0.5 = bilmiyor
		1.0 = diğerleri kadar iyi
		2.0 = diğerlerinden daha iyi
	Yaş	0: >85 1: 80-85 2: <80
Toplam skor	0-17	

VKİ: Vücut kitle indeksi

	Test mean ± SD median(Q <sub>1</sub> -Q <sub>3</sub> )	Retest mean ± SD median(Q <sub>1</sub> -Q <sub>3</sub> )	p-value	ICC	95% CI
A	1.92±0.30 2(2-2)	1.92±0.33 2(2-2)	0.317	0.958	0.940-0.970
B	2.76±0.78 3(3-3)	2.76±0.78 3(3-3)	1.000	1.000	1.000-1.000
C	1.93±0.31 2(2-2)	1.93±0.31 2(2-2)	1.000	1.000	1.000-1.000
E	2.01±0.09 2(2-2)	2.01±0.09 2(2-2)	1.000	1.000	1.000-1.000
F	2.88±0.47 3(3-3)	2.88±0.47 3(3-3)	1.000	1.000	1.000-1.000
H	0.77±0.42 1(1-1)	0.77±0.42 1(1-1)	1.000	1.000	1.000-1.000
P	1.18±0.72 1(1-2)	1.17±0.70 1(1-2)	0.739	0.956	0.937-0.969
Age	1.64±0.62 2(1-2)	1.64±0.62 2(1-2)	1.000	1.000	1.000-1.000
Total score	15.10 ± 1.95 14(14-16)	15.09 ± 1.95 14(14-16)	0.470	0.993	0.990-0.995

ICC: Intraclass correlation coefficient, Wilcoxon signed-rank test, CI: Confidence interval, SD: Standard deviation

	A	B	C	E	F	H	P	Age
A	1							
B	0.769	1						
C	0.312	0.249	1					
E	0.024	0.028	0.020	1				
F	0.239	0.316	0.003	0.023	1			
H	-0.003	0.146	0.012	-0.170	-0.050	1		
P	0.043	0.121	0.243	-0.023	-0.013	0.190	1	
Age	0.035	0.138	0.224	0.054	-0.031	0.138	0.144	1

Pearson product-moment correlation coefficient

## Discussion

Recently, there has been an increase in the elderly population; this increase changed patients' management and became a major health problem. CGA is the gold-standard method for evaluating the health status of elderly patients. CGA is a multidimensional, interdisciplinary diagnostic process used for determining the functional, psychological, and medical capabilities of frail older patients to establish a coordinated and integrated plan for treatment and follow-up. CGA is part of oncologic care to assess the overall health status of older patients; however, it is time-consuming and requires a specialist staff. Therefore, various screening tools, including the G8, have been used to determine which patients need CGA before treatment decision (4,5,6,7,8,9). The G8 is the first screening tool designed specifically for older patients with cancer to distinguish fit patients from frail ones (9). Several validation studies, including

those on patients with cancer, have been published, with G8 being one of the most robust screening tools currently available in systematic reviews (11,12,14,15,16,17,18,19). Moreover, it was noted that the G8 screening tool could be used in predicting the prognosis and overall survival (OS) in several types of cancer (14,15,16). Agemi et al. (14) investigated the role of the G8 screening tool in predicting the OS and clinical outcomes in older patients with lung cancer, who received chemotherapy or chemoradiotherapy, and they found that a low G8 score was significantly associated with poor OS. They emphasized that the G8 screening tool was as useful as the Eastern Cooperative Oncology Group performance status in predicting the prognosis of older patients with lung cancer and can be used in preventing patients from receiving inappropriate anticancer treatment (14). Deluche et al. (15) designed a study to validate the G8 screening tool and evaluate its role in predicting OS in elderly patients with glioblastoma. They noted that the G8 screening tool could effectively distinguish healthy patients from frail ones (15). Sakurai et al. (16) evaluated the role of the G8 screening tool in survival outcomes in elderly patients with diffuse large B-cell lymphoma. They showed that, in these patients, a low G8 score is an independent risk factor for poor prognosis and OS.

Most urological cancers are detected in advanced ages, and the treatment choices depend on the patient's age and health status. Few reports on the feasibility of the G8 screening tool in elderly patients with urological cancer are available in the literature (20,21,22). Prostate cancer is the most frequently occurring cancer in men, with a median age at diagnosis of 68 years (10,23). It is expected that there will be a 70% increase in the annual diagnoses in men above 65 years of age by 2030 in Europe and the USA (23,24). In localized disease, a life expectancy of more than 10 years requires a local definitive treatment. Patients with a moderate- or high-risk prostate cancer with a long life expectancy can benefit from active definitive treatment regimens (10). A poor baseline health status is associated with less benefit from definitive treatment regimens, including surgery, radiotherapy, and active surveillance in patients with prostate cancer. While definitive treatment regimens do not increase the life expectancy of patients with worse baseline health status, increased morbidity negatively affects patients' quality of life. Watchful waiting, including symptomatic or palliative treatment, is more appropriate for this group of patients. Thus, it is important to evaluate the baseline health status (fit or frail) in elderly patients with prostate cancer. The International Society of Geriatric Oncology Prostate Cancer Working Group recommends that treatment for senior adults should be based on a systematic evaluation of health status using the G8 screening tool (21), and this recommendation has been included in the EAU 2017 guidelines on prostate cancer (10). Moreover, in a recent publication, Beardo et al. (22) investigated the safety and outcomes of new-generation hormonal therapy (NGHT) (enzalutamide and abiraterone acetate) in elderly chemotherapy-naïve metastatic castration-resistant patients with prostate cancer and concluded that the G8 screening tool could help identify patients aged 75 years or older who would most benefit from NGHT. The results of this study showed that the G8 screening tool can be used at

different points of treatment decision in elderly patients with prostate cancer. There is one study in which the use of the G8 screening tool in patients with bladder cancer was investigated. Maebayashi et al. (20) evaluated using the G8 screening tool to determine whether to add intra-arterial chemotherapy (IAC) to radiotherapy in elderly patients with muscle-invasive bladder cancer and found that the G8 screening tool was potentially applicable in determining the feasibility of adding IAC in these patients.

## Conclusion

The G8 screening tool is an easy and ideal screening tool, which requires less time to perform, covers all domains routinely evaluated by geriatricians, and effectively separates fit patients from frail ones. In this study, the Turkish version of the G8 screening tool was obtained and validated. We believe that this Turkish version of the G8 screening tool can be used in deciding the treatment options for elderly patients in daily clinical practice.

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## Ethics

**Ethics Committee Approval:** The Institutional Review Board of Dokuz Eylül University approved the study protocol (decision number: 2019/02-43).

**Informed Consent:** All patients provided written informed consent.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Concept: V.Ş., H.E., U.M., Design: V.Ş., O.B., H.E., U.M., Data Collection or Processing: V.Ş., A.Y., Analysis or Interpretation: H.E., Literature Search: V.Ş., A.Y., Writing: V.Ş.

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# Evaluation of Sexual Function According to the Size of the Needle Used in Transrectal-Ultrasonography-Guided Prostate Biopsy

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## Abstract

**Objective:** This study aimed to evaluate the sexual function in patients who underwent a transrectal ultrasonography-guided prostate needle biopsy (TRUS-Bx) using 16G and 18G needles.

**Materials and Methods:** Ninety patients underwent TRUS-Bx. Group 1 included patients who underwent biopsy with an 18G needle (n=45), and group 2 included patients who underwent biopsy with a 16G needle (n=45). Sexual function in both groups was prospectively compared. Additionally, the patients' age, prostate-specific antigen (PSA), prostate volume, cancer detection rate, complication rates, visual analog scale (VAS), and International Index of Erectile Function (IIEF) scores were compared.

**Results:** Age, PSA, prostate volume, cancer detection rate, complication rates and VAS were not found statistically different between the groups. No difference was observed between the two groups in terms of the five main items of IIEF before the procedure. The intercourse satisfaction value was found to be significantly lower after the procedure than before the procedure in group 1 (p<0.05). Orgasmic function, intercourse satisfaction, and overall satisfaction were statistically significantly lower after the procedure than before the procedure in group 2 (p<0.001). Orgasmic function and overall satisfaction were lower in group 2 and significantly different between the two groups four weeks after the procedure (p<0.001).

**Conclusion:** Although erectile function, sexual desire, and intercourse satisfaction were not different on using different needle sizes, in patients where 16G needles were used, orgasmic function and overall satisfaction were lower four weeks after the procedure.

**Keywords:** Prostate biopsy, sexual function, visual analog score

## Introduction

Transrectal ultrasonography-guided prostate biopsy (TRUS-Bx) is the standard for detection of prostate cancer (PCa) (1). TRUS-Bx is mostly preferred due to its short application time, not requiring special equipment, and reusability of the equipment used (2,3). It is not considered a complication-free procedure since 1.0%-6.9% of men who undergo the procedure can experience adverse effects, such as hematuria, hematospermia, dysuria, fever, and septicemia (0.5%-5%) (4,5). The repercussion of TRUS-Bx for erectile function is not described as one of the main side effects; however, few studies have demonstrated the relationship between erectile function and TRUS-Bx. On

reviewing the literature, it was shown that the effect of TRUS-Bx on erectile dysfunction (ED) was investigated. In these studies, the short form of International Index of Erectile Function (IIEF) was used (6,7). However, these studies have some limitations, such as using only the short form of IIEF-5 and using only 18G needle for TRUS-Bx.

This study aimed to evaluate the effect of different sizes of biopsy needles (16G and 18G) on male sexual functions using the IIEF-15 questionnaire, focusing on five main items: erectile function, orgasm function, sexual desire, sexual satisfaction, and overall satisfaction.

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## Materials and Methods

An approval was obtained from our institutional review board (number: 2018/01/277) for this study. In this prospective study, all patients who had a suspicious digital rectal examination or high level of prostate-specific antigen (PSA >4.0 ng/mL) who were good candidates for prostate biopsy during the period of February 2018 to March 2020 were evaluated. Ninety patients were included in the study. Demographic data, including age, PSA level, prostate volume, body mass index, cancer detection rate, and complication rates based on TRUS-Bx, were recorded (Table 1). Patients were randomly divided into two groups according to the order of arrival (1:1 ratio). Group 1 included patients who underwent biopsy with an 18G needle (n=45), and group 2 included patients who underwent biopsy with a 16G needle (n=45).

No patients were administered a rectal enema on the day before the biopsy. However, all patients received povidone-iodine rectal preparation and were prescribed 1000 mg of ciprofloxacin, divided in two doses, starting 24 h before the biopsy. The procedure was explained in detail, and all patients signed an informed consent.

All patients were positioned in the lateral decubitus position with knee and hip flexion. Four to five minutes before probe introduction, 2% lidocaine and chlorhexidine gel were introduced in the patient's rectum and 5 cc lidocaine injections were administered in the right and left periprostatic area. Twelve core biopsies of six right lobes and six left lobes were taken from all patients. The duration of the biopsy was 20±5 minutes.

All patients completed the IIEF questionnaire on the day of the biopsy and four weeks after. IIEF evaluates male sexual function using 15 questions. The fifteen questions are as follows: six questions on erectile function, two questions on orgasm function, two questions on sexual desire, three questions on sexual satisfaction, and two questions on overall satisfaction. Additionally, after the biopsy, all patients completed a visual pain score (VAS) assessment. The five main items of IIEF were compared between groups and with each other before the procedure and four weeks after.

Exclusion criteria were patients who used anticoagulants or aspirin in the seven days before the procedure, had any prior prostatic surgery, had any bleeding problem, had any known anal or rectal problems, had any neurological sensory deficit,

and scored below the normal value in any of the five main items in the IIEF done before the biopsy.

### Sample Size Calculation

The sample size calculation was performed using G\*Power 3.1.9.2 program. It was calculated according to the previous article (8). After considering the alpha level, 0.05, beta error, 0.20, and the effect size, 0.7, the total required sample size was calculated as 78. Since the possible drop-out rate was selected as 10%, 90 patients (45 for each group) were recruited as the final sample size for the study before the prospective design.

### Statistical Analysis

Continuous variables were presented as mean ± standard deviation. Normal distribution was assessed using the Kolmogorov-Smirnov test. Independent groups were analyzed using Student's t-test and Mann-Whitney U test. For normal distribution comparisons between the same groups, Paired-t-test or Wilcoxon Signed-rank test was used when suitable. Data obtained in the study were statistically analyzed using SPSS version 20 (SPSS, Chicago, IL, USA). The significance level was p<0.05.

## Results

Demographic, clinical, and pathological data for the two groups are shown in Table 1. There were no significant differences between the evaluated values of the two groups.

In group 1, erectile function, sexual desire, orgasmic function, intercourse satisfaction, and overall satisfaction were not statistically different after the procedure compared with before the procedure. However, the intercourse satisfaction was significantly lower after the procedure compared with before the procedure (p<0.05). In group 2, erectile function and sexual desire were not statistically different after the procedure compared with before the procedure. However, orgasmic function, intercourse satisfaction, and overall satisfaction were statistically significantly lower after the procedure than before the procedure (p<0.001).

No differences were observed between the five main items before the procedure when both groups were compared. However, orgasmic function and overall satisfaction were lower in group 2 and significantly different between the two groups after the procedure (p<0.001) (Table 2). No significant difference was observed between the two groups in terms of VAS (p=0.14).

## Discussion

The findings of this study suggest that the size of the needle used in the biopsy affects the orgasmic function and overall satisfaction. In practice, two sizes of needles (16G and 18G) are used in prostate biopsy. A 16G needle is approximately 1.5 times wider than an 18G needle, and the volume of a cylinder (the specimen) is  $4/3 \pi r^2$  times the length (9). There are many studies in the literature that evaluate the effects of prostate biopsy on ED (6,9). However, in the literature, male sexual functions have not been evaluated considering the needle size.

**Table 1. Demographic, clinical, and pathological data for the two groups**

	Group 1	Group 2	p-value
Age (years)	58.6±4.2	57.4±4.5	0.51
PSA (ng/mL)	8.76±3.1	8.4±4.1	0.46
Prostate volume (mL)	54.7±8.2	56.8±6.9	0.48
Body mass index (kg/m <sup>2</sup> )	25.8±2.9	24.3±2.7	0.41
Cancer detection rate (%)	8/45 (17.7%)	9/45 (20%)	0.89
Gross rectal bleeding	0	0	
Gross hematuria	0	0	
Fever	2/45	2/45	
PSA: Prostate-specific antigen			

Function domain		Group 1 (n=45; 18G needle; mean $\pm$ SD)	Group 2 (n=45; 16G needle; mean $\pm$ SD)	p1	p2	$\Delta$ 1	$\Delta$ 2
Erectile function (Q1, 2, 3, 4, 5, and 15)	Before After	27.2 $\pm$ 1.3 26.6 $\pm$ 1.5	26.9 $\pm$ 1.4 26.8 $\pm$ 1.4	0.75	0.736	0.6 $\pm$ 1.2	0.1 $\pm$ 1.2
Orgasmic function (Q9, 10)	Before After	8.2 $\pm$ 1.2 8.1 $\pm$ 0.9	8.0 $\pm$ 1.2 6.9 $\pm$ 1.2	0.43	<b>0.001</b>	0.1 $\pm$ 1.1	1.1 $\pm$ 1.3*
Sexual desire (Q11, 12)	Before After	7.3 $\pm$ 0.9 7.2 $\pm$ 0.9	7.4 $\pm$ 1 7.3 $\pm$ 1	0.45	0.43	0.1 $\pm$ 0.7	0.1 $\pm$ 0.6
Intercourse satisfaction (Q6, 7, and 8)	Before After	11.8 $\pm$ 1.1 11.1 $\pm$ 1.7	12 $\pm$ 0.9 10.6 $\pm$ 1.9	0.36	0.14	0.7 $\pm$ 1.2*	1.4 $\pm$ 1.7*
Overall satisfaction (Q13, 14)	Before After	7.8 $\pm$ 0.7 7.7 $\pm$ 0.6	7.9 $\pm$ 0.8 6.9 $\pm$ 0.7	0.41	<b>0.001</b>	0.1 $\pm$ 0.6	1 $\pm$ 0.6*
Visual pain score		2.6 $\pm$ 0.7	2.8 $\pm$ 0.8	0.147			

P1: it indicates the differences between values before the procedure in the study groups.  
P2: it indicates the differences between values after the procedure in the study groups.  
 $\Delta$ 1: it indicates the differences between values before and after the procedure in group 1.  
 $\Delta$ 2: it indicates the differences between values before and after the procedure in group 2.  
\* $p$ <0.05

Murray et al. (10) show that, a significant decrease in erectile function score was detected in the first month after prostate biopsy. Similarly, Sönmez et al. (7) showed a significant decrease in erectile function scores at the end of the first month compared with before the procedure. Generally, and as shown in studies, ED presents during the first month after the biopsy. Patients who had a degree of erectile function showed signs of recovery, and the majority of patients returned to their baseline in the long term (10). It is difficult to determine the physiological etiology of ED in a population that undergoes TRUS-Bx, especially those without concomitant ED-related systemic diseases and/or received medications. ED might be caused by a direct anatomical injury (neurovascular bundle damage) or secondary trauma (nerve compression because of hematoma or edema) (11). Moreover, dilated periprostatic plexus is a common ultrasonography finding in the pathology of the prostate after TRUS-Bx and a frequent cause of ED (12). The two needle sizes used in this study had no effect on erectile function after the procedure compared with before the procedure. However, when both groups were compared in terms of orgasmic function and overall satisfaction values after the procedure, values were significantly lower in group 2 before the procedure. A thicker needle may cause edema in the prostate or hematoma on ejaculation and decrease in intercourse satisfaction and overall satisfaction. The physiopathology causing ED may be the reason for this decrease, and when these patients are evaluated in the long term, these functions may improve.

On evaluating group 1, only the intercourse satisfaction was lower after the procedure compared with before the procedure. Intercourse satisfaction was also lower after the procedure compared with before the procedure in group 2. However, on evaluating the intercourse satisfaction after the procedure, no difference was found between the two groups, which might be related to the approximately similar decreasing values in both groups. On searching the literature, there was no study comparing between orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction scores in IIEF

before and after performing a prostate biopsy. Therefore, we could not compare the scores in our study with other studies.

Due to patients experiencing pain, postprocedure VAS values were compared for sexual dysfunctions. In one study, the use of lidocaine gel combined with periprostatic local anesthesia showed a significant improvement in pain scores compared with lidocaine gel only (13). In our study, we applied local anesthesia with a combination of periprostatic nerve blockage and lidocaine gel for all patients. It was observed that the periprostatic blockade is an effective anesthetic, and no significant difference was observed between the two groups in terms of VAS scores.

One of the strategies for the diagnosis of PCa has been to increase the size of the biopsy needle (14). There are many studies on the relation between cancer detection rate and needle size (9,14). Cicioone et al. (9) and McCormack et al. (14) showed that there were no significant differences between 16G and 18G needles in terms of cancer detection. Similarly, in this study, no differences were seen in the cancer detection rate between the two groups. In TRUS-Bx, the biopsy is obtained through the rectum. Potential risks include infectious complications, such as pyuria, bacteriuria, and fever; hemorrhagic complications including hematuria; relatively minor complications such as vasovagal syncope due to the pain caused by biopsy; major complications, such as structural damage to surrounding anatomical structures and infectious septicemia (15,16). Bleeding after TRUS-Bx is reportedly the most common minor complication (17). In our study, high fever (>38 °C in two patients) that did not require hospitalization was observed in both groups. No major complications were observed in any patient.

### Study Limitations

There were some limitations in this study. While waiting for a pathology result, there may be changes in IIEF scores due to anxiety occurring in patients. Since this situation is not homogeneously distributed, we cannot know which group is affected more. We evaluated the patients in the fourth week,

but the evaluation in the sixth or twelfth months may provide different results in the long term. The required sample size seemed acceptable in our study. However, the use of samples of a larger size in further research would probably indicate better outcomes.

## Conclusion

Overall, TRUS-Bx did not affect ED. However, on using different needle sizes, significant changes in orgasmic functions and overall satisfaction were observed. It was concluded that using a small needle size is important for sexually active patients.

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## Ethics

**Ethics Committee Approval:** An approval was obtained from our institutional review board (number: 2018/01/277) for this study.

**Informed Consent:** All patients signed an informed consent.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Concept: H.T., Design: H.T., K.Ö., Data Collection or Processing: H.T., G.K.Ö., Analysis or Interpretation: M.S., Literature Search: K.Ö., K.Y., Writing: H.T.

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# Comparison between the Success of Prostate and Breast Cancer Awareness Campaigns over “Google Trends” in Turkey

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## Abstract

**Objective:** This study aimed to compare the success of breast and prostate cancer awareness campaigns using the search rates on the internet as an indicator of the public's interest in the subject.

**Materials and Methods:** The periodic median search rates of the “breast cancer” and “prostate cancer” terms searched between January 2010 and December 2019 annually, 2010-2014 (first period), and 2015-2019 (second period) were compared over Google Trends™. The effect of the awareness campaigns and isolated rises (an increase of at least 25%) in the normal trend were evaluated.

**Results:** It was observed that the median search rates for both cancer types increased in the second period ( $p < 0.05$ ). When trends were compared before and after the awareness months annually, an increase above the normal trend was detected for breast cancer ( $p < 0.001$ ). However, this increase was not observed in prostate cancer ( $p > 0.05$ ). Moreover, we found that the isolated rises for both types of cancer coincided with celebrity-related news covered in the media.

**Conclusion:** Although breast cancer awareness was created in the society, it was determined that the situation was not the same for prostate cancer. More studies are needed to enlighten the public on prostate cancer, and Google Trends™ may be an important tool that can assist the follow-up on this subject.

**Keywords:** Breast cancer, google trends, prostate cancer, awareness month

## Introduction

Prostate cancer is the second most common cancer in males and breast cancer is the most common cancer in females. According to 2018 data, prostate cancer constitutes 8.2% of cancer diagnosis with 17.332 new patients and 4.4% of all cancer-related deaths with 5165 deaths due to prostate cancer. Alternately, breast cancer is a serious health problem with 22.345 (10.6%) new patients and 5.452 (4.7%) deaths in 2018 (1).

In Turkey, October is recognized as the breast cancer awareness month, and September 15 is accepted as the prostate cancer day. The success of a breast cancer awareness campaign has been detected in various studies. It was revealed that the number of applications to hospitals for early diagnosis increased in October compared with other months of the year. The importance of increasing awareness of early diagnosis has been put forward (2,3,4). Although there is no study examining the effect of prostate cancer awareness efforts in our country, the

breast cancer awareness campaign, which has proven effective, is seen as an important scale in the evaluation of the success of prostate cancer awareness efforts (5).

Today, the internet is one of the most commonly used tools to access medical information (6). Google™ is the most used search engine worldwide, and Google Trends™ application has been widely used in the medical field in the follow-up on an online interest. It is used as an indicator of public attitude toward health as well as identifying popularities specific to terms in the performed searches (7,8). This study aimed to compare the effectiveness of breast and prostate cancer awareness campaigns in our country using searches on the Internet as an indicator of the public's interest.

## Materials and Methods

The Ethics Committee of Aksaray University approved this cross-sectional study (2020/08-28). All patients who took part in the study provided informed consent.

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Google Trends™ application provided the search levels of the searched term(s) by the selected time interval and country in numerical values [relative search rate (RSR)]. Additionally, it can arrange these values so that the searched terms can be compared. “Zero” indicates that there is no data for the word we are searching for, and “100” indicates that the term has the highest search rate. The application scores other instances between zero and 100.

The searches made on Google Trends™ application using the terms “breast cancer” and “prostate cancer” in Turkish between January 2010 and December 2019 in Turkey were examined, and the rates of interest shown to each term in the annual median period were obtained. Afterwards, periodic RSR values were compared in terms of both cancer types in the periods of 2010-2014 (first period) and 2015-2019 (second period). Furthermore, by comparing the median monthly RSR values of all years for breast and prostate cancers, we tried determining whether a different course than the normal trend occurred during the awareness campaigns. Moreover, rises in the interest rates 25% higher than normal within a specified period except for the awareness months were evaluated as rapid rises, and the reasons behind such increases in these searches were investigated. Moreover, the cities that had the most searches for both terms were identified.

**Statistical Analysis**

SPSS 20.0 (SPSS, Chicago, IL) was used for the statistical analysis. Discrete quantitative data were shown as median (interquartile range). Shapiro-Wilk test was used to evaluate the homogeneous distribution of the data. Mann-Whitney U test was used to compare two independent groups, while the Wilcoxon test was used to compare two dependent groups. The ANOVA procedure with linear models was used to assess changes over time in different outcomes measured and separate repeated measures. A p-value less than 0.05 was considered statistically significant.

**Results**

The median RSR was 35 (9.75) and 45 (8.5) for breast cancer and 12 (3.75) and 18 (5) for prostate cancer in the first and second periods, respectively. Although the median RSR favored breast cancer in all periods (p<0.001), the RSR value increased for both cancers in the second period (p<0.05) (Table 1; Figure1).

When the effect of breast cancer awareness month was examined, it was found that the median RSR of October in all years was higher than the median RSR of the normal trend (p<0.001) (Figure 2). When the years were evaluated within

Table 1. Comparison of the relative search rates by years				
Period (year)	2010-2019	2010-2014 (1 <sup>st</sup> period)	2015-2019 (2 <sup>nd</sup> period)	p-values†
Breast cancer (RSR)	41 (10.38)‡	35 (9.75)‡	45 (8.5)‡	<b>0.043</b>
Prostate cancer (RSR)	13.75 (6.88)	12 (3.75)	18 (5)	<b>0.041</b>

Values are reported as median (interquartile range); RSR: Relative search rate  
 ‡p<0.001 vs. prostate cancer (Mann-Whitney U test)  
 †Wilcoxon test

themselves, it was observed that the median RSR indexes of October in every year were higher than the median RSR of the normal trend in its own year (p<0.001) (Figure 3).

When the effect of the prostate cancer awareness campaign was examined, it was observed that the median RSR of September in all years and the normal trend were similar (p>0.05). When the years were evaluated within themselves, it was determined that this situation continued in the same way (p>0.05) (Figure 4).

Except for the awareness campaign months, when the situations detected as rapid rise were examined, it was seen that the value, which was 60 in October 2011, when the RSR was at the highest level for breast cancer, increased by 53.33% and reached 92 in December 2011. The RSR value for prostate cancer increased from 10 to 29 in January 2014 (190%) and from 19 in June 2017 to 36 in July 2017 (89.47%). It was seen that, in the periods when there was a rapid rise for breast cancer, the most searched term accompanying breast cancer on Google was “Deniz Uġur,” and this coincided with the period when this famous person was diagnosed with breast cancer. In the periods when there was a rapid rise for prostate cancer, the most searched term accompanying prostate cancer on Google was “Harun Kolġak,” and this coincided with the period when this famous person was diagnosed with prostate cancer and died as a result (Figure 1).

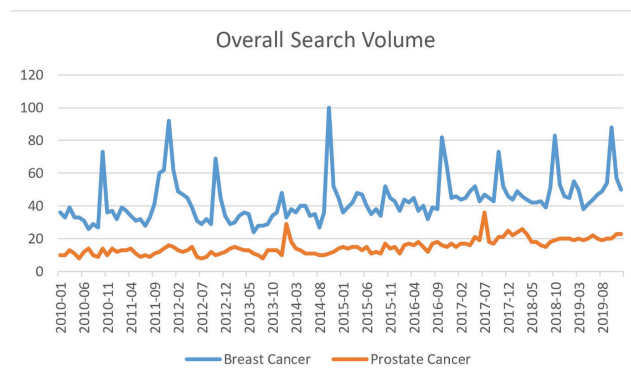


Figure 1. Comparison between the prostate and breast cancer search rates

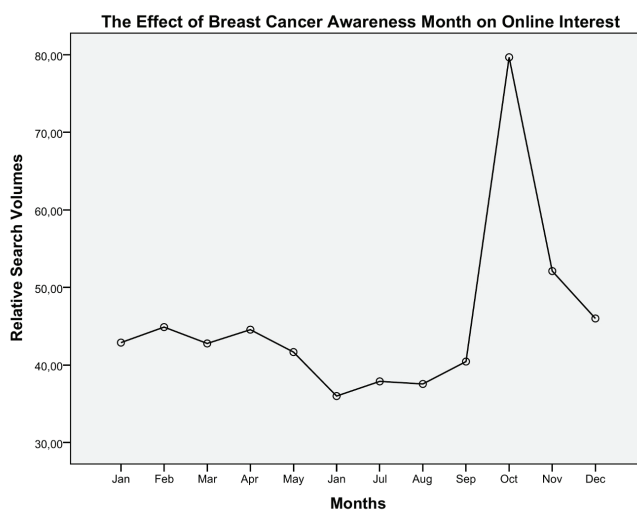
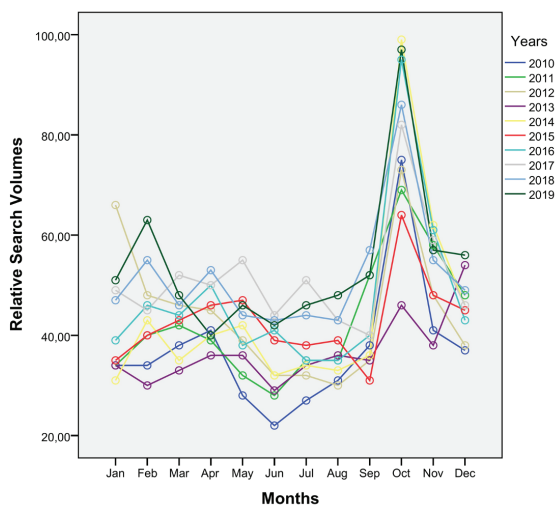
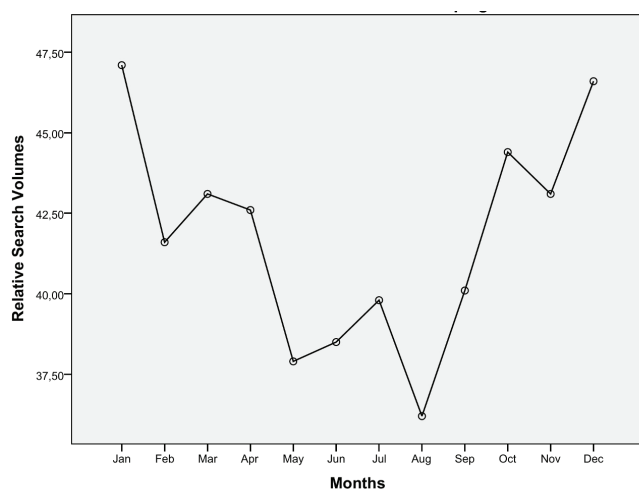


Figure 2. The effect of breast cancer awareness month on online interest

When the cities that had the most searches on the Internet for both cancers were examined, it was determined that the first three cities, where the most searches for breast cancer were performed, were Izmir (RSR: 100), Ankara (RSR: 96), and Eskiřehir (RSR: 95), while for prostate cancer they were Izmir (RSR: 100), Eskiřehir (RSR: 91), and Istanbul (RSR: 90).



**Figure 3.** The effect of breast cancer awareness month on online interest by years



**Figure 4.** The effect of prostate cancer awareness campaign on online interest

## Discussion

This study found that the searches for prostate and breast cancer have increased especially in the last five years, and breast cancer is more popular than prostate cancer. When the current literature was examined, according to the data of the World Health Organization for both cancers, it was observed that the incidence of prostate cancer, standardized by age, increased from 31.1 to 41.7 per 100.000, and the incidence of breast cancer increased from 43.3 to 45.6 in 2018 compared with 2014 (1,9). According to the data of the Ministry of Health,

in Turkey, in 2005, prostate and breast cancer incidence was reported to be 24.33 and 17.96 per 100,000, respectively (10). In another multicenter study conducted in Turkey, the incidence of prostate cancer, standardized by age, was 35 per 100,000 in 2009, and according to Middle East Cancer Consortium in 2016, the breast and prostate cancer incidence in Turkey was 50.7 and 47.4 per 100.000, respectively (11,12). A study examining the relationship between online search rates and cancer incidence revealed that there was a positive correlation between these for all cancer types (13). In Turkey, no regular data could be obtained for the incidence of breast and prostate cancers. However, studies conducted in our country revealed that although the incidence of breast cancer was higher than prostate cancer, the incidence increased for both cancers from 2005 to 2016. Although this situation is in line with the data obtained in our study, it is thought that online interest can be used in the detection of cancer incidence.

It was revealed that the national breast cancer awareness campaign held in October every year, which started in the USA in 1985, increased the awareness of breast cancer in the society. On examining breast cancer diagnoses made from 1973 to 2005, the number of diagnosed patients gradually increased, especially starting from the period when the awareness campaign was initiated (14). A study conducted in our country showed that the number of females presenting to a health institution for breast examination increased in October, during the breast cancer awareness campaign, compared with other months (2). When the situation was examined for prostate cancer, a study conducted with 1400 participants from six European countries showed that the necessary awareness of prostate cancer symptoms, tests used in the detection, and treatment alternatives could not be created (15). A review article stated that the males who participated in the studies for prostate cancer screening were willing but hesitated for reasons such as social reasons, indecisiveness, uncertainties, and cost, and this was due to inadequate education of the society on this subject (16). Moreover, a study conducted in our country showed that prostate cancer awareness was not at the sufficient level (17).

It was found that the rates of searches made on the Internet for breast cancer increased during the breast cancer awareness period. However, this did not occur during prostate cancer awareness period for the "prostate cancer" term. On reviewing the studies examining the effects of cancer awareness activities in terms of searches on the Internet, a study, where cancer awareness campaigns were examined over Google Trends between 2010 and 2017, showed that there was a consistent increase in breast cancer in its awareness period; however, it was a stable course for prostate cancer (5). Our study detected that breast cancer awareness was reflected in online interest in our country and people used the Internet to obtain more information about breast cancer in this period. However, this was not the same for prostate cancer. For prostate cancer awareness, it is thought that online interest can be used for follow-up, and more activities are needed both worldwide and in our country.

In our study, the situations with significant changes in online interest in prostate and breast cancers, except for the months of awareness campaigns, were investigated, and it was detected

that two famous names caused an increase (25% above normal trend) in RSR value in the last 10 years. It was determined that Angelina Jolie's bilateral protective mastectomy caused a significant increase in the USA in the search of the term "breast cancer" made over GoogleTM during the period of 2004-2017, apart from the awareness months. This was introduced to the literature as the "Angelina Jolie Effect" and directed people to make searches on the Internet regarding mastectomy and BRCA-1 gene at a high rate. However, it was observed that celebrities diagnosed with prostate cancer did not have such an effect on RSR level (18). Between 2004 and 2016 in the UK, there was a distinct increase in breast cancer searches made over the Internet after Kylie Minogue was diagnosed with breast cancer in addition to the "Angelina Jolie Effect." This situation created its own trend for each country (19). Although celebrities other than Deniz Uġur were diagnosed with breast cancer, the increase in breast cancer trend caused by the diagnosis of Deniz Uġur may have resulted from the fact that her high-rating TV series coincided with the December 2011 period. It can be stated that the increase of prostate cancer trend due to the diagnosis of Harun Kolçak with prostate cancer and his death was evident in our country and not anywhere else. Google TrendsTM is a tool that can be used to follow the influence of celebrities and public awareness, and the use of such online data can increase cancer awareness in the society and contribute to activities conducted in this regard.

In our study, the cities that had the highest search rates for breast and prostate cancers were examined, and the city with the highest search rate for both cancers was İzmir. A study examining cancer incidence rates showed that the city with the highest prostate cancer rate in our country was İzmir with an incidence rate of 38.2/100,000, and the cities with the highest breast cancer rates were İzmir and Eskişehir with incidence rates of 45.6/100,000 and 35.3/100,000, respectively (20). Our results put forward that real epidemiological data may have a parallel reflection on searches on the Internet. It is thought that, with the widespread use of the Internet and addition of more demographic data of users to Google TrendsTM application, more progress can be made in terms of digital epidemiology.

### Study Limitations

Our study limitations are as follows: not being able to obtain data from areas where there is no Internet usage, not being able to see the searches made in different languages, accessing the search statistics of only those using GoogleTM search engine, and not being able to know the age, gender, and occupation of the searchers.

### Conclusion

In terms of the society's interest, success of breast cancer awareness campaigns on real grounds has been reflected in the search rates on the Internet. However, this success has not been achieved in awareness campaigns of prostate cancer. Although there is a need for improvement in the program, we can save money and time using Google TrendsTM instead of conventional field research to detect epidemiology and public cancer awareness. Moreover, we believe that Google TrendsTM can be

useful in analyzing the success of the breast cancer awareness campaign and guide us to plan a successful prostate cancer awareness campaign and determine the targeted population.

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### Ethics

**Ethics Committee Approval:** The Ethics Committee of Aksaray University approved this cross-sectional study (2020/08-28).

**Informed Consent:** All patients who took part in the study provided informed consent.

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### Authorship Contributions

Supervision: A.L.S., Critical Review: A.L.S., Concept: A.D., Design: A.D., Data Collection or Processing: A.D., Analysis or Interpretation: A.D., Literature Search: A.D., Writing: A.D.

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# Increased Prostate Imaging-Reporting and Data System Scores in Multiparametric Magnetic Resonance Imaging May Predict More Extensive Disease in Radical Prostatectomy Specimens

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## Abstract

**Objective:** This study aimed to investigate the correlation between index lesion prostate imaging-reporting and data system (PI-RADS) version-2 score and histopathological outcomes of prostatectomy specimens.

**Materials and Methods:** A total of 78 male patients with prostate cancer (PCa) treated with robot-assisted radical prostatectomy between August 2015 and June 2020 were included in this study. In this cohort, suspicious lesions on multiparametric magnetic resonance imaging (mpMRI) were scored according to PI-RADS version-2 criteria. MpMRI-targeted prostate biopsy was performed for all suspicious lesions with a PI-RADS score of  $\geq 3$  followed by systematic prostate biopsy. The relationship between index lesion PI-RADS score and histopathological outcomes of prostatectomy specimens were evaluated statistically.

**Results:** The mean age of the patients was  $65.0 \pm 7.0$  years. The distribution of PI-RADS scores of 3, 4, and 5 of the index lesions were 6 (7.7%), 29 (37.2%), and 43 (55.1%), respectively. Lower tumor volume and tumor volume ratio were observed in patients with a PI-RADS score of 3 when they were compared with patients with PI-RADS scores of 4 and PI-RADS-5 ( $p < 0.001$ , for each). No significant correlation was found between index lesion PI-RADS score in mpMRI and clinically significant PCa in prostatectomy specimens ( $r = 0.200$ ,  $p > 0.05$ ). However, a significant correlation was observed between index lesion PI-RADS score and extracapsular extension (ECE), as well as seminal vesicle invasion (SVI) and pT stage ( $r = 0.327$ ,  $p = 0.004$ ;  $r = 0.276$ ,  $p = 0.014$ ,  $r = 0.348$ ,  $p = 0.002$ , respectively).

**Conclusion:** Increased index lesion PI-RADS scores were associated with ECE, SVI, higher tumor volume, tumor volume ratio, and pT stages. Increased index lesion PI-RADS score in mpMRI may be helpful in prediction of locally advanced PCa in prostatectomy specimens.

**Keywords:** Index lesion, multiparametric magnetic resonance imaging, PI-RADS, prostate neoplasms, radical prostatectomy

## Introduction

Prostate cancer (PCa) is the second most common cancer in men worldwide with an estimated 1,276,106 new cases and 358,989 deaths (1). Transrectal ultrasound-guided systematic prostate biopsy (SBx) with a minimum of 10-12 cores has been accepted as the standard diagnostic approach for the evaluation of patients who have a clinical suspicion for PCa (2). Recently, multiparametric prostate magnetic resonance imaging (mpMRI), which provides a better depiction of prostate anatomy as well as

functional imaging, has been recommended for the evaluation of any patient who has a suspicion of PCa with or without a history of prior biopsy (2,3,4).

The European Society of Urogenital Radiology introduced the prostate imaging-reporting and data system (PI-RADS) version-1 (v1) for standardization of interpretation and reporting of mpMRI in 2012 (5). A Likert-type scoring system is used in PI-RADS to demonstrate the likelihood of the presence of clinically significant (cs) PCa. Several limitations such as suboptimal definition of the exact scoring with relatively higher subjectivity in the evaluation

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of suspicious lesions in PI-RADSV1 system restricted its use (6). Subsequently, PI-RADS version-2 (v2) was introduced in 2015 and several studies suggested that PI-RADSV2 is more suitable for routine clinical use due to its higher reproducibility and better inter-observer agreement for malignant lesions when compared to PI-RADSV1 (6,7,8).

Although higher detection rates of csPCa in mpMRI-targeted prostate biopsy (TBx) specimens in patients with increased PI-RADS scores have been reported in many studies, currently, the exact relationship between PI-RADS scores and pathological outcomes at the final prostatectomy specimens remains unclear (3,9,10,11,12,13,14). Several retrospective studies have investigated this topic with controversial outcomes (15,16,17). In this context, the present study aimed to evaluate the association of PI-RADS scores in mpMRI with the pathological outcomes of prostatectomy specimens.

## Materials and Methods

### Study Population

We retrospectively reviewed medical records of 329 male patients who underwent transperineal prostate needle biopsy in Acibadem Mehmet Ali Aydınlar University, Altunizade and Kadıköy Hospitals, Clinic of Urology, between August 2015 and June 2020. Patients who underwent transperineal TBx, with concomitant 12-core SBx, diagnosed with PCa and treated with robot-assisted radical prostatectomy were included in the study. The study was approved by the local Institutional Ethics Committee (IRB No:2021-15/01).

All steps of the study were planned and conducted in accordance with the principles of the Declaration of Helsinki. A written informed consent on admittance to hospital was obtained from all individuals, which permitted the use of respective medical information in clinical studies.

Demographic characteristics, preoperative clinical characteristics, pathological findings of each biopsy type, and prostatectomy specimens were noted in detail for each patient. Patients who had benign tissue in biopsy pathology, underwent SBx only, had metastatic PCa at clinical staging, did not accept surgery or treated with radiotherapy and had missing clinical data were excluded. Finally, a total of 78 male patients who met the selection criteria were included in this study. The PI-RADS score groups (scores of 3, 4, and 5) were compared statistically.

### mpMRI and Determination of Suspicious Lesions

All patients were evaluated with 3-T mpMRI (Magnetom Skyra, Siemens Healthineers, Erlangen, Germany) before the prostate biopsy. All mpMRI studies were evaluated by the same dedicated radiologist (A.D.), and all PI-RADSV2 lesions  $\geq 3$  were mapped. The border of the prostate and lesions were outlined and saved as a biopsy plan by MIM Symphony Dx™ Software Inc. version 6.7 (Cleveland, OH, USA). The lesion with the highest PI-RADSV2 score was determined as the index lesion in case of multiple suspicious lesions in mpMRI. If more than one lesion had the same highest PI-RADSV2 score, the lesion with the largest volume calculated by MIM Symphony Dx™ software was accepted as the index lesion.

### Transperineal mpMRI-targeted and Systematic Prostate Biopsy

All transperineal TBx and SBx procedures were performed under sedoanalgesia in a dorsal lithotomy position. An 18-gauge automatic biopsy gun with a 19-mm sample notch was used in biopsy procedures (Tru-Core™ II URO Automatic Biopsy Instrument, Argon Medical Devices, Inc., TX, USA). A single-dose parenteral antibiotic as prophylaxis was administered to all patients during anesthesia induction (ceftriaxone sodium 1 g or cefuroxime sodium 1.5 g, intravenous). Moreover, 2-4 samples were taken from each of the suspicious lesions with PI-RADS score of  $\geq 3$  using a stepper and template grid as previously reported (18). Additional biopsies were performed if necessary (e.g., for the hypoechoic lesions on ultrasonography). All biopsy samples and whole-mount sections after radical prostatectomy were evaluated by a dedicated uropathologist (H.D.) in accordance with the 2014 International Society of Urologic Pathology (ISUP) criteria (19). csPCa in prostatectomy specimens was defined as the presence of Gleason score (GS)  $>6$  or GS 6 disease with tumor volume greater than 0.5 cm<sup>3</sup> (20).

### Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 22.0 software (IBM Corp., Armonk, NY, USA). Shapiro-Wilk test was used to check the normality of data for quantitative variables. Descriptive data were expressed in mean  $\pm$  standard deviation and median (interquartile range), or number and frequency. Fisher's exact and Kruskal-Wallis tests were used to determine homogeneity, independence, and differences between related groups as indicated. The post-hoc analysis was conducted by Tamhane's test. The correlation coefficient and significance for the relationships between the index lesion PI-RADS scores and various variables in biopsy and prostatectomy specimens were calculated with Spearman's test. A two-sided p-value of  $<0.05$  was considered statistically significant.

## Results

The mean age of the patients was 65.0 $\pm$ 7.0 years, and the median PSA and PSA density were 5.52 (4.20-8.80) ng/mL and 0.13 (0.09-0.17) ng/mL<sup>2</sup>, respectively (Table 1). Preoperative demographic and clinical characteristics of the participants and prostatectomy pathology results are summarized in Table 1.

The distribution of PI-RADS scores of 3, 4, and 5 of the index lesions were 6 (7.7%), 29 (37.2%), and 43 (55.1%), respectively. The median number of suspicious lesion detected in mpMRI was 3 (2-4), and the median number of tumor-positive lesion was 1 (1-2) in TBx. The median number of cores sampled and tumor-positive cores in SBx were 12 (12-12) and 3 (1-5), respectively. PCa was detected in 66 (84.6%) patients by TBx and 68 (87.2%) patients by SBx. csPCa was detected by TBx and SBx in 57 (73.1%) and 61 (78.2%) patients, respectively.

Increased PSA levels was observed in patients with higher PI-RADS score; however, no significant difference was found between the PSA levels of the patients when they were compared according to index lesion PI-RADS score ( $p>0.05$ ) (Table 2). A significant difference was noted among the PI-RADS score groups in terms

of the median number of tumor positive lesions in TBx ( $p=0.041$ ) (Table 2). In the post-hoc analysis, significant difference was found between PI-RADS-3 and PI-RADS-5 groups in terms of the number of tumor positive lesions in TBx ( $p=0.047$ ). In the post-hoc analysis, lower tumor volume and tumor volume ratio were observed in PI-RADS-3 when compared with PI-RADS-4 and PI-RADS-5 groups ( $p<0.001$ , for each). Higher pT stages were observed with increased PI-RADS score, pT3b disease was only seen in the PI-RADS-5 group, while none of the patients in the PI-RADS-3 group had  $\geq$ pT3a disease (Table 2).

No significant correlation was found between index lesion PI-RADS score and PSA and PSA density ( $r=0.121$ ,  $p=0.293$ ;  $r=0.120$ ,  $p=0.296$ , respectively). Moreover, no significant correlation was noted between index lesion PI-RADS score and number of tumor positive lesions in TBx ( $r=0.151$ ,  $p=0.188$ ). Significant linear correlation was observed between index lesion PI-RADS score and csPCa in TBx and SBx ( $r=0.300$ ,  $p=0.008$ ;  $r=0.249$ ,  $p=0.030$ , respectively) (Table 3). Similarly, a significant correlation was observed between index lesion PI-RADS score and extracapsular extension (ECE), as well as seminal vesicle

invasion (SVI) and pT stage ( $r=0.327$ ,  $p=0.004$ ;  $r=0.276$ ,  $p=0.014$ ,  $r=0.348$ ,  $p=0.002$ , respectively). Correlation analysis between the index lesion PI-RADS score and prostate biopsy and prostatectomy pathology are summarized in Table 3.

### Discussion

This study aimed to assess the relationship between index lesion PI-RADS score in mpMRI and various pathological features of prostatectomy specimens in patients who underwent transperineal TBx and/or SBx and subsequently treated with robot-assisted radical prostatectomy. Based on our study results, increased index lesion PI-RADS scores were associated with higher tumor volume, tumor volume ratio, and pT stages in prostatectomy specimens. Moreover, the frequency of csPCa in prostatectomy specimens increased in patients who had a higher index lesion PI-RADS score. However, no significant difference was found between the PI-RADS score groups in terms of csPCa, and no correlation was noted between the index lesion PI-RADS score and csPCa in prostatectomy specimens. The lack of significant correlation noted between the index

**Table 1. Demographic and clinical characteristics of the participants**

		Mean $\pm$ SD	Median (IQR)	n, %
Age (year)		65.00 $\pm$ 7.00		
BMI (kg/m <sup>2</sup> )		26.59 $\pm$ 3.81		
Preoperative PSA (ng/mL)			5.52 (4.20-8.80)	
Prostate volume (mL)			47.00 (34.00-58.00)	
Abnormal digital rectal examination (yes)				10 (12.8%)
Preoperative cT stage	cT1c			69 (88.5%)
	cT2			9 (11.5%)
ISUP-GG in RARP	ISUP-1			4 (5.1%)
	ISUP-2			44 (56.4%)
	ISUP-3			23 (29.5%)
	ISUP-4			2 (2.6%)
	ISUP-5			5 (6.4%)
csPCa in RARP (yes)				75 (96.2%)
Tumor volume in RARP (cm <sup>3</sup> )			3.45 (1.70-6.00)	
Tumor volume ratio in RARP (%)		8.84 $\pm$ 6.80		
Vascular invasion in RARP (yes)				1 (1.3%)
Lymphatic invasion in RARP (yes)				5 (6.4%)
Perineural invasion in RARP (yes)				72 (92.3%)
Surgical margin in RARP (positive)				10 (12.8%)
pT stage in RARP	pT2			52 (66.7%)
	pT3a			19 (24.4%)
	pT3b			7 (9.0%)
Extracapsular extension (yes)				26 (33.3%)
Seminal vesicle invasion (yes)				7 (9.0%)
Total number of lymph nodes dissected in PLND			14 (10-18)	
Lymph node metastasis (yes)				2 (3.9%)
Number of lymph node with metastatic deposits			0 (0-0)	

SD: Standard deviation, IQR: Interquartile range, BMI: Body mass index, PSA: Prostate-specific antigen, RARP: Robot-assisted radical prostatectomy, ISUP: International Society of Urologic Pathology, GG: Grade group, csPCa: Clinically significant prostate cancer



**Table 2. Comparison of the participants in terms of pathological features in RARP according to index lesion PI-RADS score**

Variables	Index lesion PI-RADS score						p-value
	PI-RADS-3 (n=6, 7.7%)		PI-RADS-4 (n=29, 37.2%)		PI-RADS-5 (n=43, 55.1%)		
	median (IQR)	n, %	median (IQR)	n, %	median (IQR)	n, %	
Abnormal digital rectal examination (yes)		0		3 (10.3%)		7 (16.3%)	<sup>a</sup> 0.670
Preoperative PSA (ng/mL)	4.70 (3.20-4.90)		5.50 (4.07-8.80)		5.72 (4.40-9.70)		<sup>b</sup> 0.275
Number of positive lesions in TBx	0 (0-1)		1 (1-2)		1 (1-3)		<sup>b</sup> 0.041*
ISUP-GG in RARP	ISUP-1	2 (33.3%)		1 (3.4%)		1 (2.3%)	<sup>a</sup> 0.268
	ISUP-2	3 (50.0%)		19 (65.5%)		22 (51.2%)	
	ISUP-3	1 (16.7%)		7 (24.1%)		15 (34.9%)	
	ISUP-4	0		0		2 (4.7%)	
	ISUP-5	0		2 (6.9%)		3 (7.0%)	
csPCa in RARP (yes)		5 (83.3%)		28 (96.6%)		42 (97.7%)	<sup>a</sup> 0.264
Tumor volume in RARP (cm <sup>3</sup> )	0.80 (0.50-1.30)		3.00 (1.70-5.50)		4.50 (2.50-7.30)		<sup>b</sup> 0.001*
Tumor volume ratio in RARP (%)	1.90 (1.75-2.60)		6.00 (3.10-10.50)		9.30 (6.00-14.50)		<sup>b</sup> 0.001*
Perineural invasion in RARP (yes)		5 (83.3%)		25 (86.2%)		42 (97.7%)	<sup>a</sup> 0.159
Surgical margin in RARP (positive)		0		5 (17.2%)		5 (11.6%)	<sup>a</sup> 0.576
pT Stage in RARP	pT2	6 (100.0%)		23 (79.3%)		23 (53.5%)	<sup>a</sup> 0.031*
	pT3a	0		6 (20.7%)		13 (30.2%)	
	pT3b	0		0		7 (16.3%)	
Extracapsular extension (yes)		0		6 (20.7%)		20 (46.5%)	<sup>a</sup> 0.015*
Seminal vesicle invasion (yes)		0		0		7 (16.3%)	<sup>a</sup> 0.053

<sup>a</sup>Fisher's Exact test, <sup>b</sup>Kruskal-Wallis test, \*p<0.05  
RARP: Robot-assisted radical prostatectomy, PI-RADS: Prostate imaging-reporting and data system, IQR: Interquartile range, PSA: Prostate-specific antigen, TBx: Targeted prostate biopsy, ISUP: International Society of Urologic Pathology, GG: Grade group, csPCa: Clinically significant prostate cancer

**Table 3. Correlation analysis between index lesion PI-RADS score and prostate biopsy and prostatectomy pathology**

	csPCa in TBx		csPCa in SBx		csPCa in Prostatectomy		Tumor volume in prostatectomy (cm <sup>3</sup> )		Tumor volume ratio in prostatectomy (%)		pT Stage		ECE		SVI	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Index lesion PI-RADS	0.300**	0.008	0.249*	0.030	0.124	0.279	0.376**	0.001	0.381**	0.001	0.348**	0.002	0.327**	0.004	0.276*	0.014

Spearman correlation analysis. \*Correlation is significant at p<0.05 level (two-tailed). \*\*Correlation is significant at the 0.01 level (two-tailed).  
csPCa: Clinically significant prostate cancer, TBx: Targeted prostate biopsy, SBx: Systematic prostate biopsy, ECE: Extracapsular extension, SVI: Seminal vesicle invasion, PI-RADS: Prostate imaging-reporting and data system

lesion PI-RADS score and csPCa in prostatectomy specimens is most likely caused by the very high ratio of csPCa in this cohort. As we presented above, nearly all patients (96.2%) had csPCa in prostatectomy specimens. By contrast, we observed significant correlation between the index lesion PI-RADS scores and csPCa in both TBx and SBx. Therefore, indirect evidence may suggest that increased index lesion PI-RADS scores may also play a role in predicting csPCa in prostatectomy specimens. Furthermore, higher index lesion PI-RADS scores were correlated with ECE and

SVI in prostatectomy specimens as well as higher volume tumors with higher ISUP-grade group category. In this context, our data may suggest that increased index lesion PI-RADS score in mpMRI may predict locally advanced PCa in prostatectomy specimens. Currently, mpMRI has been widely accepted as a standard imaging modality in the diagnostic pathway and treatment decision process of PCa with its claimed higher sensitivity for the detection of csPCa (9,21). Previously reported detection rates

of csPCa for PI-RADS lesions with a score of 3, 4, and 5 ranges from 0% to 66%, 21% to 98%, and 75% to 99%, respectively (9,10,11). Our observation for csPCa ratios for index lesions with PI-RADS scores of 4 and 5 in prostatectomy specimens were similar; however, the csPCa ratio for the index lesion with a PI-RADS score of 3 was relatively higher in our study than in other studies. The higher csPCa ratios for PI-RADS 3 lesions may be attributed to the inclusion of only 6 patients with a PI-RADS score of 3 in our study cohort. In addition, although more than 95% of our patients had csPCa, these patients with an allocated PI-RADS score of 3 may represent biologically aggressive tumors with deceiving radiological characteristics. An observer bias is also a possibility.

The role of PI-RADS scoring in evaluation of tumor characteristics for clinical decision-making has been a topic of interest more recently. Several studies have reported the effect of PI-RADS vs. scoring on selecting possible candidates for active surveillance (AS) (22,23,24). Woo et al. (23) reported that PI-RADSV2 and PSA density were independent predictors of pathological downgrading in prostatectomy specimens in patients who had GS 7 (3+4) PCa in the prostate biopsy. In this study, the authors concluded that mpMRI might help identify patients who had an overestimated GS in SBx and assist in selecting potential candidates for AS (23). Similarly, a study reported that combination of PSA density (for threshold  $\geq 0.15$  ng/mL<sup>2</sup>) and PI-RADS score could help minimize the number of missed csPCa in men with a PI-RADS score of  $\leq 3$  (25). In another interesting study, PI-RADSV2 score of  $>3$  and front-to-total ratio of periprostatic fat tissue, which was measured in mpMRI and hypothesized as an influencer of the tumor microenvironment by paracrine effect, were independent risk factors for pathologic upgrading in prostatectomy specimens in patients with a biopsy GS 6 (3+3) (24). In the present study, we observed worse pathological outcomes such as higher frequency of ECE and SVI in prostatectomy specimens in patients with increased PI-RADS scores. Therefore, we also suggest that AS may not be a good treatment choice for patients with high PI-RADS (4 and 5) scores.

Slaoui et al. (15) investigated the correlation between PI-RADSV2 score in mpMRI and GS of both prostate biopsies and prostatectomy specimens. In this retrospective study, no significant concordance was found for GS in TBx and prostatectomy specimens according to the index lesion PI-RADS score (15). By contrast, similar to our study results, a retrospective study reported a significant association between PI-RADS scores and ECE and large tumor volume in a large number of patients who were eligible for AS (16). In this study, upgrading in prostatectomy specimens and unfavorable prognosis were also demonstrated, and the authors concluded that mpMRI and PI-RADS scoring could be used as a supporting parameter for a more accurate selection of patients eligible for AS (16). Similarly, adverse pathological outcomes such as tumor volume, ECE, lymphovascular invasion, and SVI were also reported in patients with increased PI-RADS scores in the most recent and well-designed multicenter study that investigated the correlation between PI-RADS and histopathological outcomes of prostatectomy specimens (17). Another recent study evaluated the correlation between PI-RADSV2 scores and several outcomes of prostatectomy specimens for central and

peripheral tumors separately (26). A poor correlation between PI-RADSV2 score and final GS was reported for both central and peripheral tumors, while a moderate-to-high correlation was reported between PI-RADSV2 score and tumor volume (26). Similar to these studies, in the present study, we observed worse histopathological outcomes such as higher tumor volume, pT stage, ECE, and SVI in prostatectomy specimens in patients with increased index lesion PI-RADS scores.

### Study Limitations

This study has several limitations. First, the retrospective and non-randomized nature of this study and the relatively small sample size introduce the possibility of selection bias. Second, all PI-RADS lesions in mpMRI were interpreted by only one radiologist, and all histopathological specimens were evaluated by only one pathologist. Therefore, we were unable to evaluate the inter-observer variability for outcomes. By contrast, we believe that our study results may contribute to the body of knowledge on this subject, in which no consensus has been revealed and has not been well investigated yet. Further investigations with larger cohorts, particularly including more patients with index lesion PI-RADS score of 3, are needed to validate the correlation between index lesion PI-RADS score in mpMRI and histopathological outcomes of prostatectomy specimens.

### Conclusion

In this study, higher tumor volume, tumor volume ratio, and pT stages in prostatectomy specimens were observed in patients with increased index lesion PI-RADS score in mpMRI. The frequency of csPCa in prostatectomy specimens also increased in these patients. However, no significant difference was found between the PI-RADS score groups in terms of csPCa, and no correlation was observed between the index lesion PI-RADS score and csPCa in prostatectomy specimens. In addition, higher index lesion PI-RADS scores were correlated with ECE and SVI in prostatectomy specimens. In this context, increased index lesion PI-RADS scores in mpMRI may predict locally advanced PCa in prostatectomy specimens. Therefore, AS may not be a good treatment choice for patients with increased PI-RADS scores. Further well-designed prospective, randomized studies with larger cohorts are needed to confirm our study results.

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### Ethics

**Ethics Committee Approval:** Acibadem Mehmet Ali Aydınlar University and Acibadem Healthcare Institutions Medical Research Ethics Committee, IRB No:2021-15/01.

**Informed Consent:** A written informed consent on admittance to hospital was obtained from all individuals, which permitted the use of respective medical information in clinical studies.

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### Authorship Contributions

Supervision: A.D., H.D., L.T., Concept: B.Ö., C.A., L.T., Design: B.Ö., C.A., L.T., Data Collection or Processing: N.K., Analysis or Interpretation: N.K., M.B.Ö., Literature Search: N.K., M.B.Ö., Writing: N.K., M.B.Ö.

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# Robot-Assisted Laparoscopic Versus Retropubic Radical Prostatectomy: Comparison of Functional and Oncological Outcomes, A Single-Center Experience

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## Abstract

**Objective:** This study aimed to investigate the effect of robot-assisted laparoscopic radical prostatectomy (RARP) and open retropubic radical prostatectomy (RRP) on perioperative functional and oncological outcomes.

**Materials and Methods:** This single-center retrospective study analyzed data of 443 patients who had undergone radical prostatectomy (RP) with localized prostate cancer. Surgical and clinicopathologic data, oncological and functional outcomes, and complications were compared between RRP and RARP groups. The comparison was made by the Mann-Whitney U test, chi-square test, and t-test for qualitative and quantitative variables, as appropriate. Log rank test was used to determine the biochemical recurrence-free survival of both surgical methods. Kaplan-Meier analysis was performed to estimate survival rates.

**Results:** The RRP and RARP groups included 231 and 212 patients, respectively. Blood loss, indwelling catheter duration, and hospitalization rates were low in the RARP group. Although the continence rates were better in the RARP group at 3 months, they were comparable at 12 months. In both groups, erection sufficient for sexual intercourse was comparable at 3 and 12 months. The mean lymph node yield was higher in the RRP group than in the RARP group. On median 28-month follow-up, no difference was found in the oncological results.

**Conclusion:** Although the oncological and functional results of RRP and RARP are comparable, RARP is a more minimally invasive procedure. In our opinion, the surgeon's experience is more effective than the chosen technique.

**Keywords:** Retropubic radical prostatectomy, prostate cancer, robotic prostatectomy, surgical technique

## Introduction

Radical prostatectomy (RP), a curative treatment option for prostate cancer (PCa), was first described by Young in 1904 (1). After Young described the perineal approach, the retropubic approach, which is widely used today, was described by Millin in 1947 (2). Following the popularity of the dorsal vein complex and neurovascular bundle anatomy, the first nerve-sparing radical prostatectomy (NS-RP) was performed by Walsh in 1982 (3). Significant improvements in RP have been achieved in the last 30-40 years, and for the first time in 2001, this operation was performed by a robot-assisted laparoscopic approach (4).

RP is a treatment option widely used in clinically localized and locally advanced disease. The main purpose of RP is to remove the tumor tissue by preserving continence and potency. Currently, no specific data can show the superiority of any approach in

terms of oncological and functional results after RP. Given the minimally invasive nature of robot-assisted laparoscopic radical prostatectomy (RARP), it may be associated with less blood loss and blood transfusion requirements, shorter hospitalization duration, and less pain.

In this study, we compared the preoperative, perioperative, and postoperative oncological and 3<sup>rd</sup> month and 12<sup>th</sup> month functional results of RARP and open retropubic radical prostatectomy (RRP).

## Materials and Methods

### Patient Selection

The study included patients who underwent RRP or RARP with a diagnosis of localized PCa between January 2016 and March

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2019, followed by at least 1 year, and whose data were fully available. The local ethical committee's registration number is 13-192-20. The study was conducted in a single center, and data of 443 patients were analyzed retrospectively. After a suspected digital rectal examination or a high prostate-specific antigen (PSA) value, diagnosis was made by transrectal ultrasound-guided prostate biopsy. If there are indications, bone scintigraphy, computed tomography, and multiparametric magnetic resonance imaging were performed. After the diagnosis was made, treatment options such as active surveillance, radiotherapy (RT), and RP were explained to the patients. The life expectancy of the patients was evaluated by the Charlson comorbidity index, and the risks of anesthesia were evaluated by using the American Society of Anesthesiologists score. The operation was planned for patients who had a life expectancy of at least 10 years and preferred RP as a treatment. Patients were informed about RRP and RARP by the surgeons who would perform the surgery. Patients decided whether the surgical approach was RRP or RARP. RP was performed at least 6 weeks after prostate biopsy to reduce possible surgical complications. On the night before the operation, enema as bowel preparation was performed and compression stockings were applied for all patients. Some of the RARP cases were performed by surgeons who were in the early phase of the learning curve. During the operation, extended lymph node (LN) dissection was performed in patients whose preoperative positive LN rate was more than 5%. Nerve-sparing surgery was not performed on patients with a high risk of extracapsular diseases, such as any cT3a or cT3b PCa or any International Society of Urologic Pathology (ISUP) grade >3 on biopsy. Penile rehabilitation with phosphodiesterase-5 inhibitors was recommended to patients with sufficient erection capacity for sexual intercourse in the preoperative period, after the indwelling catheter was withdrawn in the postoperative period. Patients who had received RT as definitive therapy and then underwent salvage RP and those who performed transurethral prostatectomy before RP were excluded. The patients were divided into the RRP and RARP groups to compare selected parameters. The preoperative characteristics of the patients are shown in Table 1.

### Preoperative Parameters

Age, body mass index, inguinal hernia or abdominal surgery history, potency and continence conditions, PSA value, biopsy ISUP grade, and clinical T stages were recorded.

### Intraoperative and Pathological Parameters

Nerve-sparing LN dissection and intraoperative blood loss were recorded. NS-RP surgery was not performed on patients at high risk of extracapsular disease. Pathology specimens were evaluated by a single pathologist. Surgical margin positivity, pathology ISUP grade, and T stage were recorded in the examined pathology samples.

### Postoperative Parameters

The postoperative parameters of the patients, such as hospitalization and catheterization time, and biochemical recurrence (BCR) were examined. In follow-up measurements, PSA >0.2 ng/mL in two consecutive measurements were accepted as BCR (5). Functional results, such as continence

and erectile function, were questioned during the outpatient clinic controls performed at 3 and 12 months. Patients using more than one protective pad were considered incontinent, and patients who were unable to achieve a sufficient erection in more than half of their sexual intercourse were considered impotent. Patients using 2-3 protective pads daily were considered to have mild incontinence, and patients using more than 3 protective pads were considered to have serious incontinence.

### Statistical Analysis

IBM SPSS® Statistics version 25 was used for statistical analysis. The normal distribution of the continuous variables was tested using the Kolmogorov-Smirnov test. Independent group t-test, Mann-Whitney U test, and chi-square test were used to compare independent variables with normal distribution, independent variables without normal distribution, and categorical data, respectively. Log rank test was used to determine the BCR-free survival of both surgical methods. Kaplan-Meier analysis was performed to estimate survival rates. P-values of <0.05 in the 95% confidence interval were considered significant.

### Results

In total, 231 and 212 of the patients underwent RRP and RARP, respectively. The demographic characteristics of the patients were generally comparable in both surgical groups (Table 1). Only, the PSA value was lower in the RARP group (Table 1).

Intraoperative blood loss was less in the RARP group (540 mL vs 265 mL;  $p < 0.001$ ) (Table 2). The mean hospitalization

Variables	RRP (n=231)	RARP (n=212)	p-value*
Mean age at surgery ± SD (yr)	65.54±6.57	69.59±6.51	0.372
Body mass index (kg/m <sup>2</sup> )			
<30 (kg/m <sup>2</sup> )	171 (74%)	160 (75.5%)	0.874
≥30 (kg/m <sup>2</sup> )	60 (26%)	52 (24.5%)	
History of inguinal hernia	21 (9.1%)	22 (10.3%)	0.614
History of abdominal surgery	45 (19.5%)	46 (21.6%)	0.490
Preoperative erection sufficient for sexual intercourse	153 (66.2%)	142 (67%)	0.780
Preoperative continent	231 (100%)	212 (100%)	-
Median preoperative PSA (ng/mL) (IQR)	13.22 (5.68-17.98)	9.30 (5.19-12.5)	0.018*
Biopsy ISUP grade			
ISUP grade 1	119 (51.5%)	121 (57.1%)	0.112
ISUP grade 2-3	59 (25.5%)	54 (25.5%)	
ISUP grade 4-5	53 (22.9%)	37 (17.4%)	
Clinical T-stage			
cT1	120 (51.9%)	109 (51.4%)	0.767
cT2	111 (48.1%)	103 (48.6%)	

\*Mann-Whitney U test, IQR: Interquartile range, RRP: Retropubic radical prostatectomy, RARP: Robot-assisted radical prostatectomy, PSA: Prostate-specific antigen, SD: Standard deviation, ISUP: International Society of Urologic Pathology

duration was 5.62 days in the RRP group and 4.24 days in the RARP group, and the difference was significant ( $p=0.046$ ) (Table 2). The indwelling catheter duration was shorter in the RARP group (15.11 vs 8.75;  $p<0.001$ ) (Table 2). The modified Clavien classification system was used to evaluate postoperative complications (6). In total, 28 complications were observed, including 17 (7.4%) in the RRP group and 11 (5.2%) in the RARP group. The number of patients with grade 3 complications was 2 (0.8%) in the RRP group and 1 (0.5%) in the RARP group. Clavien 4-5 complications were not observed in any patient. The number of patients with postoperative complications was not significantly different ( $p=0.224$ ) (Table 2).

Better continence rate was found in the RARP group at 3 months postoperatively (58.9% vs 74.5%;  $p=0.021$ ). Despite the higher continence rate in the RARP group at 12 months postoperatively, this difference was not significant (79.2% vs 84.9%;  $p=0.398$ ) (Table 3).

While the potency rates of the patients were lower at 3 months postoperatively (10.5% vs 10.6%), the potency rates improved at 12 months postoperatively (39.2% vs 42.3%). Although better potency rates were recorded in the RARP group, the difference was not significant ( $p=0.695$ ) (Table 3).

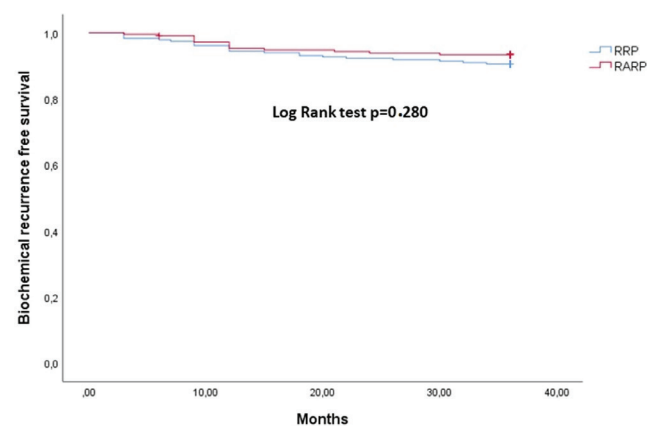
Variables	RRP (n=231)	RARP (n=212)	p-value*
Pathology ISUP grade			
ISUP grade 1	101 (43.7%)	82 (38.7%)	0.064
ISUP grade 2-3	84 (36.4%)	90 (42.4%)	
ISUP grade 4-5	46 (19.9%)	40 (18.9%)	
Pathology T-stage			
pT2	184 (79.7%)	177 (83.5%)	0.517
pT3a	42 (18.2%)	31 (14.6%)	
pT3b	5 (2.1%)	4 (1.9%)	
Mean pathology prostate weight $\pm$ SD	48.08 $\pm$ 17.84	47.92 $\pm$ 21.09	0.769
Lymph node dissection performed	145 (62.8%)	126 (59.4%)	0.390
Mean lymph node yield $\pm$ SD	13.36 $\pm$ 6.18	11.19 $\pm$ 5.79	0.044*
Nerve sparing	174 (75.3%)	165 (77.8%)	0.419
Pathology negative surgical margin	178 (77.1%)	172 (81.1%)	0.259
Blood loss $\pm$ SD (mL)	540 $\pm$ 67	265 $\pm$ 41	<0.001*
Indwelling catheter $\pm$ SD (day)	15.11 $\pm$ 3.14	8.75 $\pm$ 3.05	<0.001*
Hospitalization $\pm$ SD (day)	5.62 $\pm$ 1.78	4.24 $\pm$ 1.73	0.046*
Postoperative complication			
Grade 1	10 (4.3%)	6 (2.8%)	0.224
Grade 2	5 (2.2%)	4 (1.9%)	
Grade 3a	1 (0.4%)	1 (0.5%)	
Grade 3b	1 (0.4%)	-	

\*Independent simple t-test; SD: Standard deviation, RRP: Retropubic radical prostatectomy, RARP: Robot-assisted radical prostatectomy, ISUP: International Society of Urologic Pathology

**Table 3. Functional and oncological results**

	RRP (n=231)	RARP (n=212)	p-value*
Erection sufficient for sexual intercourse			
Postoperative 3 mo	16 (10.5%)	15 (10.6%)	0.695
Postoperative 12 mo	60 (39.2%)	60 (42.3%)	
Continence at postoperative 3 mo			
0-1 pads	136 (58.9%)	158 (74.5%)	0.021*
2-3 pads	69 (29.9%)	39 (18.4%)	
>3 pads	26 (11.2)	15 (7.1%)	
Continence at postoperative 12 mo			
0-1 pads	183 (79.2%)	180 (84.9%)	0.398
2-3 pads	40 (17.3%)	26 (12.3%)	
>3 pads	8 (3.5%)	6 (2.8%)	
Median follow-up (IQR) (mo) for biochemical recurrence	28 (20-36)	27 (18-35)	0.782
Biochemical recurrence rate	22 (9.5%)	17 (8.1%)	0.280
Overall mortality rate	3 (1.2%)	2 (0.9%)	0.271

\*Chi-square test, IQR: Interquartile range, RARP: Robot-assisted radical prostatectomy, RRP: Retropubic radical prostatectomy



**Figure 1.** Kaplan-Meier curves for biochemical recurrence-free survival

Biochemical recurrence-free survival was 90.5% in the RRP group versus 91.9% in the RARP group. Kaplan-Meier analysis did not show a significant difference between biochemical recurrence-free survival rates of the two groups ( $p=0.280$ ) RARP: Robot-assisted radical prostatectomy, RRP: Retropubic radical prostatectomy

The median follow-up for BCR was 28 (20-36) and 27 (18-35) months in the RRP and RARP groups, respectively. The mean follow-up time of both groups was comparable (Table 3). The BCR-free survival rate was 90.5% in the RRP group versus 91.9% in the RARP group. Kaplan-Meier analysis did not demonstrate any significant difference between BCR-free survival rates of both groups ( $p=0.280$ ) (Figure 1).

NS-RP was performed at comparable rates in both surgical arms (75.3% vs 77.8%;  $p=0.419$ ) (RRP arm: unilateral NS-RP, 54; bilateral NS-RP, 120; RARP arm: unilateral NS-RP, 50; bilateral NS-RP, 115). NS-RP was not performed on patients with cT3 or ISUP grade >3. Patients with positive surgical margins were similar in both surgical groups (22.9% vs 18.9%;  $p=0.259$ ) (Table 2).

The rates of patients who underwent pelvic LN dissection (PLND) among the groups were close to each other (75.3% vs 77.8%;  $p=0.419$ ). The mean number of LN yield was 13.36 and 11.19 in the RRP and RARP groups, respectively, and the difference was significant in favor of RRP ( $p=0.044$ ) (Table 2).

## Discussion

In this study, we evaluated oncological results with total PSA measurements in the postoperative follow-up. We found that the proportion of patients with BCR was higher in the RRP arm than in the RARP arm, but this difference was not significant. Some of the risk factors for BCR include pathology with ISUP grade  $\geq 2$ , positive surgical margin, extracapsular spread, seminal vesicle involvement, and positive LN. Providing negative surgical margin is very important for cancer control. The detection of surgical margin positivity in patients with pT2 increases the risk of BCR by 12% (7). Surgeon's experience, prostate volume, risk group of tumor, tumor volume, and degree of excision of the neurovascular bundle may affect surgical margin positivity (8). In both groups with a similar rate of NS-RP, more than 80% negative surgical margins were achieved. Despite a proportionally small difference in favor of RRP, this difference was not significant. A study compared the positive surgical margin in both surgical arms, which revealed favorable results of RARP, but the patient population was worse in the RRP arm (8). However, results of a large-scale meta-analysis on this topic are similar to our results (9). Similarly, a prospective randomized controlled study comparing RRP and RARP did not find a difference between the two groups in terms of receiving additional oncological treatments such as RT or androgen deprivation therapy (10).

In PCa, PLND is important for ensuring correct staging, providing information about prognosis, and determining adjuvant treatment needs. In addition, the number of LN yield in patients with positive LN and cancer-specific survival was correlated (11). The probability of LN invasion in high-risk PCa is 20% (12). While LN metastasis is detected in 10-24.1% of patients with extended PLND, this rate decreases to 0-5.2% in standard PLND (13). Owing to the variable lymphatic drainage of the prostate, extended PLND is recommended for all patients with PLND indication (14). Although the rates of patients with extended PLND in our study were similar in the RRP and RARP groups, the number of LN yield was significantly higher in the RRP group. Studies with large patient populations using the Surveillance Epidemiology and End Results medicare-linked database have shown that extended PLND is less common in patients undergoing RARP (15,16). These results may be due to limited movements of the robot arms, difficulty of the learning curve, and RARP performed by urologists with little experience in uro-oncology.

In studies comparing continence, the lack of standardization due to the definition of continence and differences in research makes it difficult to evaluate these results. In the literature, post-prostatectomy incontinence rates were 7-39% and 4-31% in the RRP and RARP groups, respectively (17,18). The wide range of these ratios was related to both the lack of a standard definition for incontinence and the surgeon's experience. According to our study, although a difference was found between the two

groups for the continence rates at 3 months postoperatively, the rates were comparable at 12 months postoperatively. Some studies have shown that it is better to report continence in the RARP group; however, in meta-analysis of long-term prospective studies, the two groups showed a similar rate of continence. (10,18). Bladder neck protector technique, neurovascular bundle dissection, and prolonged urethra can be made easier in RARP with high magnification. This may explain that early continence is better in the RARP group.

In studies comparing the two surgical approaches in terms of potency, there is no standard definition for potency. While some used symptom scores for potency, such as IIEF-5, some defined potency as a coit ability. We considered patients who were able to provide adequate erections for sexual intercourse as potent. The rates of patients who were potent at the 3 and 12 months postoperatively were very comparable in both groups. Preoperatively, the rate of achieving erection sufficient for sexual intercourse in all patients who underwent RP was 66.6% (RRP group, 66.2%; RARP group, 67%). Regardless of the surgical approach, the 3- and 12-month potency rates of all patients who underwent NS-RP were 10.5 and 40.7%, respectively. In other words, 59.3% of the patients who underwent NS-RP developed erectile dysfunction. This high rate may be attributed to our preference for the rate of achieving erection sufficient of sexual intercourse rather than the IIEF-5 score when evaluating erectile function. Studies have shown that 25-75% of patients who performed RP develop erectile dysfunction later (19). A meta-analysis showed that RARP is a superior procedure than RRP in terms of the 12-month potency rates (20). However, 2-year results of a randomized controlled study reported no difference in sexual function between both surgical techniques (10). The postoperative sexual function is thought to be related to patient age, surgeon experience, and neurovascular bundle preservation (21,22).

The hospitalization duration of patients who underwent RARP was shorter. In accordance with our routine practice, the catheters were removed on average in 14 days in patients with RRP and in 7 days in patients with RARP. Therefore, the duration of catheterization was shorter in the RARP group.

There was more blood loss in the RRP group than in the RARP group. Generally, blood loss is less in the RARP arm due to the buffering effect of the intra-abdominal pressure and the ability of the robot arms to be used under the good vision of the surgeon. The fact that the hospitalization duration, catheterization time, and amount of blood loss is less in the RARP arm is caused by the fact that RARP is a more minimally invasive procedure.

The total complication rates were 7.3% and 5.2% in the RRP and RARP groups, respectively. Complication rates were comparable. Different complications may occur in patients undergoing RARP depending on the patient position (Trendelenburg), intra-abdominal pressure, and robotic arms, unlike RRP.

## Study Limitations

This study has some limitations. This study is a retrospective study from a single center with multiple surgeons. This may cause differences between surgical indications, techniques, and managements. The short follow-up period is also another

limitation, especially for the monitoring of oncological outcomes. Nevertheless, our functional outcomes were similar to those of previous studies (10,23).

## Conclusion

Although the oncological and functional results of RRP and RARP are comparable, perioperative adverse events tend to be less common in RARP because of the minimally invasive characteristics of the procedure. We believe that the surgeon's experience has larger effect than the chosen technique on oncological and functional results.

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## Ethics

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# Fiducial Marker Practice in Prostate Radiotherapy in Turkey

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## Abstract

**Objective:** During prostate radiotherapy (RT), localization strategies of the prostate gland are essential. Fiducial markers (FMs) are one of the various methods for prostate localization. FMs for prostate RT have been in use for several years. This study aimed to evaluate the current trends in FM practices used in the treatment of prostate cancer in Turkey.

**Materials and Methods:** An electronic survey containing 15 questions was developed on SurveyMonkey.net and sent to the email addresses of 600 radiation oncologists (ROs) via the Turkish Society for Radiation Oncology. Then, the data were collected and analyzed.

**Results:** A total of 33 ROs completed the survey. Upon analysis, results revealed that the mean FM experience duration was 6.6 years (range: 1-18 years). FM replacement was mainly done transrectally (90%) by urologists (67.7%). Antibiotic prophylaxis and anticoagulant cessation were often practiced. At least three gold FMs were inserted in most of the cases.

**Conclusion:** Many centers use FMs for prostate RT in Turkey. There are some differences in FM usage. Standardization of the practice could help to investigate and improve FM utilization in prostate RT.

**Keywords:** Fiducial marker, prostate cancer, radiotherapy, stereotactic

## Introduction

Prostate cancer is the most common cancer in males (1). Radiotherapy (RT) is one of the main treatment options for prostate cancer. The effectiveness of RT depends on the delivery of a high dose of radiation to a tumor site while limiting the side effects of radiation on surrounding structures (2,3). Advances in technology have enabled the delivery of highly conformal radiation doses. However, it may be difficult to localize the prostate gland during irradiation because it is a moving organ (4). Fiducial markers (FMs), which are implanted within the prostate gland before RT, are one of the various methods employed to localize the prostate gland. FMs for prostate RT have been in use for several years in Turkey. A variety of FMs are available, and the insertion procedure of FMs can differ among clinics. This study aimed to evaluate the current trends in FM practices used in the treatment of prostate cancer in Turkey.

## Materials and Methods

The Turkish Society for Radiation Oncology Urooncology Subgroup has approved this study. An electronic survey was

developed on SurveyMonkey.net. The questionnaire contained 15 questions with a combination of yes/no, multiple-choice, and open-ended questions.

This questionnaire was sent to several radiation oncologists (ROs) in Turkey, who are members of the Turkish Society for Radiation Oncology. Each participant was contacted through email and invited to complete the survey. The survey was concluded on November 30, 2018.

## Results

Completed questionnaires were received from 34 ROs. One of the responders who did not use FMs routinely in clinical practice was excluded from the study. Upon analysis of the data collected from the questionnaires, it was revealed that the mean FM experience duration was 6.6 years (range: 1-18 years).

Approximately 90% of the FMs were inserted transrectally, whereas 16.7% were inserted transperineally. Three responders stated that they use both methods. Approximately 73.3% of the responders administered antibiotics to patients before FM implantation. The duration of prophylaxis varied from 1 to 10

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days among specialists. Ciprofloxacin, as a single agent, was the most preferred antibiotic (87.5%). Almost half of the responders (45.8%) suggest a special diet to patients mostly a fiber-rich diet and avoid forming bloatedness.

The seventy-five percent of the responders asked patients to stop consuming aspirin, an NSAID, or anticoagulants 2-14 days before FM insertion. Poor agreement between practices was presented. Less than half (42.9%) of the responders administered anesthetics before FM insertion.

Most of the responders (77.3%) used gold markers of various shapes and sizes from different vendors. One of the responders used PEEK fiducials, whereas the other responders did not specify the FMs they utilized. Majority of the responders (64.3%) inserted three FMs, 28.6% inserted four seeds and 7.1% inserted five seeds. FM positioning was not consistent between responders. Approximately 35% of the responders prefer to insert at least one FM into the prostate base and another into the apex, whereas 27% of the responders prefer to insert one FM into the prostate base, one into the mid-gland, and one into the apex. The remaining responders did not specify the positioning of the FM.

Except for one, all ROs preferred to wait for 1-15 days between FM insertion and computed tomography (CT) planning. The most common waiting periods were 7 (55.1%) and 10 (20%) days. Different imaging methods were used. The most common methods are listed in Table 1.

<b>Table 1. Characteristics of fiducial marker practice</b>	
<b>Center responders working in</b>	<b>(%)</b>
University hospital	24.2
State hospital	36.4
Private hospital	39.4
<b>Primary responsible person for insertion</b>	<b>(n)</b>
Urologists	22
Interventional radiologists	12
Radiation oncologist	2
<b>Radiotherapy methods</b>	<b>(%)</b>
IMRT	71
SBRT	58.1
IGRT	54.8
3D-conformal RT	3.2
<b>Imaging methods</b>	<b>(%)</b>
CBCT	63.3
MCVT	36.7
2D-kV imaging	33.3
2D-MV imaging	13.3
Cyberknife fiducial tracking system	43.3
Other	10
IMRT: Intensity-modulated radiation therapy, SBRT: Stereotactic body radiation therapy, IGRT: Image-guided radiation therapy, 3D: T-dimensional, CBCT: Cone-beam computer tomography, MVCT: Megavoltage computed tomography, 2D-kV: Two-dimensional kilovoltage, 2D-MV: Two-dimensional megavoltage	

## Discussion

In recent years, several developments have been recorded in prostate cancer RT. Advanced techniques, such as intensity-modulated RT, image-guided RT, and stereotactic body RT have been developed and different fractionation schedules, such as moderate or ultra-hypofractionation, require more precision than conventional treatments. Decreased margins are needed for lowering potential side effects of escalating doses for tumor control (2,3). Two-dimensional (2D) megavoltage or kilovoltage imaging uses pelvic bone structures to verify the position of the prostate gland. FMs allow superior verification of the prostate position relative to the bony anatomy, with 3D position corrections (4,5). Cone-beam CT (CBCT) offers three-dimensional (3D) imaging; however, prostate gland visualization remains a challenge, owing to inadequate soft-tissue contrast. In some treatment delivery systems, FMs provide intrafraction target motion information that is not obtained using CBCT. Also, internal organ motion causes daily variations in rectal and bladder filling. This makes it challenging to target the prostate accurately.

FMs have been used for almost two decades in Turkey. The absolute number of centers routinely inserting FMs for prostate RT is unknown. FM insertion is not covered under health insurance, being the main limitation for its use in Turkey.

FM insertion into the prostate gland is an invasive procedure. There are two main approaches: transrectal and transperineal. The transrectal approach is most widely used for FM placement, which is the same as the practice in Turkey. It requires the same equipment and setup used for prostate biopsies. Therefore, urologists are more familiar with this approach. In one study, Moman et al. (6) found that there were no differences between these two approaches in terms of toxicity and quality of life. Some series reported less than 1% toxicity with the transperineal approach (7,8).

The practice of administering antibiotics before implantation is nearly standard in Turkey; however, there is no standard regime in terms of the antibiotic type, dose, and duration. Fluoroquinolones are the most frequently used antibiotics before FM insertion just as before prostate biopsy (9). The use of prophylactic antibiotic therapy before transrectal procedures can cause increased rates of antibiotic-resistant infection (9). In their study, Moman et al. (6) reported no infection after transperineal FM implantation without routine prescription of prophylactic antibiotics.

In our series, most of the responders stopped anticoagulant treatment before the procedure; however, this may not be necessary. In a series by locolano et al. (10), a total of 57 patients on chronic anticoagulation therapy who did not stop the medication before FM insertion were observed. Neither rectal bleeding nor cardiac event was noted. Therefore, they suggested that the use of anticoagulant medication is not an absolute contraindication to FM insertion.

Transrectal prostate biopsy is generally performed under local anesthesia. In our study, although the FM insertion procedure was mostly performed transrectally (90%), the rate of anesthesia usage was less than half. A possible explanation for this may

be that the insertion procedure is less painful than biopsy. In a prospective study on pain score with transperineal FM insertion under local anesthetic, a total of 30 patients were evaluated (11). A visual analog scale from 0 to 10 was used to assess pain before, during, and after the procedure. It was revealed that transperineal ultrasound-guided gold seed implantation without conscious sedation is well-tolerated and associated with a low complication rate.

There is generally a time interval between implantation and CT planning for possible inflammation, edema, bleeding, and fiducial migration. Delouya et al. (12) reported less FM migration and a better match with delayed CT planning for a minimum of 3 days. Mostly, a delay of 7 or 10 days is preferred in Turkey practice. Linam et al. (13) reported no significant differences in table shifts between the same day and delayed CT simulation.

There is limited information on the ideal number of FMs and their location within the prostate gland. Three or four FMs are generally used in different studies. At least three FMs allow ROs to determine the prostate position in different imaging planes. Igdem et al. (14) suggested that implanting three FMs is safe and well-tolerated. Kudchadker et al. (15) reported that a single FM does not always reliably represent the position of the entire prostate and that three FMs were suitable. Theoretically, a fewer number of FMs may be associated with lower rates of implantation-related side effects.

There is no consensus on where to place the FMs. For optimal results, the markers should be implanted in a triangular configuration with a minimum distance of 1 cm between them (16). In many studies, at least one FM is inserted into the apex and another into the base for a correct prostate gland localization and laterally considering the urethra damage (14,16,17).

### Study Limitations

The main limitation of the study was that the responders were ROs. They may not be aware of the insertion procedure, because the procedure is mainly performed by urologists and interventional radiologists.

### Conclusion

FMs allow the localization of the prostate gland during treatment and are used in many centers by ROs for prostate RT in Turkey. However, the real numbers of the FMs used are not known. There are some differences in the FM insertion procedure and clinical usage. Standardization of FM practice could help investigate and improve the utilization of FM in prostate RT.

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### Ethics

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### Authorship Contributions

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# Effect of Diabetes Mellitus and Metformin Usage on Treatment Outcomes and Side Effects on Prostate Cancer Treated with Radical Radiotherapy

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## Abstract

**Objective:** Diabetes mellitus (DM) is a common comorbidity in patients with prostate cancer. Radiotherapy was reported to induce acute and late side effects in patients with DM due to vascular damage. Moreover, some studies have shown that metformin, an oral antidiabetic drug, can reduce biochemical and disease recurrence in patients with prostate cancer. This study aimed to evaluate retrospectively the effect of metformin on biochemical disease control and to observe the acute and late side effects of prostate cancer treated with radiotherapy.

**Materials and Methods:** This study enrolled 94 patients who received radical radiotherapy between 2010 and 2017. However, out of 22 patients with DM, 17 received metformin and five received metformin plus insulin treatment. Biochemical recurrence-free survival (bRFS), overall survival, and side effects were assessed between patients with and without DM.

**Results:** The median follow-up time was 57 (15-128) months. The 5-year bRFS rate in patients with and without DM were 100% and 89.2%, respectively ( $p=0.10$ ). Acute grade 1-2 side effects were observed in all patients with DM, while 56 (78%) patients without DM had acute side effects, and the difference is significant ( $p=0.02$ ). Acute grade 3 genitourinary and gastrointestinal toxicity was found in one patient without DM, whereas late grade 3 gastrointestinal toxicity was observed in one patient with DM.

**Conclusion:** Although patients with DM were found to have better bRFS than patients without DM, we could not show the benefit of metformin, and the difference was not significant. By contrast, acute side effects were significantly higher in patients with DM.

**Keywords:** Prostate cancer, diabetes mellitus, metformin, radiotherapy, side effects

## Introduction

Prostate cancer is the most common cancer in men, the second leading cause of cancer-related death, and usually observed in older men (1). Diabetes mellitus (DM) is a common chronic endocrine disease developed by either genetically or acquired deficiency. Type 1 and type 2 are the common forms of DM, and more than 90% of patients have type 2 DM (2). Type 2 DM is mainly caused by insulin resistance, particularly common in the older population, and the prevalence of DM in individuals aged >65 years is 26.9% (3). Therefore, coexisting diagnoses of prostate cancer and DM increased because of aging. Metformin is an orally administered and frequently used as an insulin sensitizer drug that belongs to the biguanide antidiabetic family. Recently, the antineoplastic activity of this compound shown in some in vitro models is gaining interest (4). Several retrospective studies have demonstrated that metformin treatment can reduce the

incidence of prostate cancer, prostate-specific antigen (PSA) levels, and disease recurrence (5,6).

Especially, breast, colorectal, endometrium, liver, and pancreatic cancers occur more commonly in individuals with DM, and the prevalence of DM in patients newly diagnosed with cancer is even higher, ranging from 8% to 18% (7). DM can cause long-term complications, such as cardiovascular disease, retinopathy, and neuropathy. Patients with both cancer and DM have an increased risk of long-term mortality in comparison with patients without DM (8).

Radiotherapy is one of the main treatment modalities for locally advanced prostate cancer. Management and side effects of prostate cancer treatment are particularly affected by comorbidities. Some studies have reported that patients with DM experienced more radiation-induced genitourinary and gastrointestinal system side effects than patients without DM after prostate cancer radiotherapy (9).

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This single-center retrospective study aimed to evaluate the effect of metformin on biochemical disease control and to observe the acute and late side effects of prostate cancer treated with definitive radiotherapy.

## Materials and Methods

### Study Population

This study included 94 consecutive patients with prostate cancer treated by definitive radiotherapy between 2010 and 2017. Moreover, 22 (23%) patients had DM and received metformin treatment (1.000 mg/day), while five patients received insulin treatment in addition to metformin treatment. Metformin therapy had varied duration. Patients had T1-T2 (79%) and T3-T4 (21%) disease. At presentation, 16 (17%) patients had high-grade tumors (Gleason score  $\leq 8$ ) and 43 (46%) had high-risk disease. The cohort comprised of 26% low, 28% medium, and 46% high-risk groups according to the National Comprehensive Cancer Network risk category (10). Luteinizing hormone-releasing hormone agonists were used for 6 months in 16 and for 24 months in 43 patients as androgen deprivation therapy. Characteristics of the patients are listed in Table 1.

### Treatment Preparation and Planning

Patient preparation was performed before radiotherapy planning computer tomography (CT) and every treatment fraction as reported previously (11). The patients were asked to avoid eating gas-producing food and to consume a low-fiber diet before simulation and during treatment. Organs at risk and target volumes were contoured according to Radiation Therapy Oncology Group guidelines in planning CT.

Table 1. Patient characteristics	
Patient characteristics	n (%)
<b>T-stage</b>	
T1	4 (4%)
T2	70 (75%)
T3	17 (18%)
T4	3 (3%)
<b>N-stage</b>	
N1	5 (5%)
<b>Risk groups</b>	
Low	24 (26%)
Intermediate	27 (28%)
High	43 (46%)
<b>Androgen deprivation therapy</b>	
Short-term	16 (17%)
Long-term	43 (46%)
Diabetic patients	22 (23%)
<b>DM treatments</b>	
Metformin	17 (18%)
Metformin + insulin	5 (5%)
DM: Diabetes mellitus	

### Treatment

Intensity-modulated radiotherapy plans were generated for each patient using the Eclipse version 8.6 treatment planning system by using 6 MV photon beams. The median dose of radiation therapy was 78 Gy (range, 70-80 Gy) in 39 (range, 28-40) fractions. Only prostate volume is irradiated in 78 patients, whereas pelvic lymphatics were added to the treatment volumes in 16 patients. Field verification for image-guided radiation therapy was carried out with cone-beam CT every day.

### Follow-up

During radiotherapy, all patients were examined once a week for urinary symptoms such as dysuria, urinary incontinence, and hematuria, gastrointestinal symptoms such as the number of daily defecation and stool density, and complaints about abdominal pain and gas. After the radiotherapy, patients were followed up every 3 months for the first 2 years, every 6 months between 2 and 5 years, and annually after 5 years. PSA was evaluated at each follow-up, and additional examinations were postulated according to the PSA result. All patients were examined at each visit and assessed for late toxicity.

### Statistical Analysis

This study was conducted retrospectively. Biochemical recurrence-free survival (bRFS) was defined as the time from the end of radiotherapy to PSA recurrence. Kaplan-Meier survival analysis was performed for medicine use (i.e., antidiabetic drugs) with the endpoint of bRFS. Univariate and multivariate analyses performed by Cox-regression method were adjusted for the baseline characteristics, including age, stage, Gleason score, PSA, treatment field, radiotherapy doses, androgen deprivation therapy, doses of organs at risk, other comorbidities (hypertension and coronary artery disease), and DM. Common Terminology Criteria for Adverse Events v5.0 was used for the evaluation of acute and late gastrointestinal and genitourinary side effects. Comparisons of acute and chronic side effects for patients with and without DM were made by the chi-square test. The retrospective study protocol was approved by the Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine and the study was conducted in accordance with the tenets of the Helsinki Declaration. SPSS version 21 for Windows (IBM Corp., Armonk, NY) was used for all statistical analyses, and  $p < 0.05$  was considered for significance.

### Results

The median follow-up time was 57 (15-128) months, and the median age was 69 (53-88) years. Thirteen patients died; however, only three of them died from prostate cancer. PSA relapse was observed in eight patients without DM. The 5-year and 8-year overall survival (OS) for the total study population were 91.4% and 75.4%, respectively (Figure 1). Patients aged  $\geq 70$  years were significantly associated with a higher risk of mortality [ $p = 0.023$ , confidence interval (CI) = 0.22 (0.06-0.81)] than patients aged  $< 70$  years in the univariate analyses. Results of the univariate and multivariate analyses are listed in Table 2.

In this study, the 5-year and 8-year bRFS rates were 91.6% and 89.5%, respectively. In the multivariate analyses, Gleason score

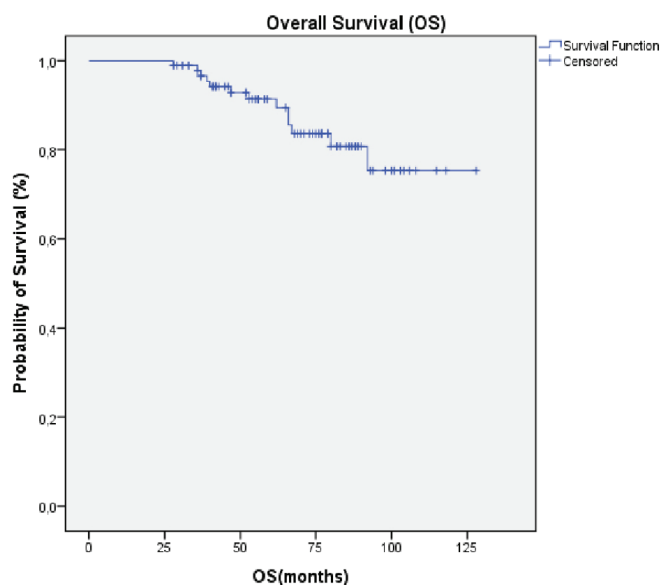


Figure 1. Overall survival for patients

Characteristic	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
<b>Risk category</b>				
Intermediate	0.78 (0.17-3.54)	0.73	NS	
High	0.70 (0.19-2.53)	0.59		
Older age	4.53 (1.24-16.59)	0.02	4.87 (1.30-18.24)	0.019
PSA level	0.99 (0.33-2.99)	0.94	NS	
TNM stage	1.03 (0.28-3.76)	0.96	NS	
<b>ADT</b>				
Short-term	2.49 (0.55-11.18)	0.23	NS	
Long-term	1.22 (0.30-4.93)	0.78		
Pelvic nodal RT	1.42 (0.31-6.55)	0.65		
DM status	2.6 (0.33-20.1)	0.30	1.36 (0.16-11.29)	0.775
Recurrence	4.64 (1.43-15.11)	0.01	5.12 (1.51-17.34)	0.009

ADT: Androgen deprivation therapy, DM: Diabetes mellitus, CI: Confidence interval, RT: Radiation therapy, HR: Hazard ratio, PSA: Prostate-specific antigen

≥8 (p=0.003; CI=0.11 (0.03-0.49) and age <60 years (p=0.019; CI=0.19 (0.05-0.76) were found to be negative factors for bRFS.

Subgroup analyses showed similar OS and bRFS rates. The 5-year OS rates in patients with and without DM were 93% and 91%, respectively (p=0.30) (Figure 2). The 5-year bRFS rates in patients with and without DM were 100% and 89.2%, respectively (p=0.10) (Figure 3). A comparison of the survival results of patients with and without DM are listed in Table 3.

As regards side effects, acute grade 1-2 side effects were observed in all patients with DM, whereas 78% of patients without DM had acute side effects, and the difference is significant (p=0.02)

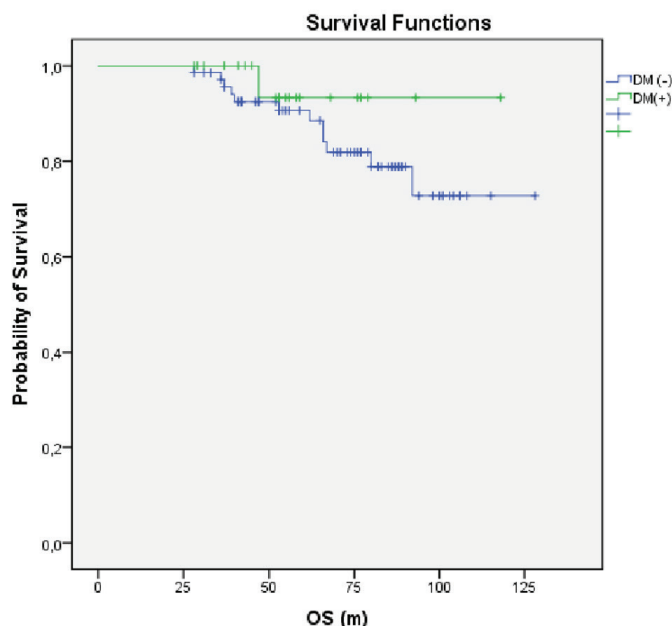


Figure 2. Overall survival for diabetic and non-diabetic patients

	DM (-)		DM (+)		p
	n	%	n	%	
<b>Risk category</b>					
Low	18	25	6	27.3	0.557
Medium	19	26.4	8	36.4	
High	35	48.6	8	36.4	
<b>PSA</b>					
<10	33	45.8	13	59.1	0.199
≥10	39	54.2	9	40.9	
<b>TNM</b>					
Stage 1-2	53	73.6	19	86.4	0.138
Stage 3-4	19	26.4	3	13.6	
<b>Age</b>					
<70	37	51.4	14	63.6	0.313
≥70	35	48.6	8	36.4	
<b>ADT</b>					
None	26	36.1	9	40.9	0.213
Short-term	10	13.9	6	27.3	
Long-term	36	50	7	31.8	
<b>Pelvic nodal RT</b>					
Absent	59	81.9	20	90.9	0.315
Present	13	18.1	2	9.1	

DM: Diabetes mellitus, ADT: Androgen deprivation therapy, RT: Radiation therapy, PSA: Prostate-specific antigen

(Table 4). Urinary side effects were more common in all patients. Side effects such as dysuria, nocturia, urinary incontinence, pollakiuria, and hematuria were observed in 95.5%, 45.5%, 22.5%, 18.1%, and 4.5% of the patients, respectively. Six

patients experienced diarrhea as an acute gastrointestinal side effect. Late side effects especially dysuria and nocturia were found in 23% and 13% of the patients, respectively (p=0.26) (Table 5). Acute grade 3 genitourinary and gastrointestinal toxicity was observed in one patient without DM, whereas late grade 3 gastrointestinal toxicity was seen in one patient with DM.

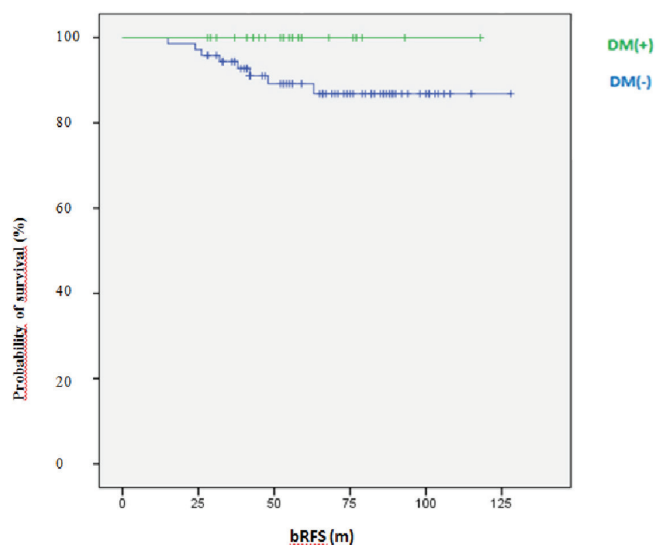


Figure 3. Biochemical recurrence free survival (bRFS) for diabetic and non-diabetic patients

DM	Acute gastrointestinal side effects				Total
	Absent	Grade 1	Grade 2	Grade 3	
Diabetic	16 (73%)	4 (18%)	2 (9%)	0 (0%)	22 (100%)
Non-diabetic	54 (75%)	9 (12%)	7 (10%)	2 (3%)	72 (100%)
	Acute genitourinary side effects				
	Absent	Grade 1	Grade 2	Grade 3	
Diabetic	2 (9%)	18 (82%)	2 (9%)	0 (0%)	22 (100%)
Non-diabetic	18 (25%)	34 (47%)	19 (26%)	1 (2%)	72 (100%)

DM: Diabetes mellitus

DM	Late gastrointestinal side effects				Total
	Absent	Grade 1	Grade 2	Grade 3	
Diabetic	19 (85%)	1 (5%)	1 (5%)	1 (5%)	22 (100%)
Non-diabetic	69 (96%)	1 (1%)	2 (3%)	0 (0%)	72 (100%)
	Late genitourinary side effects				
	Absent	Grade 1	Grade 2	Grade 3	
Diabetic	18 (82%)	3 (14%)	1 (4%)	0 (0%)	22 (100%)
Non-diabetic	63 (88%)	8 (10%)	1 (2%)	0 (0%)	72 (100%)

DM: Diabetes mellitus

## Discussion

Prostate cancer is the most common male cancer and the second leading cause of death among other malignancies. The incidence rates of prostate cancer and DM are increasing in the last decades. At present, treatment guidelines recommend metformin as the first-line therapy for DM (12). Metformin is an insulin sensitizer and a potent adenosine monophosphate-activated protein kinase activator. It inhibits the mammalian target of rapamycin complex-1 pathway in carcinogenesis (13). In the last decades, many studies have investigated the effect of DM and metformin on cancer incidence and mortality (11). It is believed that metformin may have a greater effect on cancer survival by modulating cellular energy rather than the transformation of benign cells to malignant cells.

Studies examining the influence of metformin on prostate cancer have inconsistent results. In addition to cancer incidence, several studies have investigated the role of metformin on prostate cancer-specific mortality as well as recurrence. However, data are limited about the positive effect of metformin on treatment results with radiotherapy. Spratt et al. (8) conducted a retrospective study and revealed that metformin may improve bRFS, distant metastases-free survival, prostate cancer-specific mortality, and OS and reduce the development of castration-resistant prostate cancer. A previous large database study about the effect of DM and metformin in prostate cancer demonstrated that metformin users have reduced recurrence rates when compared with non-metformin users (14). Moreover, patients with DM had a worse OS than those without SM. In a surgical series, metformin was not associated with bRFS in patients who underwent radical prostatectomy (15). Kaushik et al. (16) found that metformin use was not associated with bRFS or OS in their retrospective cohort study (16). Coyle et al. (17) conducted a systematic review and reported that patients receiving prostate cancer radiotherapy had better OS, bRFS, and CSS, which might be related to metformin usage, although no any significant benefit was found for patients who underwent surgery. In the present study, metformin caused a 10% increase in bRFS rate; however, it was not significant, and results of the present study were similar to those of previous investigations.

In the present study, we also evaluated acute and late side effects and observed that patient with DM were more likely to have acute gastrointestinal and genitourinary side effects. Several previous studies have indicated that DM increases treatment-related toxicity in many cancers such as breast, colorectal, and lung cancer (18,19,20). Several theses were put forward about this association. DM might negatively affect leukocyte functions, including chemotaxis, phagocytosis, and insufficient bacterial killing; therefore, it negatively affects host immunity. More tissue damage occurs especially in fast proliferating cells such as the epithelium of the gastrointestinal and genitourinary tract and endothelial tissues after radiotherapy. Consequently, because of endothelial tissue damage, the coagulation system is also activated, resulting in diminished blood flow, thrombosis, and capillary necrosis (21). In patients with DM, endothelial dysfunction is a common reason for morbidity and mortality. Therefore, those with DM would have increased impairment in tissue repair after radiotherapy.



Gastrointestinal disorders are one of the common complications of DM and include gastroparesis, nonalcoholic fatty liver disease, gastroesophageal reflux disease, and chronic diarrhea (22). Moreover, metformin has some gastrointestinal side effects such as diarrhea. Although patients were asked to report the symptoms that occurred or increased after the start of radiotherapy, it may be sometimes difficult for the patient to tell the difference and distinguish gastrointestinal symptoms related with DM, metformin treatment, or radiotherapy. Some other factors such as androgen deprivation therapy and pelvic field radiotherapy may induce the occurrence and severity of side effects.

### Study Limitations

This study has several limitations. The small sample size, heterogeneous patient characteristics, and retrospective nature of the analysis are the main limitations of this study. Metformin was used in different durations and may influence independently the outcomes of metformin-dependent factors. Moreover, the study did not include a group with DM not treated with metformin. In addition, no analysis was performed on patients with DM who received metformin and did not receive metformin. Furthermore, glycemic control data and hemoglobin A1c levels were not available in this study, which might have some effects on toxicity. Finally, the study had a relatively short follow-up time for observing late side effects and recurrence.

### Conclusion

In this retrospective study, patients with DM and prostate cancer who used metformin and underwent radical radiotherapy have a better bRFS, but significance was not reached. Patients with DM experienced significantly more grade 1-2 acute side effects, whereas a trend toward increased low grades of late side effects was found. Vascular damage in DM may cause impairment in tissue repair after radiotherapy and increase radiotherapy-related toxicities. Controlled trials in patients with both DM and prostate cancer should be performed to evaluate the effect of DM and metformin usage on outcomes of radiotherapy.

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

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

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

### Ethics

**Ethics Committee Approval:** The retrospective study protocol was approved by the Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine and the study was conducted in accordance with the tenets of the Helsinki Declaration (approved no: 150113, date: 02.10.2019).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Supervision: S.Ç.K., Concept: M.D., H.F.Ö.D., Design: H.F.Ö.D., Data Collection or Processing: C.B., Analysis or Interpretation: C.Y., Literature Search: C.Y., Writing: M.D.

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# Relationship Between Lymph Node Metastasis and Lymph Node Density and Preoperative Neutrophil-Lymphocyte Ratio in Patients Undergoing Radical Cystectomy

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## Abstract

**Objective:** This study aimed to evaluate the relationship between the preoperative neutrophil-lymphocyte ratio (NLR) and lymph node metastasis and lymph node density after radical cystectomy in patients with invasive urinary bladder cancer.

**Materials and Methods:** Data of 89 patients who underwent radical cystectomy were examined. Our study included only cases with stage 2 urothelial bladder cancer. They were classified according to the lymph node status based on the surgical specimen. Patients with negative results were classified as group 1 and those with positive results as group 2. Patients in group 2 were further evaluated in two subgroups according to their lymph node density. Accordingly, group 2A consisted of patients with lymph node density of <20%, and group 2B involved those with lymph node density of ≥20%. Groups were compared statistically according to NLR.

**Results:** Of the patients, 71 (79.8%) were male. The patients' mean ages and neutrophil and lymphocyte counts were 67.36±8.64 years, 6.89±3.02 K/μL, and 3.08±2.18 K/μL, respectively. NLRs of groups 1 and 2 were 2.80±2.25 and 4.59±2.97, respectively. The relationship between group 1 and 2 tumors was significant (p=0.008). NLR values were 3.82±2.49 and 5.20±3.25 in groups 2A and 2B, respectively. However, no significant relationship was found between these values (p=0.235).

**Conclusion:** Although no positive correlation was found between NLR and lymph node density, we think that this inflammation marker is an invaluable parameter to predict lymph node metastasis.

**Keywords:** Lymphocyte, neutrophil, bladder cancer, cystectomy

## Introduction

Bladder cancer is the second most common urogenital cancer after prostate cancer (1). The frequency of bladder cancers is increasing with the growing rates of tobacco use and industrialization in societies (2). A study predicted that there will be 81,400 new cases of bladder cancer and 17,980 deaths by 2020 (3). Painless hematuria is the main symptom of patients with bladder cancer (1,4). Bladder cancer is a highly heterogeneous disease in terms of recurrence rate (50-80%) and progression rate (5-50%). In terms of tumor stage, approximately 25% of cases show muscular invasion. Many authors suggested radical cystectomy and pelvic lymph node dissection as the gold standard diagnostic method (5). However, approximately 50% of these patients can develop distant metastases even after

radical cystectomy (6). In this context, oncologists continue to develop neoadjuvant chemotherapy strategies to achieve better clinical outcomes after surgery. These protocols aim to prolong disease-free survival in patients with bladder cancer. However, these approaches have several negative side effects. Previous studies have reported that approximately 20-30% of patients who underwent neoadjuvant chemotherapy protocols had errors in the clinical staging of bladder tumors, and there may be a delay in the timing of cystectomy or even mortality due to toxicity associated with drug reactions (7). Generally, prognostic models become extremely important in the management of patients with bladder cancer. Numerous studies have demonstrated the clinical significance of various parameters such as tumor size and stage, histopathology, lymphovascular invasion, hydronephrosis, lymph node metastases, lymph node

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density, comorbidity, clinical experience in surgery, and various molecular markers such as p53, p21, p27, and cyclin E1 in predicting the prognosis of patients with bladder cancer (5,8).

The relationship between inflammation and cancer was firstly revealed in 1863 when Rudolf Virchow detected the presence of leukocytes in tumor cells. Numerous studies have been conducted since then to examine the molecular basis of cancer and inflammation. According to these studies, tumor cells, stromal structures, and inflammatory cells surrounding these cells interact coordinately to form an inflammatory tumor microenvironment. Generally, this microenvironment is extremely labile with high plastic properties. Thus, tumor microenvironment and inflammatory reactions are thought to be associated with all the steps of carcinogenesis (9,10). Inflammatory reactions lead to various changes in routine complete blood count parameters. One of these parameters is reproducible, simple, and low-cost neutrophil-lymphocyte ratio (NLR). During systemic inflammation, the increase in neutrophil count and the decrease in lymphocyte count are expected to increase the NLR (6). Based on the link between cancer and inflammation, we aimed to evaluate the relationship between NLR and lymph node metastasis and lymph node density that are shown as a prognostic marker in patients undergoing radical cystectomy for invasive urothelial bladder cancer.

## Materials and Methods

This retrospective analysis analyzed data of patients who underwent radical cystectomy with a diagnosis of bladder cancer in the Urology Clinic of the Faculty of Medicine, Tokat Gaziosmanpaşa University, between 2011 and 2019. The study only included cases with stage 2 urethral bladder cancer according to the 2002 TNM classification. Exclusion criteria were high-grade stage 1 bladder cancer, patient with BCG recurrence, history of neoadjuvant chemotherapy or radiotherapy, other histological subtypes such as adenocarcinoma, squamous cell carcinoma, and small cell carcinoma. In addition, patients with clinical conditions that would change NLR such as secondary malignancy, rheumatological disease, immune deficiency, acute infective pathology, severe endocrinologic disorder, and antiaggregant or anticoagulant use were not included.

The patients' ages, gender, symptoms, and preoperative hemogram parameters were noted. Hemogram parameters were examined in a biochemistry device with regular maintenance and control (Mindray BC-6800, China). These parameters were obtained from preoperative blood analysis results routinely monitored by the anesthesia clinic. NLR was calculated by dividing the neutrophil count obtained in the complete blood count by the lymphocyte count. All patients underwent extended lymph node dissection (obturator, internal and external iliac nodes, deep obturator, common iliac, presacral, precaval, inter-aortocaval, and para-aortal nodes up to the inferior mesenteric artery) during radical cystectomy. The number of positive lymph nodes was determined for each patient. According to the lymph node status in the surgical specimen, patients with negative status were determined as group 1 and those with positive status as group 2. In total, 62 and 27 patients comprised groups 1 and 2, respectively. The lymph node density level was

determined for each patient in group 2. It was calculated by dividing the number of positive lymph nodes by the number of total lymph nodes. Based on the lymph node density value, group 2 was divided into two subgroups. The cut-off value was 20% in accordance with the large series of studies conducted in previous years (11). Accordingly, group 2A was determined as <20%, while group 2B as ≥20%. Group 2A included only 12 patients. All groups were analyzed according to NLR. The cut-off value for groups 1 and 2 was determined as 1.63. In the evaluation of the cases in group 2 among themselves, the cut-off value was calculated as 4.33.

The study was carried out following the principles of the Helsinki Declaration and with the approval of the local ethics committee (Tokat Gaziosmanpaşa University, Ethics Committee, confirmation no. 20-KAEK-153).

## Statistical Analysis

Descriptive analyses were performed to provide information on general characteristics of the study population. Quantitative variables were presented as the mean ± standard deviation and independent samples t-test was used to compare the means of between groups. Qualitative variables were presented as frequency (percent) and chi-square test was used to compare the percentages between groups. Receiver operating characteristics (ROC) curve analysis was used to determine the cut-off value, and the area under the ROC curve was assessed. Correlation analysis was used for examine the relationship between variables. A p-value <0.05 was considered significant. Analyses were performed using commercial software (IBM SPSS Statistics 19, SPSS Inc., IBM Corp., Armonk, NY).

## Results

A total of 89 patients were included in the study, of which 71 (79.8%) were male. A total of 67 (75.3%) patients had a history of smoking. Their mean age and neutrophil and lymphocyte counts were 67.36±8.64 years, 6.89±3.02 K/μL, and 3.08±2.18 K/μL, respectively. In this study, 67 (75.3%) patients had symptoms of macroscopic hematuria (Table 1). All patients underwent open radical cystectomy and extended lymph node dissection. Procedures were performed by the same surgical team using three different urinary diversion techniques. Moreover, 79 (88.7%) patients were treated with an ileal conduit, 7 (7.9%) patients had orthotopic neobladder, and 3 (3.4%) patients had ureterocutaneostomy. All surgical samples were evaluated separately by two experienced pathologists. Of the 35 lymph nodes, 10 were removed. Group 1 consisted of 62 (66.7%) patients. The demographic data of the groups were quite similar (Table 2). Their mean NLR was 2.80±2.25. Group 2 had a mean NLR of 4.59±2.97. When analyzed with the ROC

Signs and symptoms	n	%
Macroscopic hematuria	67	75.3
Microscopic hematuria	9	10.1
Lower urinary tract symptoms	8	9
Incidental	5	5.6

curve, the cut-off value was 1.63 (Figure 1). Accordingly, we found a significantly higher NLR in group 2 ( $p=0.008$ ) (Table 3). By contrast, a significant positive and weak relationship was found between NLR and lymph node involvement ( $p=0.008$ ) (Table 4). Group 2 was further evaluated in two subgroups according to lymph node density. Group 2A was composed of 12 patients. The mean NLR in groups 2A and 2B were  $3.82\pm 2.49$  and  $5.20\pm 3.25$ , respectively. When analyzed with the ROC curve, the cut-off value was 4.33 (Figure 2). Although NLR results were higher in group 2B than in group 2A, a significant relationship could not be established ( $p=0.235$ ) (Table 5).

	Group		p
	Group 1 (n=62)	Group 2 (n=27)	
Age	67.42±9.43	67.20±5.48	0.922
Gender (Female/Male)	12/50	5/21	0.982
Smoke (Yes/No)	48/14	19/8	0.659

Quantitative datas are shown as mean ± standard deviation  
 Test: Independent Samples t-test and chi-square test  
 \*p-value less than 0.05 is regarded as statistically significant

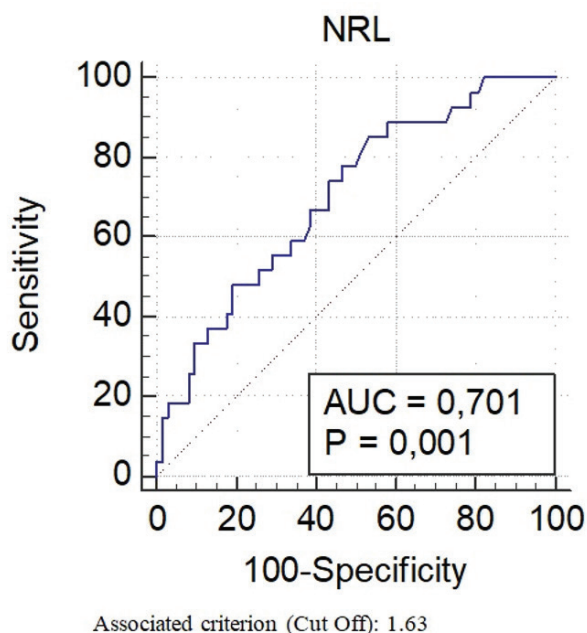


Figure 1. ROC curve for neutrophil-lymphocyte ratio (groups 1-2)  
 ROC: Receiver operating characteristics, AUC: Area under curve

	Group		p
	Group 1 (n=62)	Group 2 (n=27)	
NLR	2.80±2.25	4.59±2.97	0.008*

NLR: Neutrophil-lymphocyte ratio  
 Datas are shown as mean ± standard deviation  
 Test: Independent Samples t-test  
 \*p-value less than 0.05 is regarded as statistically significant

NLR	Lymph node Involvement	
	r	p
	0.499	0.008

NLR: Neutrophil-lymphocyte ratio  
 r: Pearson's correlation coefficient.  
 A significant positive and weak relationship was found between NLR and lymph node involvement

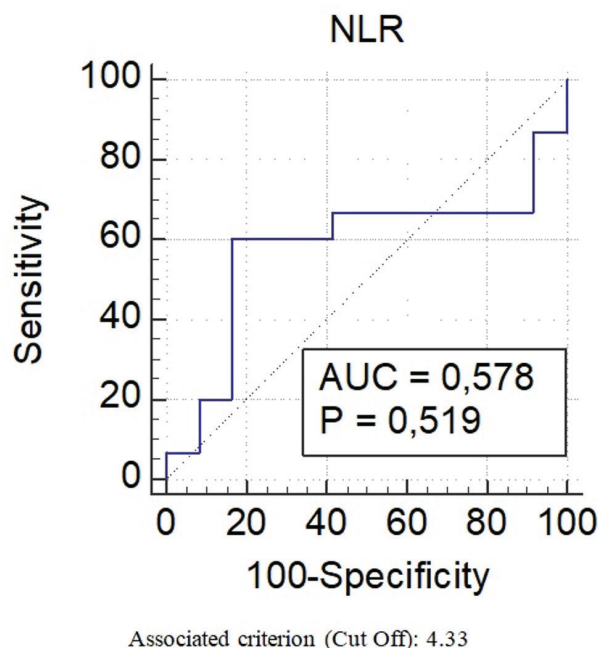


Figure 2. ROC curve for neutrophil-lymphocyte ratio (groups 2A-2B)  
 ROC: Receiver operating characteristics, AUC: Area under curve

	Group		p
	Group 2a (n=12)	Group 2b (n=15)	
NLR	3.82±2.49	5.20±3.25	0.235

NLR: Neutrophil-lymphocyte ratio

### Discussion

Radical cystectomy has a critical place in the treatment of patients with invasive bladder cancer. However, its clinical results have yet reached the targeted levels (12). In a multicenter study, Shariat et al. (13) evaluated the results of 888 patients who underwent radical cystectomy and reported 5-year mean non-recurrent and bladder cancer-specific survival rates of 58% and 66%, respectively. Recently, Stein et al. (14) reported a 5-year recurrence-free and overall survival rates of 68% and 66%, and a 10-year recurrence-free and overall survival rates of 60% and 43% in their extensive series involving 1.054 patients. The tumor stage is directly related to the heterogeneous biological characteristics of the tumor and still cannot provide clinicians with the desired level of information regarding cancer-specific

survival in cases of invasive bladder cancer. Determining survival rates and predicting it before surgery is critical in deciding whether to provide treatments in addition to cystectomy such as neoadjuvant chemotherapy. Many models have been developed in this context, and detailed studies are still underway. One of these models is based on lymph node dissection, which is now considered the most important step in radical cystectomy (15). Numerous studies have reported that, on average, one in four patients who underwent radical cystectomy had lymph node involvement (16). In this context, research on the effect of lymph node involvement and its degree on survival have gained great importance in our century. Hautmann et al. (17) reported 10-year recurrence-free and overall survival rates of 59.1% and 44.9%, respectively, in their study of 788 cases where they discussed the clinical course of the tumor after radical cystectomy. However, analysis of 142 patients with lymph node involvement obtained the same values of 20.9% and 14.6%, respectively. In a similar study, the results of 336 patients undergoing radical cystectomy and extended pelvic lymphadenectomy were analyzed and 5-year overall and recurrence-free survival rates were 68% and 69%, respectively. The same study found that 19% of the patients had lymph node metastases, and lymph node involvement proved a significant adverse prognostic factor with a 5-year probability of survival of 39% and 76% (18). Ho et al. (19) evaluated the clinical course of patients after radical cystectomy and reported recurrence-free survival and overall survival rates of 61% and 53%, respectively, and finally concluded that the number of positive lymph nodes was significantly associated with survival.

Following the acceptance of the effects of lymph node involvement on survival after radical cystectomy by many authors, the scientific world has started to investigate the clinical importance of lymph node density since the beginning of this century. The lymph node density is calculated by dividing the number of density-positive lymph nodes by the number of removed lymph nodes. Herr (11) examined 711 patients with invasive transitional cell carcinoma of the bladder and reported that 162 of his patients had a positive lymph node and an average of 13.3 lymph nodes was removed. His cut-off value for lymph node density was 20%, and he reported a 5-year survival rate of 64% in cases below the cut-off value and 8% in those with a cut-off value >20%. In the same period, Stein et al. (20) examined 1,054 patients who underwent radical cystectomy and lymphadenectomy and reported that 23% of patients had lymph node metastases, with 5- and 10-year overall recurrence-free survival rates of 35% and 34%, respectively. Similarly, the lymph node density was analyzed, and the cut-off value was 20%. Moreover, when the lymph node density was  $\leq 20\%$ , the 10-year recurrence-free survival rate was 43%, while it was only 17% in patients with lymph node density >20%. Similarly, Wiesner et al. (1) reported 1- and 3-year cancer-specific survival rates of 76% and 23% in their study of 152 bladder tumor cases. There was lymph node metastasis in 30% of the cases. The average lymph node density was 0.11, and they concluded lymph node density is an independent predictor of cancer-specific survival.

After understanding the importance of lymph node involvement and lymph node density in the clinical course of the tumor

following radical cystectomy, clinicians started to investigate how these parameters could be predicted preoperatively. However, a limited number of studies have been conducted on this subject and showed the basis of the relationship between cancer and inflammation (21). Scientists began to understand this relationship when the presence of leukocytes in tumor cells was observed about 1.5 centuries ago. The link between inflammation and cancer has become clearer with the introduction of many molecular-based new technologies in medicine. Infection and inflammation are held responsible for nearly a quarter of cancer cases today (9,10). Macrophages and T-cells are active immune cells around the tumor microenvironment. Increased cytokine and chemokine expression are directly related to the specificity of these cells. This medium triggers tumor growth, angiogenesis, invasion, and metastasis. Many cytokines such as interleukin (IL)-1, IL-6, IL-17, and IL-23 have an extremely important place in cancer progression. In addition, tumor necrosis factor-alpha, transforming growth factor-beta, FasL, and estimated glomerular filtration rate ligands contribute to the development and survival of tumor cells. Reactive oxygen species also play a role in a different pathway. These molecules can trigger cancer formation by neutralizing important tumor suppressor genes such as Tgfr2 and Bax. Similarly, irreversible protein modification is caused by oxidative stress that causes critical damage to the cellular genome. All these vital steps affecting carcinogenesis constitute the molecular basis of many types of cancer, for example, several clinical conditions such as liver or stomach cancers that develop due to viral effects, colorectal cancers triggered by inflammatory bowel disease, and lung cancer secondary to chronic inflammation caused by environmental factors such as smoking (9,22).

This relationship between cancer and inflammation has been investigated in detail in patients undergoing radical cystectomy for bladder tumors. Gongo et al. (6) examined 189 patients with bladder cancer and reported that NLR was correlated with the clinical results of radical cystectomy for the first time. They concluded that tumor size, clinical T-stage, hydronephrosis, concomitance of carcinoma *in situ*, and NLR were significantly associated with poor prognosis. In another study, Kawahara et al. (23) evaluated 74 patients undergoing radical cystectomy and stated that the cut-off value for NLR was 2.38, and this parameter had predictive value in predicting the prognosis. In a similar study of 84 cases, Tan et al. (24) reported 2.7 as the cut-off value for NLR and considered high NLR to be independently associated with higher recurrence rate, higher T-staging, and lymph node involvement. In their large series of 385 cases, Kang et al. (25) reported 2 as the cut-off value of NLR and that high NLR was directly related to advanced tumor stage, lymphovascular invasion, and lymph node involvement. In the same study, cancer-specific survival and overall survival rates were poor in cases with high NLR. In another large-series study, Yoshida et al. (26) examined 323 patients with bladder cancer who underwent radical cystectomy and reported that both pre- and postoperative NLR were related to overall survival. However, Ojerholm et al. (27) suggested that NLR had no predictive value for overall survival in patients with muscle-invasive bladder cancer in their large-scale studies. Likewise, Tang et al. (28) reported

the lack of a relationship between NLR and tumor stage in their study of 302 patients with bladder cancer. Moreover, Demirtaş et al. (21) examined 201 cases and suggested that preoperative NLR was not correlated with lymph node density. In the present study, a significant relationship was found between NLR and lymph node involvement. However, NLR increased in the group with high lymph node density, albeit not significant.

### Study Limitations

As limitations, this study is a single-center retrospective study with a limited number of patients. Moreover, this study lacks long-term follow-up results such as disease-free survival and overall survival, which is another deficiency of our clinical data. However, in this study, the lymph node status, which is very important in clinical follow-up after cystectomy, was studied in detail.

In this study, lymph node involvement and lymph density are directly related to prognosis in patients with bladder cancer as reported in many studies. The clinical importance of neoadjuvant chemotherapy in patients with bladder cancer is currently accepted by nearly all authors of tumors. Moreover, it is critical to consider the side effects of current treatment strategies that can result in serious mortality and morbidity. In this context, clinicians should select the ideal patient by managing the benefit-loss equation correctly.

### Conclusion

NLR evaluated before radical cystectomy in patients with stage 2 ureteral bladder cancer is extremely useful in predicting lymph node involvement with high prognostic significance after surgery. However, we believe that our results should be supported by large-scale, randomized, multicenter studies.

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

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

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### Ethics

**Ethics Committee Approval:** The study was carried out following the principles of the Helsinki Declaration and with the approval of the local ethics committee (Tokat Gaziosmanpaşa University, Ethics Committee, confirmation no. 20-KAEK-153).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: E.K., D.A., Y.E.K., Design: E.K., D.A., Y.E.K., L.M.Ö., V.U., Data Collection or Processing: D.A., Y.E.K., Analysis or

Interpretation: L.M.Ö., V.U., Literature Search: E.K., L.M.Ö., V.U., Writing: E.K.

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# Effects of Lymphovascular Invasion on Overall and Cancer-specific Survival after Radical Cystectomy in Patients with Bladder Cancer

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## Abstract

**Objective:** We aimed to investigate the effects of lymphovascular invasion (LVI) on survival rate, as well as the relationship of this parameter with lymph node (LN) involvement and other prognostic factors, in patients undergoing radical cystectomy (RC) for bladder cancer.

**Materials and Methods:** Patients who underwent RC in our clinic for muscle invasive bladder cancer (MIBC) or high-risk non-muscle invasive bladder cancer (NMIBC) between 2006 and 2019 were retrospectively reviewed. Patients were divided into four groups: LVI (-) and LN (-) patients were in group 1, LVI (+) and LN (-) patients were in group 2, LVI (-) and LN (+) patients were in group 3, and LVI (+) and LN (+) patients were in group 4. All data were compared among the groups.

**Results:** A total of 177 patients with a mean age of 64.4 years and mean follow-up time of 30.2 months were evaluated in this study. The mean overall survival (OS) and cancer-specific survival (CSS) of the patients were 56.6±4.2 and 68.9±4.5 months, respectively. When factors affecting survival rates were analyzed, LN positivity was not a significant factor influencing the OS ( $p=0.570$ ) and CSS ( $p=0.533$ ) of the patients. However, LVI [ $p=0.002$ , hazard ratio (HR)=0.402] and surgical margin (SM) positivity ( $p=0.001$ , HR=0.321) were significant factors influencing OS. SM positivity ( $p=0.003$ , HR=0.314), LVI ( $p=0.011$ , HR=0.416), and adjuvant chemotherapy (ACT) ( $p=0.009$ , HR=0.460) were also found to be independent factors affecting CSS. ACT was higher in group 3 than in other groups, and overall and cancer-specific mortality rates were lower in group 1 than in other groups. OS and CSS in group 2 (15.3±2.9 and 21.2±4.6 months, respectively) and group 4 (21.5±7.2 and 24.5±8.1 months, respectively) were lower than those in other groups ( $p<0.001$ ).

**Conclusion:** SM positivity and LVI are independent factors affecting OS and CSS. ACT, especially in group 3, could increase CSS. OS and CSS were lower in patients with LVI than in those without.

**Keywords:** Bladder cancer, lymphovascular invasion, lymph node involvement, overall survival, cancer-specific survival

## Introduction

Bladder cancer is one of the most common malignancies of the urinary system, and its prevalence is high in developing countries (1). The annual mortality rate of this type of cancer is 1-5/100000 for males and 0.5-1.5/100000 for females (2). Approximately, 98% of all bladder cancers originate from the epithelial layer, and 80-90% of these carcinomas are urothelial in nature (3). At the time of diagnosis, approximately 75% of patients are found to have non-muscle invasive bladder cancer (NMIBC), while 25% have muscle invasive bladder cancer (MIBC) (4,5). Radical cystectomy (RC) with extended lymph node (LN) dissection and urinary diversion is the gold standard treatment for patients with MIBC (6). Besides this treatment, adjuvant chemotherapy (ACT) is required for patients with poor prognosis. Morbidity and mortality can be observed in

approximately 50% of patients after RC (7). The prognostic criteria of bladder cancer include LN metastasis, surgical margin (SM) positivity, presence of carcinoma *in situ* (CIS), lymphovascular invasion (LVI), and ineligibility to receive ACT (8,9,10,11,12). LVI is defined as the presence of tumor cells in lymphatic vessels and the vascular wall, which could increase the frequency of LN metastasis. Intravasation of cancer cells to the circulation via LVI and the development of micrometastases is one of the most important processes for metastatic disease (13). Previous research showed that LVI is a poor prognostic marker for testicular cancer and penile cancer (14). LVI in RC specimens is also known to be an independent prognostic factor for LN involvement, recurrence, and survival in patients with MIBC (15). Earlier studies demonstrated that LVI has negative effects on survival, especially among LN (-) patients (16). Therefore, in the present study, we aimed to investigate the effects of LVI and

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LN involvement on the overall survival (OS) and cancer-specific survival (CSS) of patients groups divided according to LVI and LN status after RC; the relationships of LVI with other prognostic factors are also evaluated.

## Materials and Methods

Patients who underwent RS for MIBC or high-risk NMIBC between 2006 and 2019 in our clinic were retrospectively evaluated. Patients who had complete data and followed up in our clinic were included in the study. Patients diagnosed with other types of bladder cancer except urothelial carcinoma, those who received neoadjuvant chemotherapy, and those who had missing follow-up data were excluded from the study. The patients' characteristics and preoperative, perioperative, and postoperative data were reviewed. Clinical (i.e., age, gender, and preoperative hydronephrosis), preoperative pathological (i.e., preoperative T-stage and grade and presence of CIS), postoperative pathology (i.e., RC T-stage, number of LNs removed, LN involvement, and LVI), and oncological (i.e., upstaging, ACT, overall mortality, OS, cancer-specific mortality, and CSS) data were evaluated. Patients were divided into four groups according to their LVI and LN status described their final RC pathology reports. LVI(-) and LN(-) patients were categorized into group 1, LVI (+) and LN (-) patients were categorized into group 2, LVI (-) and LN (+) patients were categorized into group 3, and LVI (+) and LN (+) patients were categorized into group 4. All data were compared among the groups.

## Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences version 22.0 (SPSS, Chicago, IL, USA). The Kruskal-Wallis and chi-squared tests were used for univariate analysis. For multivariate analysis, Cox regression analysis was used to investigate the factors affecting OS and CSS. Inter-group survival analysis was evaluated by Kaplan-Meier survival analysis. Statistical significance was accepted as  $p < 0.05$ .

## Results

A total of 177 patients with a mean age and follow-up time of  $64.4 \pm 9.4$  years (range, 32-83 years) and  $30.2 \pm 31.1$  months (range, 1-116 months) were evaluated in this study. The mean OS and CSS of the patients were  $56.6 \pm 4.2$  and  $68.9 \pm 4.5$  months, respectively. When factors affecting survival rates were analyzed, LN positivity was not a significant predictive factor for OS ( $p = 0.570$ ) and CSS ( $p = 0.533$ ). However, LVI [ $p = 0.002$ , hazard ratio (HR) = 0.402] and SM positivity ( $p = 0.001$ , HR = 0.321) were significant predictive factors for OS. SM positivity ( $p = 0.003$ , HR = 0.314), LVI ( $p = 0.011$ , HR = 0.416), and ACT ( $p = 0.009$ , HR = 0.460) were also found to be independent predictive factors for CSS.

When we analyzed the groups based on LN and LVI status, 121 patients were categorized into group 1, 15 were categorized into group 2, 24 were categorized into group 3, and 17 were categorized into group 4. The distribution of pathological and clinical features and comparative results of the groups are given in Table 1. The demographic and preoperative pathological data were statistically similar between the groups. However, T-stage

in the RC final pathology, SM positivity, and upstaging were significantly lower in group 1 and higher in group 4 than in other groups. The numbers of dissected LNs were similar between the groups. The ACT rate was higher in group 3 than in other groups, and overall and cancer-specific mortality rates were generally lower in group 1 than in other groups. The OS and CSS of group 2 ( $15.3 \pm 2.9$  and  $21.2 \pm 4.6$  months, respectively) and group 4 ( $21.5 \pm 7.2$  and  $24.5 \pm 8.1$  months, respectively) were found to be lower compared with those of other groups ( $p < 0.001$ ). The OS and CSS plots are given in Figures 1 and 2.

## Discussion

MIBC often leads to high mortality despite RC and additional adjuvant or neoadjuvant treatments. Several prognostic factors have been found to be related to this high level of mortality. Thus, in the present work, we aimed to focus on one of these prognostic factors.

LVI has been shown in previous studies to be a risk factor for LN metastasis, recurrence, and poor OS (13). In our study, when we examined the effect of LVI on OS and CSS, we found that it was an independent factor for poor prognosis ( $p = 0.002$ , HR = 0.402 and  $p = 0.011$ , HR = 0.416, respectively). OS and CSS times were found to be lower in group 2 (15.3 and 21.2 months, respectively) and group 4 (21.5 and 24.5 months, respectively) than in group 1 (66 and 77.8 months, respectively) and group 3 (43.9 and 54.8 months, respectively) ( $p < 0.001$ ). This finding reveals that LVI is an independent prognostic factor that is as equally effective as LN positivity for predicting survival. Previous research reported that LVI is an independent predictor for LN metastasis (17,18). An earlier meta-analysis also showed that LVI occurred in 64.4% of LN (+) patients and 36% of LN (-) patients (19,20). In the current study, LVI was found in 41.5% (group 4) of LN (+) patients (groups 3 and 4) and in 11% (group 2) of LN (-) patients (groups 1 and 2). LN positivity is generally acknowledged to have a negative effect on survival rates. However, in the present study, LN positivity did not have a statistically significant effect on OS and CSS ( $p = 0.570$  and  $p = 0.533$ , respectively). When we examined the factors responsible for this finding, we found that the rate of patients receiving ACT in group 3 was as high as 54.2%. The rates of patients receiving ACT were not distributed similarly among the groups. Moreover, group 4 revealed the highest upstaging rates and RC T-stages. As an important limitation of this study, the low number of patients in the groups may have contributed to this finding.

Another prognostic factor affecting OS in our study was SM positivity ( $p = 0.001$ , HR = 0.321). The independent prognostic factors affecting CSS were SM positivity ( $p = 0.003$ , HR = 0.314) and ACT ( $p = 0.009$ , HR = 0.460). OS and CSS were higher in group 3 than in group 4. Although LVI positivity in group 4 may contribute to this finding, the higher rate of ACT in group 3 than in group 4 may also explain this result (54.2% vs 35.3%). When we planned this study according to our hypothesis, we aimed to investigate how LVI affects OS and CSS, especially among LN (-) patients. However, our findings appeared to be more important than our hypothesis (21). Similar to our hypothesis, Lotan et al. (22) showed the prognostic significance of LVI in LN (-) patients

Table 1. Distribution of pathological and clinical features in groups based on LVI and LN status						
		Group 1 LVI (-) and LN (-) (n=121)	Group 2 LVI (+) and LN (-) (n=15)	Group 3 LVI (-) and LN (+) (n=24)	Group 4 LVI (+) and LN (+) (n=17)	p
Age		64.2±9.7 (32-83)	66.3±9.1 (54-80)	64.9±8.3 (47-79)	63.5±9.3 (46-79)	0.903
Gender	Male	111 (91.7)	13 (86.7)	22 (91.7)	16 (94.1)	0.894
	Female	10 (8.3)	2 (13.3)	2 (8.3)	1 (5.9)	
Preoperative hydronephrosis		37 (30.6)	5 (33.3)	14 (58.3)	5 (29.4)	0.082
Preoperative T-stage	≤T1	15 (12.7)	2 (13.3)	1 (4.3)	0 (0)	0.06
	T2	101 (85.6)	11 (73.3)	22 (95.7)	17 (100)	
	T3	2 (1.7)	2 (13.3)	0 (0)	0 (0)	
Preoperative grade	G1	3 (2.5)	1 (6.7)	0 (0)	0 (0)	0.577
	G2	5 (4.2)	0 (0)	1 (4.3)	1 (5.9)	
	G3	110 (93.2)	14 (93.3)	22 (95.7)	16 (94.1)	
Presence of CIS		30 (24.8)	6 (40)	6 (25)	6 (35.3)	0.528
T-stage at the RC final pathology	≤T1	30 (25.4)	2 (13.3)	1 (4.2)	0 (0)	<0.001
	T2	63 (53.4)	5 (33.3)	10 (41.7)	0 (0)	
	T3	14 (11.9)	4 (26.7)	9 (37.5)	6 (35.3)	
	T4	11 (9.3)	4 (26.7)	4 (16.7)	11 (64.7)	
Number of dissected lymph nodes		12±5.7 (1-30)	11.7±4.1 (7-24)	13.4±6.2 (4-33)	14.1±4.2 (8-21)	0.333
Upstaging		31 (25.8)	9 (60)	9 (90)	17 (100)	<0.001
SM positivity		9 (7.4)	4 (26.7)	5 (20.8)	7 (41.2)	0.001
ACT		25 (20.7)	5 (33.3)	13 (54.2)	6 (35.3)	0.01
Overall mortality		46 (38)	12 (85.7)	14 (58.3)	9 (69.2)	0.001
Overall survival		66±4.9 (56.4-75.6)	15.3±2.9 (9.7-20.9)	43.9±10.6 (23.2-64.6)	21.5±7.2 (7.5-35.6)	<0.001
Cancer-specific mortality		31 (25.6)	8 (57.1)	11 (50)	8 (61.5)	0.003
Cancer-specific survival		77.8±5 (68-87.6)	21.2±4.6 (12.1-30.2)	54.8±12.2 (30.7-78.8)	24.5±8.1 (8.6-40.4)	<0.001

LVI: Lymphovascular invasion, LN: Lymph node, RC: Radical cystectomy, CIS: Carcinoma *in situ*, SM: Surgical margin, ACT: Adjuvant chemotherapy

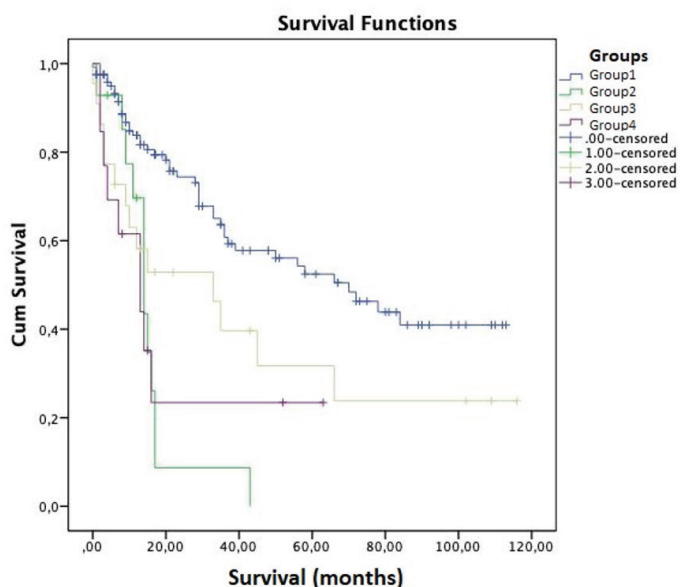


Figure 1. Overall survival curves of the groups based on LN and LVI status  
LN: Lymph node, LVI: Lymphovascular invasion

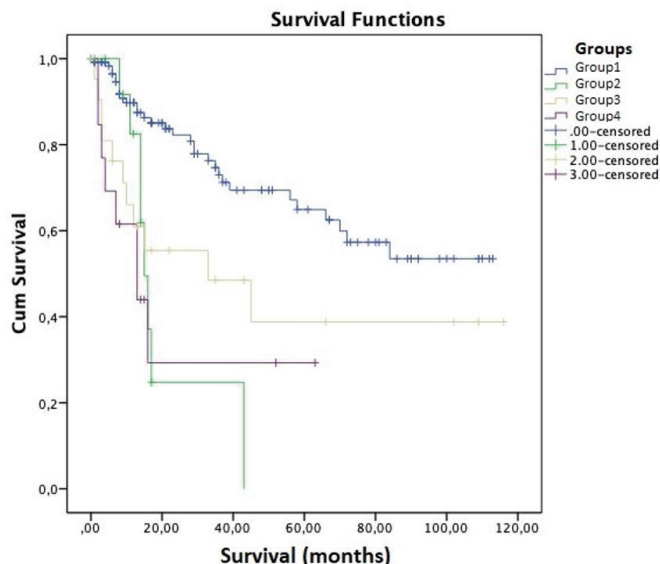


Figure 2. Cancer-specific survival curves of the groups based on LN and LVI status  
LN: Lymph node, LVI: Lymphovascular invasion

only. Another study conducted by Lotan et al. (22) revealed that LVI is also an important risk factor for local recurrence, distant metastasis, and overall disease recurrence in LN (-) patients only. LVI was observed to have a negative effect on OS and CSS in LN (-) patients (16). When we evaluated the OS and CSS data of group 1 [LVI (-); 66 and 77.8 months, respectively] and group 2 (LVI (+); 15.3 and 21.2 months, respectively), survival was favored in LVI (-) patients, in accordance with the literature. These data reveal that the negative effect of LVI on survival is more important in LN (-) patients than in LN (+) ones. Therefore, these patients should be followed up regularly. Despite the limited number of patients included in this research, complete data and detailed examinations of the four groups reduced the possibility of bias. Thus, the oncological results determined in this work are similar to those reported in previous studies. This similarity and additional findings highlight the importance of our study.

### Study Limitations

The small number of patients and the weak distribution among the groups are important limitations in our study.

### Conclusion

LVI was observed to be an independent prognostic factor affecting OS and CSS. ACT, especially in group 3, improved CSS, but SM positivity had a negative effect on survival rates. Although LVI is an important factor for predicting survival, especially in LN (-) patients, large-series studies are needed to investigate the importance of LVI in LN (+) patients and clarify its relationship with LN positivity.

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### Ethics

**Ethics Committee Approval:** This study is a retrospective cohort study.

**Informed Consent:** Retrospective study.

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### Authorship Contributions

Concept: G.C., S.Ç., İ.B., Design: G.C., S.Ç., E.Ş., Data Collection or Processing: A.Y., Analysis or Interpretation: S.Ç., İ.H.B., T.D., Literature Search: G.C., S.Ç., B.G., Writing: G.C., S.Ç., S.Y.

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# Postoperative Early and Late Outcomes of Simultaneous Ureter and/or Bladder Resections and Reconstructions in Colorectal Malignancies with Locally Advanced Disease or Peritoneal Metastases

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## Abstract

**Objective:** This study aimed to investigate the early and late outcomes of simultaneous urological procedures performed in patients who underwent surgery for primary or recurrent colorectal cancers with locally advanced disease or peritoneal metastases and effects of resection and reconstruction of the ureter and bladder on survival.

**Materials and Methods:** All patients with locally advanced disease or peritoneal metastases requiring concurrent urological procedures in our clinic between January 2014 and December 2020 were evaluated for this study. Only patients with bladder and ureter intervention were included in the study. Postoperative complications and urological complications were evaluated and classified according to the Clavien-Dindo classification. Imaging studies, interventional procedures, and follow-ups of patients with problems related to the urinary system in the long-term were recorded. The survival times of the patients were investigated.

**Results:** A total of 52 patients underwent simultaneous urological resection (ureter and bladder). As a synchronous urological procedure, an end-to-end anastomosis was performed after ureter resection in 12 patients, transureter anastomosis to 4, partial cystectomy in 20, ileal conduit with total cystectomy in 7, orthotopic neobladder in 1, and ureteroneocystostomy in 8. The most common early complication in all patients was urinary leakage (10 patients), followed by wound infection (6 patients). The shortest and longest follow-up period of the whole group was 8 and 78 months, respectively, and the mean survival time was 38 months. No difference was found between patients with malignant ureter and benign ureter resections in terms of survival ( $p=0.888$ ).

**Conclusion:** In patients with clinical T4b and colorectal malignancies, en bloc resection should be the oncological procedure for bladder resections; if possible, organ-preserving surgery should be performed with sufficient negative margin. However, it is thought that the late outcomes of ureteroneocystostomy in ureter reconstruction are better and those of total cystectomy procedure are worse.

**Keywords:** Ureter, bladder, resection, colorectal malignancies, peritoneal metastases

## Introduction

At the time of diagnosis, 5-10% of colorectal cancers are tumors with adjacent organ invasion (clinical T4b), and these tumors require multivisceral organ resections. To prevent the spread of the tumor and to provide R0 resection, an en bloc resection should be performed with the adjacent organ. These R0 resections increase the 5-year survival and decrease local recurrence rate (1,2). The 5-year survival rate of 50-

90% can be attained in patients in whom tumor-negative margin can be achieved with en bloc resection (3,4). However, these multivisceral surgeries undoubtedly increase the risk of complications, and the morbidity and mortality rates after these surgeries vary between 7-76% and 0-10%, respectively (4).

Colorectal tumors may be in close relationship with urological organs due to the anatomical location of the organs, and adhesions to these urological organs can also be malignant or benign. Therefore, resection of urological organs may be

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required during colorectal surgeries. While total resection of affected organs may be needed, partial resections can be also performed. In cases with concurrence of colorectal malignancies, choosing between partial and total cystectomy in terms of oncological and functional outcomes may be difficult (5). Urological involvement can be seen in 7-20% of patients who undergo cytoreductive surgery and hyperthermic perfusion chemotherapy (CRS + HIPEC) due to peritoneal carcinomatosis, especially in those with metastases of colorectal malignancies, and simultaneous resection and reconstruction may be required (6,7). After ureter resections, reconstruction procedures can be performed by various methods such as ureteroureterostomy, ureteroneocystostomy (UNS), transureteroureterostomy, and Boari flap reconstruction, and the effects of these methods on urinary leakage rate are uncertain (5).

In this study, we investigated the outcomes of simultaneous urological procedures performed in patients who underwent surgery for primary or recurrent colorectal cancers with locally advanced disease or peritoneal metastases. Moreover, we evaluated the early and late outcomes and effects of resection and reconstruction of the ureter and bladder on survival.

## Materials and Methods

The study was planned as a retrospective analysis and before starting the study ethical permission was provided by the local hospital ethics committee. The ethical number of this study is E2-21-355.

All patients operated for colorectal cancer in our clinic between January-2014 and December-2020 were analyzed retrospectively. All patients with locally advanced disease or peritoneal metastases requiring concurrent urological procedures were evaluated. Only patients with bladder and ureter intervention were included in the study. Patients who received kidney, prostate, and urethra interventions were not included in the study because of differences in surgical techniques and complications. Both colorectal and urinary surgical margins were examined with peroperative frozen section in all patients. All patients who underwent surgery with curative intent and palliative resection were excluded from the study.

All patients were preoperatively examined for ureter and bladder invasion, hydronephrosis, and ureter dilatation from their radiological images. In a multidisciplinary council, patients who could undergo R0 resection received explanation of their radiological images before the treatment. Neoadjuvant chemoradiotherapy was performed to cases indicated for surgery due to rectal cancer and evaluated as locally advanced (T3, T4 and node positive).

Total colonoscopy was definitely performed in all patients preoperatively. Those who underwent cystoscopy, ureteroscopy, and prophylactic double-J catheter placement were recorded. All resections and reconstructions of the genitourinary tract and other resections performed in the same session were also recorded. Postoperative and urological complications were evaluated and classified according to the Clavien-Dindo classification (8). Pathological results of the resected primary tumor and urological specimen were examined separately. Imaging studies, interventional procedures, and follow-ups of

patients with problems related to the urinary system in the long-term were recorded. The survival times of the patients were investigated.

**Surgical Procedures:** Laparotomy and resection were performed in all study patients. The colorectal cancer procedure was completed with relevant lymph node dissection according to the location of the tumor and en bloc resection of the adjacent organ. All patients underwent en bloc resection, regardless of whether the adhesion was malignant or a desmoplastic reaction. Patients with peritoneal metastases who could undergo complete cytoreduction (CC0) were included in the study. HIPEC was performed with the closed method in these patients. Catheters were placed after resection, and hyperthermic perfusion was implemented at 42 °C for 60 min. Moreover, 200 mg/m<sup>2</sup> oxaliplatin was used in all patients for the perfusion procedure. All urological and gastrointestinal anastomoses were performed after the HIPEC procedure.

**Urological procedures:** Unilateral or bilateral double-J stents were placed in some of the patients who had known T4 tumor and organ invasion in the same session before the operation. In some patients, stents could not be inserted because of severe stenosis. Reconstructive procedures for the ureter and bladder include uretero-ureterostomy, transuretero-ureterostomy, UNS, partial cystectomy, total cystectomy with orthotopic neobladder, and total cystectomy with ileal conduit.

## Statistic Analysis

IBM SPSS Statistics program v. 21 (IBM Corp., Armonk, NY, USA) was used for data analysis. When evaluating the data, frequency distribution (numbers and percentages) was used for categorical variables and descriptive statistics (minimum, maximum, and median) was used for numerical variables depending on the results of the Kolmogorov-Smirnov test. Continuous variables were expressed as median (minimum-maximum) or mean ± standard deviation where applicable. The Mann-Whitney U test was performed for comparison of median values, and the mean differences were evaluated by Student's t-test. The chi-square test was performed to examine the relevance between two categorical variables. A p-value <0.05 was considered significant.

## Results

Of the 657 patients who underwent surgery for colorectal malignancy in our clinic between January 2014 and December 2020, 52 underwent simultaneous urological resection (ureter and bladder). Moreover, 30 (57.7%) patients were male and 22 (42.3%) were female, and their mean age was 57.70±14.78 years. CRS and HIPEC were performed in 21 (40.4%) of these patients because of the presence of concurrent peritoneal metastases. While 24 (46.2%) patients underwent primary malignancy surgery, 28 (53.8%) patients were operated upon because of recurrence. Depending on the location, most tumors were located in the rectum, followed by the left colon and right colon (Table 1). The median hospital stay of the patients was 21 (7-103) days.

A total of 13 patients who underwent surgery for primary rectum carcinoma received long-term neoadjuvant chemoradiotherapy,

<b>Table 1. Demographic data of the patients</b>	
Total (n)	52
Age (mean ± SD)	57.705±14.784
<b>Gender</b>	
Male (%)	30 (57.7%)
Female (%)	22 (42.3%)
<b>HIPEC</b>	
+ (%)	21 (40.4%)
- (%)	31 (59.6%)
Length of stay (day) (median) (range, min-max)	21 (7-103)
Primary (%)	24 (46.2%)
Relapse (%)	28 (53.8%)
<b>Primary tumor location</b>	
Rectum (%)	22 (42.3%)
Left colon (%)	19 (36.5%)
Right colon (%)	11 (21.2%)
<b>N stage of colorectal tumors</b>	
0	38 (73.1%)
1a	4 (7.7%)
1b	5 (9.6%)
2a	3 (5.8%)
2b	2 (3.8%)
SD: Standard deviation, HIPEC: Hyperthermic perfusion chemotherapy	

and nine patients underwent surgery for recurrent rectum carcinoma. Left colon and rectal surgery was performed in 41 (78.8%) patients, and right hemicolectomy was performed in 11 (21.2%) patients. In these patients, bladder-related procedures were performed in 28 (53.9%) patients, and ureter resection and reconstruction procedures were performed in 24 (46.1%) patients. As a synchronous urological procedure, we performed an end-to-end anastomosis after ureter resection in 12 patients, transureter anastomosis in 4, partial cystectomy in 20, ileal conduit with total cystectomy in 7, orthotopic neobladder in 1, and UNS in 8 (Table 2). In addition, bladder hitch procedure was performed to the psoas muscle in two patients who underwent UNS and thought to have a tight anastomosis.

In the pathological examination of the resection materials, the colorectal resection specimen of 49 patients revealed adenocarcinoma. While the result was benign in two patients who were thought to have recurrence preoperatively, the pathology of both colon and ureter resections was gastrointestinal stromal tumor (GIST) in one patient. The median number of harvested lymph nodes was 16.52±15.16. Positive lymph node states (N stage) of the patients are presented in Table 1.

Operation time, postoperative complications, 30-day morbidity, 30-day mortality, survival, and long-term morbidity results are shown separately in Table 3 according to the urological procedures performed. In this study, 2 (3.8%) patients died within the first 30 days, and 5 (9.61%) patients died within the first 3 months. The median age of these patients was 73 (range, 70-88) years. The most common early complication in all patients was

urinary leakage in 10 patients, followed by wound infection in six patients. Ureteral anastomotic stenosis that developed in the late period was most common after total cystectomy. Three of these patients developed conduit obstruction caused by benign stricture, and percutaneous nephrostomy was performed. At 2 months after the first operation, one patient developed a fistula between the conduit and the ileum; surgery was performed, and the ileum segment where the fistula developed with the conduit was resected. Then, ureter anastomosis was performed with the Bricker technique. To avoid conduit ischemia, the ileum was anastomosed with the right colon without cecum resection (Table 3).

Evaluation of complications that developed within 30 days postoperatively was made according to Clavien-Dindo classification (8). Complications were then compared as minor complications (grade 0-2) and major complications (grade 3-5). Factors affecting major complications are presented in Table 4.

The shortest and longest follow-up periods of the whole group were 8 and 78 months, respectively, and the mean survival time was 38 months. In terms of survival, no significant difference was found between patients who underwent malignant ureter and benign ureter resections (p=0.888).

<b>Table 2. Surgical procedures and pathology results</b>	
<b>Urological procedure (n)</b>	52
Partial cystectomy	20 (38.5%)
End to end anastomosis of ureter	12 (23.1%)
Anastomosis to the contralateral ureter	4 (7.7%)
Total cystectomy	8 (15.4)
Ureteroneocystostomy	8 (15.4)
<b>Surgical procedure</b>	
Low anterior resection	22 (42.3%)
Left hemicolectomy, anterior resection	19 (36.5%)
Right hemicolectomy	11 (21.1%)
<b>Ostomy</b>	
None	14 (26.9%)
End colostomy	20 (38.5%)
End ileostomy	7 (13.5%)
Loop ileostomy	11 (21.2%)
<b>Preoperative double-J catheter</b>	
None	30 (57.7%)
Unilateral	7 (13.5%)
Bilateral	15 (28.8%)
<b>Pathology of the colorectal specimen</b>	
Adenocarcinoma	49 (94.2%)
Benign	2 (3.8%)
Gastrointestinal stromal tumor	1 (1.9%)
<b>Pathology of the urological specimen</b>	
Adenocarcinoma	35 (67.3%)
Benign	16 (30.8%)
Gastrointestinal stromal tumor	1 (1.9%)



**Table 3. Early and late complications of urological resection and reconstructions**

Reconstructions/complications		End-to-end anastomosis	Anastomosis to the contralateral ureter	Partial cystectomy	Total cystectomy	UNS
	<b>Total (n, %)</b>	12 (23.1)	4 (7.7%)	20 (38.5%)	8 (15.4%)	8 (15.4%)
<b>Early complications</b>	None	5 (41.6)	3 (75%)	8 (40%)	1 (12.5%)	4 (50%)
	Urosepsis	0	0	1 (5%)	1 (12.5%)	
	Ileus	1 (8.3%)	0	1 (5%)	1 (12.5%)	1 (12.5%)
	Urinary leakage	3 (24.9%)	0	3 (15%)	3 (37.5%)	1 (12.5%)
	Urinary stenosis	1 (8.3%)	1 (25%)	0	1 (12.5%)	1 (12.5%)
	Intestinal leakage	0	0	4 (20%)	0	0
	Wound infection	1 (8.3%)		2 (10%)	1 (12.5%)	1 (12.5%)
	Acute renal failure		1 (25%)			
	Respiratory	1 (8.3%)		1 (5%)		
	Mortality (first 90 days)	1 (8.3%)	0	3 (15%)	1 (12.5%)	0
<b>Length of stay (days)</b>		18.6	21.75	23.7	25.87	15.37
<b>Late complications (6 months later)</b>	None	8 (66.6)	3 (75%)	16 (80%)	2 (25%)	8 (100%)
	Nephrostomy					0
	Benign stricture	2 (16.6%)	1 (25%)	1 (5%)	3 (37.5%)	
	Malign stricture	0	0	0	2 (25%)	0
	Revision surgery	0	0	0	1 (12.5%)	0

UNS: Ureteroneocystostomy

## Discussion

Urological resections and reconstructions performed for T4b colorectal malignancies vary, and en bloc resections may provide long-term survival with acceptable mortality and morbidity rates. In our clinic, en bloc resection of urinary organs (ureter and bladder) was performed in 52 (7.9%) of 657 patients who underwent surgery for colorectal malignancy due to clinical T4b tumor. With regard to the early and late outcomes of these patients, the mean survival time was 38 months. The incidence rate of anastomotic stenosis requiring interventional procedures in the late period after these procedures was 17.3% and the benign stenosis rate was 13.4%.

At the time of diagnosis, 10-20% of colorectal malignancies are T4 tumors that have invaded the neighboring organs (9). After colorectal surgery, 40% of the patients develop recurrence, mostly in distant organs. Locoregional recurrence develops within the first 3 years in 10-20% of the patients (10). The barrier function of the peritoneum against malignant cells is impaired with previous operations, especially after abdominal and pelvic procedures. Recurrent colorectal tumors and peritoneal metastases may be implanted in the retroperitoneum because of the deterioration of the protective barrier function of the peritoneum and the damage caused by lymph node dissections performed in the previous operation, and they may form masses that lead to obstruction, especially in the ureters (11). Long-term survival can be achieved with R0 en bloc resections in tumors with such locoregional recurrence and primarily locally advanced (T4b) tumors (12). In our study, 52 patients with ureter

and bladder invasion (clinically T4b tumors) underwent en bloc resection. Of these patients, 24 (46.2%) were operated upon for primary and 28 (53.8%) for recurrent colorectal malignancy. Despite the numerically higher need for urinary organ resection in recurrent cases, no significant difference was found between the two groups (p=0.660). This numerical difference can be explained by the deterioration of the protective feature of the peritoneum at the first operation and the more frequent retroperitoneal invasion.

In the examination of pathological specimen in en bloc resections, studies have reported that 30-70% of the patients actually have malignant infiltration, while the remaining patients have inflammation-induced adhesions (13,14). Despite the high rate of benign pathology, en bloc resection is the preferred method because local recurrences increase and survival decreases with the distribution of tumor cells formed by separation of these adhesions (9,14,15). While the 5-year survival rate is 49-53% in colorectal malignancies with en bloc resection, attempts to remove the organs separately causes tumor distribution and decreases the survival to 19-21% even if total resection can be performed (15). In our series, en bloc resection was performed in all patients, and when their primary pathologies were examined, 49 (94.2%) patients had adenocarcinoma of the colon; moreover, urological specimens were malignant in 35 (67.3%) and benign in 16 (30.8%) and one patient had GIST. In the present study, the pathological T4b rate was 71.4%. In a study of colorectal malignancies with bladder invasion, Gao et al. (5) stated that the pathological T4b rate was 54% and the 5-year survival is not affected by the invasion being malignant

**Table 4. Factors affecting major complications seen in the early period**

	Major Complications (+)	Major Complications (-)	p-value
Age (years)	59.95±15.74	56.53±14.05	0.480
<b>Gender (n)</b>			
Male	18	12	0.790
Female	14	8	
<b>Primary tumor location (n)</b>			
Rectum	14	8	0.865
Left colon	12	7	
Right colon	6	5	
Primary tumor	10	14	0.660
Relapse	10	18	
<b>HIPEC (n)</b>			
(+)	10	11	0.089
(-)	22	9	
<b>Preoperative double-J catheter</b>			
(+)	11	11	0.143
(-)	21	9	
<b>Urological procedures performed</b>			
End to end anastomosis of ureter	8	4	0.554
Anastomosis to the contralateral ureter	3	1	
Ureteroneocystostomy (UNS)	6	2	
Partial cystectomy	12	8	
Total cystectomy	3	5	
<b>Ostomy</b>			
(+)	22	16	0.377
(-)	10	4	

HIPEC: Hyperthermic perfusion chemotherapy

or benign. The finding of the present study was similar to that of Gao et al. (5) in that urological organ pathology does not affect survival.

In a large and multicenter study conducted by the PelvEx Collaborative group in patients with locally advanced colorectal cancer, 2.472 patients who underwent pelvic exenteration were examined, and the first 30-day major complication rate, which varied by years, was 31.2-45.1% and the mortality rate as 0%-7% (16). In the present study, the first 30-day mortality and major complication rates were 3.9% and 35.2%, respectively, in accordance with the literature.

Bladder-sparing partial cystectomy can be performed in invasions to the bladder, and the bladder can be primarily repaired. If there is trigon invasion or if the bladder volume will remain too small, en bloc pelvic exenteration should be performed (17). No oncological difference was found between total cystectomy or bladder-sparing cystectomy after a negative microscopic surgical margin was performed (17). However, studies have shown that

total cystectomy increases complications and impairs quality of life (18,19). In the present study, in accordance with the literature, early urological major complications after total cystectomy were higher than that after partial cystectomy in patients with colorectal cancer, but this difference was not significant (Table 4). Therefore, we can say that bladder-sparing surgery is more advantageous in terms of the postoperative period and quality of life if it is performed without compromising oncological principles. After total cystectomy, urinary continuity can be maintained as continent or noncontinent (20,21). As in our series, noncontinent ileal conduits are preferred more frequently in such cases. We performed orthotropic neobladder reconstruction in one patient, and reconstruction with an ileal conduit in seven patients. In the literature, after ileal conduit, the rates of urinary leakage, ileus, and ileal leakage were 7-27.7%, 22%, and 11.1%, respectively (20,22). As late complications, ureteroenteric anastomosis stenosis and renal failure and abdominal wall-related complications were reported in 7-14% and 15%-65% of the cases, respectively (20). We performed nephrostomy and dilatation in three patients who underwent ileal conduit in the late period, owing to the development of stenosis for benign reasons. Conduit revision was performed in a patient who developed a fistula between the conduit and ileum 2 months after the first surgery. We performed ureter anastomosis with Bricker technique, and the ileum was anastomosed with the right colon without cecum resection to avoid the conduit ischemia. In two patients, palliative nephrostomy was performed because of recurrence after an average of 13 (6-21) months in the postoperative period, and the Bricker type ileal conduit technique was performed. In a meta-analysis comparing the Bricker and Wallace techniques in terms of late stricture, no difference was found between the two techniques (23). Based on the literature and results of the present study, if the negative margin can be achieved, we think that the early and late outcomes of bladder-sparing surgery will be better; therefore, intraoperative frozen examination is required from the bladder margins.

In the comparison of patients with and without major complications, we found that factors such as age, gender, localization of the primary tumor, requirement of preoperative DJ, and primary or recurrence of CRC had no effect on major complications. In addition, 21 (40.4%) patients underwent CRS + HIPEC of the peritoneal metastasis of colorectal cancer. The mean PCI value of these patients was 6 (0-18). Six patients with a PCI value of 0 were those who underwent prophylactic HIPEC. In terms of major complications and mortality, no significant difference was found between patients who underwent HIPEC and those who did not. Moreover, no significant difference was noted in terms of survival between HIPEC and non-HIPEC groups. Studies have shown that the addition of urological procedures increases postoperative complications in patients who underwent CRS + HIPEC, but does not affect long-term survival, so it does not constitute a contraindication for surgery (24,25). Morkavuk et al. (26) found that preoperative hydronephrosis, primary or recurrent tumor, and ureter reconstruction type did not cause a difference in terms of complications in patients who underwent ureter resection simultaneously with CRS + HIPEC (26). We also found that ureter resection and reconstruction types have no

effect on major complications and mortality. A multicenter study of the BIG-RENAPE group examined ureter resections performed in 7-8% of patients who underwent CRS + HIPEC and found that reconstruction was better in patients who underwent UNS than in patients who underwent an end-to-end anastomosis (27). We can say that UNS is the type of anastomosis with the least anastomotic stenosis in the late period.

### Study Limitations

This study has some limitations. Although the data of patients who underwent surgery were recorded prospectively, the study was designed retrospectively. The low number of patient groups in the study also makes the study weak. Ureter and bladder resection and reconstruction types constitute a heterogeneous group. By contrast, in the literature regarding such en bloc resections, the numbers are low even in high-volume centers.

### Conclusion

In patients with clinical T4b and colorectal malignancies, en bloc resection should be the oncological procedure to be selected, and a surgical plan should be made by urological and colorectal surgeons by making a management plan approved by a multidisciplinary oncology council. In bladder resections, if possible, organ-preserving surgery should be performed with sufficient negative margin. However, it is thought that late outcomes of UNS in ureter reconstruction are better and those of total cystectomy procedure are worse. We recommend performing prospective randomized studies and meta-analyses to reach a definite conclusion.

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### Ethics

**Ethics Committee Approval:** The study was planned as a retrospective analysis and before starting the study ethical permission was provided by the local hospital ethics committee. The ethical number of this study is E2-21-355.

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### Authorship Contributions

Critical Review: Y.M.Ö., Concept: Y.M.Ö., V.Ö., M.K.Ç., Design: Y.M.Ö., V.Ö., M.K.Ç., O.A., E.B.B., Data Collection or Processing: E.P., O.A., E.T., Analysis or Interpretation: V.Ö., C.C., Literature Search: M.K.Ç., Writing: Y.M.Ö., M.K.Ç.

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# A Case of Eccrine Porocarcinoma Accompanying Renal Cell Carcinoma

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## Abstract

In this case report, we present the coexistence of eccrine porocarcinoma (EPC) and renal cell carcinoma (RCC) in a 69-year-old male patient whose surgical resection pathology of the skin lesion in the right gluteal region was reported as EPC and concurrent radical nephrectomy pathology of the right renal mass was reported as RCC.

**Keywords:** Eccrine porocarcinoma, malignant eccrine poroma, poroid neoplasm, renal cell carcinoma, sweat gland tumour

## Introduction

Eccrine porocarcinoma (EPC) is a rare, malignant skin adnexal tumour arising from the intraepidermal section of the eccrine sweat glands (1,2). The aetiology of EPC is still unclear; it can be a *de novo* lesion or develop from eccrine poroma (EP). Chronic immunosuppression and ultraviolet light are etiologic factors (1,2). EPC was firstly described by Pinkus and Mehregan (3) as a different entity in 1963. It is a solitary, pink-red nodule or plaque and typically seen in people aged  $\geq 60$  years. Its estimated incidence is below 0.3/100,000 in European countries and has comparable incidence in both genders (2). Local repeated recurrence and tumour metastasis are major clinical features of EPC, and the tumour tissue usually metastasise to local lymph nodes (LN) or skin and less common to the breast, liver, lungs, retroperitoneum and ovaries (4). In general, both local recurrence and LN metastasis can be seen in 20% of EPC cases, and the distant metastasis rate has been reported as 10% (5,6). Coexistence of EPC with haematologic malignancies, colorectal carcinoma and squamous cell carcinoma was reported separately (7,8). However, coexistence of urological malignancies and EPC has not been reported yet.

Herein, we present the coexistence of EPC and renal cell carcinoma (RCC) in a 69-year-old male patient whose surgical resection pathology of skin lesion in the right gluteal region was reported as EPC and concurrent radical nephrectomy pathology of the right renal mass was reported as RCC.

## Case Presentation

Written informed consent was obtained from patient for publication of his case and accompanying images.

A 69-year-old man presented with a swelling lesion in the right gluteal region that has been present approximately for 7 years and has grown and demonstrated ulceration for the last few months. He had no history of smoking, obesity or hypertension. A mass measuring 65×60×45 mm in the right kidney was detected by urinary system ultrasonography due to right side pain a month ago.

Dermatological examination revealed a pinkish grey oval plate of 25×25 mm in diameter, with raised skin, crusts and superficial ulcers (Figure 1). Dermoscopic examination revealed pink, yellow, white and occasionally blue-grey asymmetrical areas and hairpin-shaped, linear and spot veins (Figure 2).

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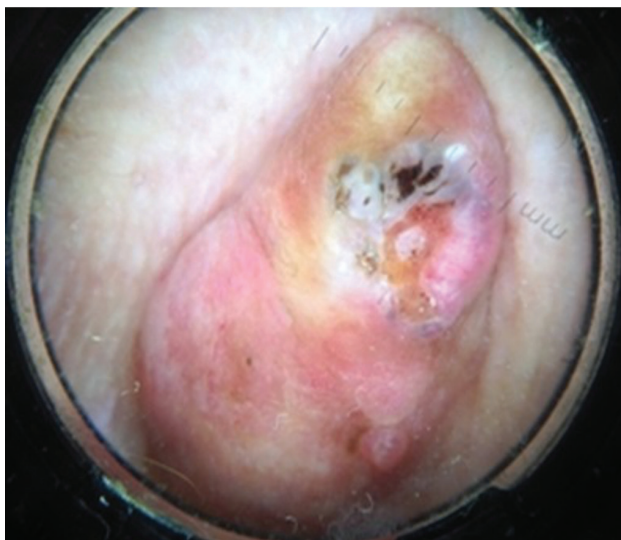
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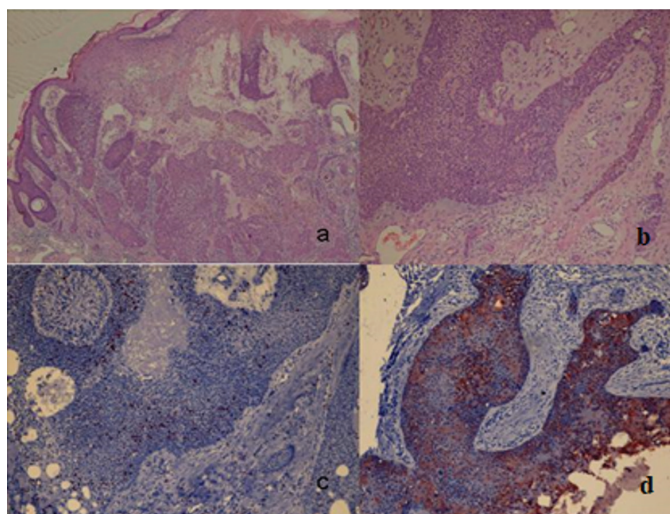
**Figure 1.** Appearance of the lesion: a pinkish grey oval plate with a diameter of 25 × 25 mm, with raised skin, crusts and superficial ulcers



**Figure 2.** Dermoscopic appearance of the lesion

Surgical resection of the lesion revealed a solid tumour with desmoplastic stroma associated with the epidermis. Tumour cells forming large and small islands were malignant cells with large, pleomorphic vesicular nuclei, prominent nucleoli and large eosinophilic cytoplasm. Ductal and squamous differentiation areas, coagulation necrosis and calcification were observed (Figure 3a and Figure 3b).

Immunohistochemical examination revealed that the cells forming the lesion were strongly positive with p63 and epithelial membrane antigen; by contrast, actin, carcinoembryonic antigen and cytokeratin (CK) 20 were negative. Ductal differentiation areas were positive for CK7 and luminal periodic acid Schiff, and squamous differentiation areas were positive for CK5. Ki-67 staining in the most intense area was 15% (Figure 3c and Figure 3d).



**Figure 3.** a. Neoplastic cells with invasion areas (hematoxylin and eosin (H&E) staining, ×50), b. Neoplastic cells with large pleomorphic and hyperchromatic nuclei and islets of invasion at the periphery (H&E, ×100), c. High Ki-67 ratio (Immunoperoxidase, ×100), d. Diffuse epithelial membrane antigen positivity (Immunoperoxidase, ×100)

The skin lesion was diagnosed as EPC according to clinical, histopathological and immunohistochemical findings.

No regional LN involvement or distant metastasis was detected in the contrast-enhanced thoraco-abdominal computed tomography, which was performed for clinical staging of the right renal mass. The patient underwent right laparoscopic radical nephrectomy, and histopathological examination of the renal mass revealed a stage 1 clear cell type RCC (pT1bN0M0). No local recurrence or distant metastasis of EPC or RCC was detected during the 2-year follow-up period.

## Discussion

Coexistence of RCC, which is an important urological malignancy, and EPC, which is a rare dermatological malignancy, was found in a 69-year-old man. Although coexistence of EPC with various malignancies has been reported previously, to the best of our knowledge, no other case in the literature showed the coexistence of EPC and RCC.

Poroid neoplasms represent a spectrum of adnexal tumours arising from the intraepidermal section of the eccrine sweat glands. EP represents benign sections of these tumours, but if untreated for a long period, the risk of malignant transformation to EPC is definite (2). Well-defined risk factors for RCC include tobacco use, obesity and hypertension (9). However, these factors are not considered to increase the risk of developing an EPC. The aetiology of EPC is still unclear; it can be a de novo lesion or develop from EP. Chronic immunosuppression and ultraviolet light are aetiological factors (1,2). Bleeding, ulceration and growth are indicative of malignant transformation in an existing EP lesion (2,10). Similarly, in the present case, the lesion in the right gluteal region grew and ulcerate during the last few months. In addition, an increase in vascularity in the lesion was detected by dermoscopic examination, as shown in Figure 2.

EP is typically seen on the palms and soles, but at least 25% of the cases may occur in other areas such as the face and scalp. Although the typical clinical appearance is a pink-red, solitary nodule or plaque, pigmented variants were also described (1,11,12). EPCs are frequently seen in the lower extremity, but can also be seen in the trunk, head, scalp and upper extremity (13). In the present case, the lesion was found in the right gluteal region, unusually.

A high mitotic activity, atypical mitosis and pleomorphic nucleus are strong indicators of EPC in histopathological examination (1). Similarly, histopathological examination revealed that the tumour cells had large eosinophilic cytoplasm, pleomorphic vesicular nucleus and prominent nucleoli. Remarkably, the lesion contained squamous differentiation, coagulation necrosis and calcification areas.

Tumours accompanying EPC include haematologic malignancies, colorectal carcinoma, tricholemmal carcinoma and squamous cell carcinoma (7,8). Immunosuppression is considered the cause for the coexistence of EPC and haematologic malignancies (8). Dewan et al. (8) reported two patients who received immunosuppressive therapy for chronic lymphocytic leukaemia and red cell aplasia and polycythaemia rubra vera in two patients who died due to septicaemia and acute myeloid leukaemia, respectively (8).

## Conclusion

EPC is a rare dermatological malignancy, typically seen in the older population. Although it is frequently observed in the lower extremities, it can also be seen in unusual areas such as the gluteal region. It is mostly seen as an isolated malignancy, but may accompany urological malignancies such as RCC.

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## Ethics

**Informed Consent:** Written informed consent was obtained from patient for publication of his case and accompanying images.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Concept: A.T.M., G.T.D., Design: A.T.M., G.T.D., Data Collection or Processing: N.K., Ş.Y., Y.A., Analysis or Interpretation: N.K., G.T.D., Literature Search: N.K., Critical Review: H.K., A.T.M., Y.A., Writing: N.K., Ş.Y.

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# Unique Approach to Paediatric Sertoliform Cystadenoma of the Rete Testis: A Case of Testis-Sparing Surgery

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## Abstract

In this case report, we presented a case of pediatric sertoliform cystadenoma of rete testis which was reported for the second time in the literature and treated for the first time with a testis-sparing approach. A 12 years old boy presented with painless mass in the scrotum. Magnetic resonance imaging showed extratesticular, 4.7x3.8 centimeter, well-circumscribed solid mass with heterogenous high degree vascularity at the postcontrast series, displacing right testicle to inferomedial. The patient underwent tumor resection without any complication. Histologic examination revealed 5x5x3 centimeter nodular mass containing uniform tubular adenomatous tumoral proliferation. Immunohistochemical examination of the tumor cells showed positivity for panCK, vimentin and WT1. A diagnosis of sertoliform cystadenoma was rendered in the case. The current case is the largest and the second pediatric case in the literature. Sertoliform cystadenoma is a benign extratesticular mass and can be treated with a testis sparing approach.

**Keywords:** Sertoliform cystadenoma, testis-sparing surgery, pediatric

## Introduction

The majority of scrotal masses originate from the testis and most of them are malignant. Paratesticular masses are less common and mostly benign pathologies originating from spermatic cord, epididymis or rete testis (1). They are often indistinguishable from testicular masses due to the close anatomical relationship between the accessory organs and the testis.

Sertoliform cystadenoma is a very rare benign paratesticular neoplasm originating from rete testis. It was first described by Jones and Young (2) in 1997 with a report of two cases. Although it is known to be a benign mass, orchiectomy has been performed in all cases in the literature because of its clinical presentation cannot be differentiated from testicular tumors.

Only 24 cases have been reported in the literature, and only one is pediatric. In this case report, we presented a case of pediatric sertoliform cystadenoma of rete testis which was reported for the second time in the literature and treated for the first time with a testis-sparing approach.

## Case Presentation

A 12 years old boy presented with painless mass in the scrotum for one month. Routine biochemical serum and urine test results, beta-human chorionic gonadotropin (0.14 mIU/mL), alpha-fetoprotein (1.91 ng/mL) and lactate dehydrogenase (261 U/L) levels were within the normal ranges. On ultrasonography, both testis were normal, no hydrocele and no focal abnormalities noted in both testicles, pathological retroperitoneal lymphadenopathy had not been detected. But ultrasonography showed extratesticular solid mass at right hemiscrotum that probably originated from proximal of spermatic cord. Testis parenchyma and margin of the mass were unrelated. The mass had displaced right testicle to inferomedial. Firstly the lesion was considered as benign nature because of the being extratesticular. However, resection of the mass was recommended to the parent of patient because of high degree vascularity of the mass. Magnetic resonance imaging showed extratesticular, 4.7x3.8 centimeter, well-circumscribed solid mass with heterogenous high degree vascularity at the post contrast series, displacing right testicle to inferomedial (Figure 1). The patient was taken to

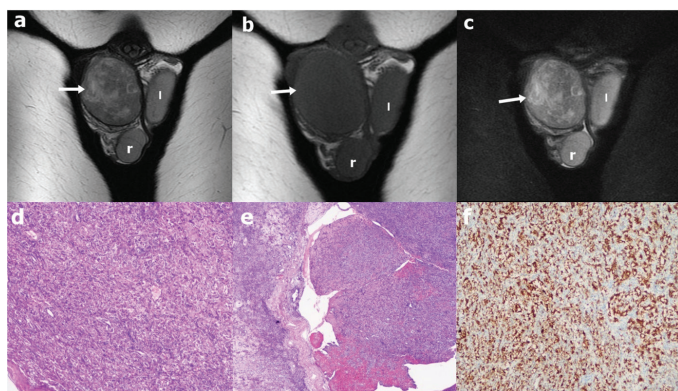
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**Figure 1.** Mass lesion (arrow) with heterogeneous signal intensity, extending from the scrotum into the distal inguinal canal, displacing the right testis (r) inferomedially. T2-weighted without fat suppression coronal magnetic resonance image section (a). Coronal T1-weighted without fat suppression image (a) shows mass (arrow) mainly isointense to the testicular parenchyma (b). Coronal T2-weighted with fat suppression image (c). (l: left testicle). Uniform tubular adenomatous tumoural proliferation (haematoxylin and eosin staining [H&E],  $\times 100$ ) (d). Microscopic cystic space in the focal area (H&E,  $\times 40$ ) (e). Sertoliform cystadenoma with pancytokeratin positivity (pancytokeratin,  $\times 100$ ) (f)

the operation room for right radical orchiectomy after informed consent was obtained from the parents. An inguinal incision was made and the contents of the right scrotum were taken out from the incision with intact tunica vaginalis. The mass, which seemed to be quite separate from the testis, was re-examined perioperatively. After scrotal exploration, the mass was thought to be an extratesticular mass. At this stage, a second interview was conducted with the parents of the patient, and it was stated that the mass could be removed by sparing the testis and informed about the possible risks and benefits. The patient underwent tumor resection without any complication.

Histologic examination revealed 5x5x3 centimeter nodular mass containing uniform tubular adenomatous tumoural proliferation (Figure 1). There was not any mitotic activity, necrosis or nuclear atypia. Immunohistochemical examination of the tumor cells showed positivity for panCK, vimentin and WT1. The cells did not express calretinin, CK5/6, CEA, D240, HBME-1 and inhibin. The vascular cells of tumor mass showed positivity for CD34. A diagnosis of sertoliform cystadenoma was rendered in the case. The patient was alive without evidence of disease recurrence after 4-month follow-up.

## Discussion

Rete testis tumors are rare neoplasms. This accessory organ is often the site of local invasion of primary testicular tumors. Cystic and adenomatoid changes are mostly seen in rete testis lined by low columnar epithelium (1). We presented a case of pediatric sertoliform cystadenoma of rete testis that underwent tumor resection with a testis-sparing approach, unlike previous literature. A testis-sparing approach is preferred for histologically confirmed benign tumors, synchronous or metachronous bilateral tumors, incidentally detected non-palpable and small-volume masses, or for tumor in solitary testis and the pediatric cases (3). The importance of testis sparing surgery in paratesticular masses, especially in those patients with normal

tumor markers, is emphasized (4). We did not orchiectomy because of negative tumor markers, paratesticular location of the tumor and no infiltrative relationship with the surrounding tissue.

Sertoliform cystadenoma may have nodular, cystic or cystic-nodular macroscopic features. Most of the cases reported in the literature (including single pediatric case) have cystic nature. Nevertheless, our case showed more rare solid macroscopic features. The largest tumor reported in the literature was 4 cm (5). Our case is 5 (radiologically 4.7) cm in diameter and is now the largest case of sertoliform cystadenoma in the literature.

Lahouti et al. (6) emphasized that tumor cells often show calretinin and inhibin positivity, considering their cases and other reports in the literature. However, our case showed a negative immunohistochemical profile for both markers. The case of Mesa et al. (7) was also negative for calretinin and inhibin. Rete testicular adenocarcinoma is a rare malignant tumor with poor prognosis (6). Therefore, differential diagnosis from sertoliform cystadenoma, which is a benign tumor and does not require further oncological treatment and postoperative surveillance, should be made. Malignant tumors can be distinguished from sertoliform cystadenoma with high mitotic activity. No mitotic activity was observed in the current case.

The current case is the largest and the second pediatric case in the literature. Sertoliform cystadenoma is a benign extratesticular mass originating from rete testis and can be treated with a testis sparing approach.

## Acknowledgements

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

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

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

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

## Ethics

**Informed Consent:** The patient underwent right radical orchiectomy after informed consent was obtained from the parents.

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## Authorship Contributions

Concept: O.Ö., M.Ö., E.G., S.G., B.A., Design: O.Ö., E.G., Data Collection or Processing: G.Y., E.K., M.Ö., Analysis or Interpretation: Literature Search: O.Ö., G.Y., Writing: O.Ö., M.Ö., F.Ç.

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# Chronic Pyelonephritis Mimicking Renal Mass: A Case Report

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## Abstract

A 72-year-old male patient presented to the hospital with right flank pain, fever and haematuria. Computed tomography revealed a horseshoe kidney, grade 2 hydronephrosis and a focal hyperdense lesion, of which differential diagnosis between mass and abscess could not be made, in the right kidney. Magnetic resonance imaging was performed subsequently and revealed a mass. Right radical nephroureterectomy was then performed. Pathological examination described a fragile, necrotic lesion, which was a sign of chronic pyelonephritis that dilated the pelvicalyceal system. It was also associated with the mucosa and formed cystic structures with a size of 5×4 cm in the cortex. Chronic pyelonephritis cases with acute episodes should be considered in the differential diagnosis of renal tumours.

**Keywords:** Chronic pyelonephritis, renal mass, case report

## Introduction

Pyelonephritis is defined as the inflammation of the renal parenchyma. Fever, costovertebral angle tenderness, nausea and vomiting might be symptoms of acute illness. Chronic pyelonephritis, which is a nonspecific infection of the kidney, may occur after recurring acute episodes of pyelonephritis (1). Although imaging methods are not routinely used for diagnosis, computed tomography (CT) and magnetic resonance imaging (MRI) can be used to determine hydronephrosis, emphysematous pyelonephritis and abscess in patients with congenital structural anomalies and predisposing factors that increase underlying morbidity, such as diabetes mellitus (2). Horseshoe kidney, which occurs from the fusion of metanephric buds in the 4<sup>th</sup>-6<sup>th</sup> weeks of embryonic development, is the most common renal fusion anomaly, with an incidence of 0.4-1.6 in 10,000 live births. People with a horseshoe kidney are at risk of urogenital system infections, because of malrotation, insufficient drainage and obstruction of the ureteropelvic junction (3). Rarely, imaging findings in atypical clinical presentations may be confusing, mimicking kidney or urothelial carcinomas (2). This case report presents the diagnosis and treatment process of a patient with horseshoe kidney, who presented with acute pyelonephritis that mimics upper urinary tract malignancy in imaging.

## Case Presentation

An informed written consent was obtained from the patient for this case report. A 72-year-old male patient who presented to the emergency department with flank pain of 1-week duration, fever, chills and macroscopic painless haematuria for 3 days was hospitalised. He had no symptoms of dysuria or frequent urination. The patient had recurrent episodes of urinary tract infection, hypertension and coronary artery disease, had undergone radical prostatectomy 6 years ago and had a history of pulmonary embolism after this surgery. Physical examination revealed right costovertebral angle tenderness. His blood pressure, pulse rate and body temperature were 88/51 mmHg, 89 beats per minute and 38.3 °C, respectively. Laboratory test results revealed white blood cell count of 40×10<sup>9</sup>/L, blood urea concentration of 32 mg/dL and serum creatinine concentration of 0.92 mg/dL. Complete urinalysis revealed over 204 leucocytes per high power field. Urine culture yielded no growth. Findings of abdominopelvic ultrasonography, performed as the first-line radiological evaluation under emergency conditions, were suboptimal. For this reason, contrast-enhanced abdominal CT was performed, and findings were interpreted as horseshoe kidney with grade 2 hydronephrosis and a focal hyperdense lesion in the upper pole of the right kidney. The relationship of the lesion with the calyces could not be evaluated, and the

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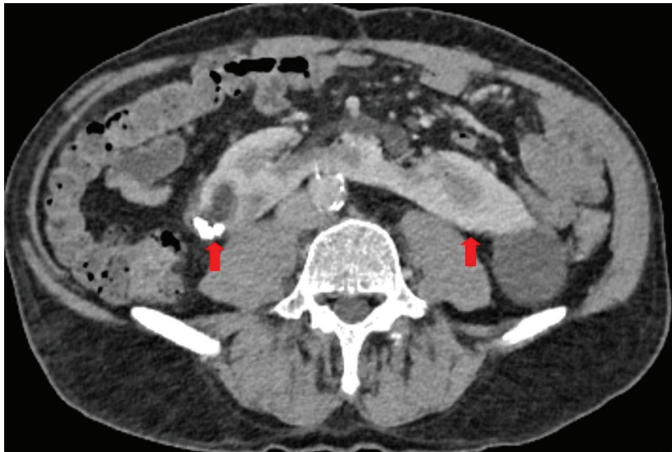
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lesion having dense content could not be distinguished as a mass or abscess.

Ertapenem treatment was initiated for pyelonephritis. Although symptoms of pyelonephritis responded to medical treatment, haematuria persisted. MRI was performed, as the differential diagnosis could not be made with contrast-enhanced CT. MRI revealed a mass lesion with a size of 7×5×4 cm, which caused dilatation in the collecting system of the right kidney with extremely thinned parenchyma, extending towards the renal pelvis and showing diffusion restriction (Figure 1A and 1B). The lesion was predicted as renal cell carcinoma (RCC) or transitional cell carcinoma according to the MRI.

Afterwards, the patient was prepared for surgery, and an open right heminephroureterectomy and cuff resection was performed with a pre-diagnosis of a right renal mass. Macroscopic pathological examination was performed on the 11.5×2.2 cm ureteral material and 17×9.5×6.5 cm renal material, and a lesion 5×4 cm in size that completely dilated the pelvicalyceal system, compressed the cortex, with a fragile necrotic appearance, connected to the mucosa and formed cystic structures in the



**Figure 1A.** Computed tomography image compatible with horseshoe kidney with stones and thinned parenchyma

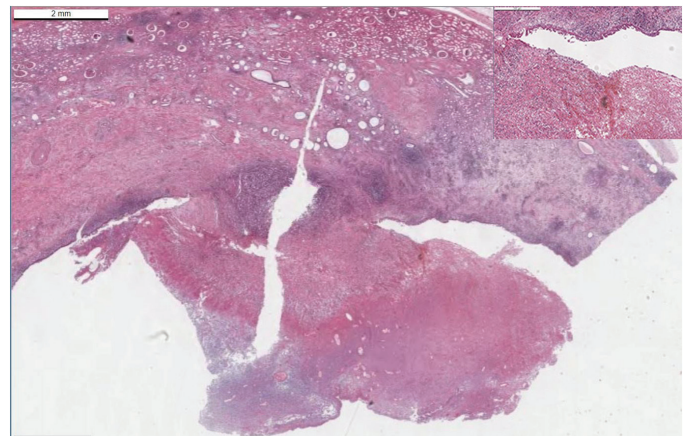


**Figure 1B.** Hyperdense lesion in the upper pole of the right kidney that cannot be distinguished as mass or abscess

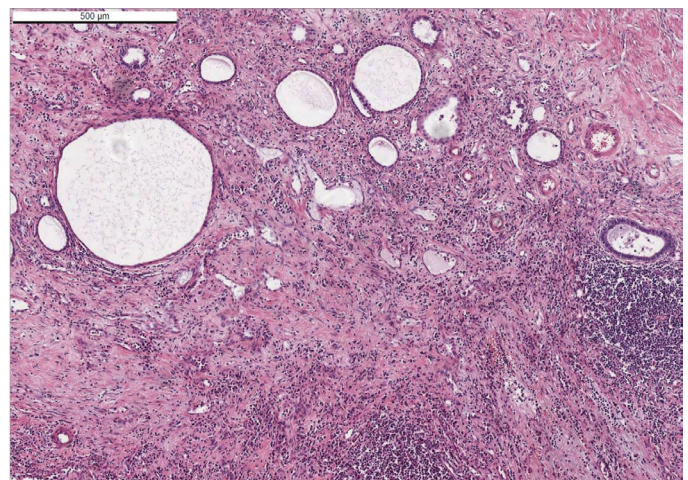
cortex, was detected in the renal material sections. Microscopic examination revealed that the described lesion was completely composed of necrosis, fibrin and inflammatory cells without neoplastic changes, and the appearance was compatible with the findings of chronic pyelonephritis showing active chronic inflammation and necrosis (Figure 2A and 2B). The patient was discharged on postoperative day 5 and did not have any problems in the follow-up.

## Discussion

Chronic pyelonephritis is an inflammation of the parenchyma and pyelocaliceal system of the kidney that occurs as a result of recurrent acute episodes over the years. Chronic pyelonephritis is a nonspecific diagnosis made as a result of excluding specific chronic variants of kidney infections, such as xanthogranulomatous and emphysematous pyelonephritis. Generally, the diagnosis is made when end-stage renal failure develops (4). A study showed that the primary cause of end-stage renal disease is chronic pyelonephritis in 13% of the patients. It occurs in 1-2 per 1.000 women and in 0.5 per 1.000 men (5). Obstructive uropathy, untreated urogenital system infections,



**Figure 2A.** Necrotic mass lesion, which forms a polypoid mass macroscopically, in the background of chronic pyelonephritis



**Figure 2B.** Inflammatory cells and tubular atrophy thyroidisation

schistosomiasis and vesicoureteral reflux are risk factors for chronic pyelonephritis. Although the incidence of RCC does not change in patients with horseshoe kidney, urinary stones and recurring urinary system infections are more common due to the obstruction caused by the abnormal anatomy of the kidney (3). In the present case, the patient had multiple stones, grade 2 dilatation and pyuria in the right kidney.

The clinical presentation of chronic pyelonephritis is related to the disease course. Similar to the present case, findings such as fever and flank pain may occur during acute episodes. However, clinical and urinalysis findings are not correlated. Bacteriuria and pyuria, which are the differential findings of urinary tract infection during acute episodes, are not predictive. The urine may be sterile in cases where the ureter or calyx is completely obstructed (6).

Radiological evaluation is required in complicated pyelonephritis in the presence of accompanying conditions such as renal colic, kidney stones, diabetes, infection with a virulent organism, history of previous surgery and immunosuppression, a history of recurrent pyelonephritis attacks and sepsis (7). For this purpose, CT, which is used as a first-line imaging method for diagnosis, can be used in low-dose renal colic protocol as well as in the portal phase (2). CT findings of chronic pyelonephritis are characterised by parenchymal atrophy of the affected areas, hypertrophy of residual normal parenchymal tissue, clubbing of the calyces secondary to retraction of the papilla from adjacent overlying renal scarring, dilatation of the calyces and overall renal asymmetry. Contrast CT is important to differentiate the non-enhancing areas of infarction from the scar tissue; it can also help in the differential diagnosis of pseudotumors due to focal parenchymal hypertrophy from the renal neoplasm (8). If renal findings cannot be fully characterised by CT, advanced techniques can be used. With MRI, which has a better soft tissue resolution, anatomical boundaries can be distinguished better, disease spread can be evaluated further and infiltrative infectious formations that mimic pathologies such as urothelial carcinoma, lymphoma and metastatic disease can be distinguished (9). However, despite these imaging methods, certain benign pathological formations cannot be distinguished from malignant lesions of the kidney. These lesions, called renal pseudotumors, are caused by developmental, granulomatous and vascular pathologies as well as inflammatory/infectious conditions including chronic pyelonephritis (10). Renal inflammatory pseudotumors are rarely localised in the kidney (11,12,13,14,15,16,17). Although renal inflammatory pseudotumors are rare lesions, they are one of the differential diagnoses of renal malignancy and thus should be considered to avoid misdiagnosis and prevent inappropriate resections (18). In the present case, mass-abscess distinction of the lesion causing dilatation in the right kidney could not be made on CT images. Therefore, MRI evaluated the lesion as a malignancy (RCC or urothelial cancer), indicating that it showed diffusion restriction and enhancement.

The treatment of choice for chronic pyelonephritis varies, as it is a nonspecific diagnosis. Medical and surgical management of the complications are the main goal of treatment. Acute episodes are generally treated with antibiotics and drainage, if necessary. However, in the presence of an atrophic kidney or

underlying conditions causing uncontrollable hypertension or recurrent infections, nephrectomy must be considered an option (6). Diagnosis is confirmed by histopathological examination of the nephrectomy material. Microscopic findings of chronic pyelonephritis are nonspecific and presented as tubulointerstitial mononuclear inflammation of the cortex and medulla. The glomeruli are also surrounded by inflammation, but the tubulointerstitial compartment is severely affected. Severe tubular atrophy may end with a finding called 'thyroidisation', which is not a specific finding for chronic pyelonephritis and can be seen in all conditions leading to tubular atrophy. Lymphocytic inflammation is encountered in the submucosa of the renal pelvis (19).

Xanthogranulomatous pyelonephritis is a chronic granulomatous inflammation that destroys the renal parenchyma. CT is the most useful examination in the diagnosis of xanthogranulomatous pyelonephritis. CT revealed a large reniform mass with the renal pelvis tightly surrounding the central calcification without pelvic dilatation. It is commonly indistinguishable from RCC on ultrasound or CT images, and radical nephrectomy is a viable option for treatment when malignancy cannot be ruled out (6). However, cases in which chronic pyelonephritis, a nonspecific infection, cannot be distinguished from renal mass are rare, and the appropriate treatment method is open to discussion. In the present case, although the patient presented with acute pyelonephritis, the structure of the horseshoe kidney, hydronephrotic appearance and thinned parenchyma of the right kidney suggested chronic pyelonephritis.

In the European Association of Urology guidelines, renal biopsy is recommended if radiological findings are suspicious for malignancy (20). However, in the present case, considering the structure of the right kidney, in which a mass lesion was described on imaging and the fact that it was a source of infection, radical nephro-ureterectomy and cuff resection were performed on the patient, as biopsy was not necessary.

In conclusion, chronic pyelonephritis cases with clinical acute episodes in patients with renal anomalies may give present as a renal mass radiologically. Differential diagnosis must be made to prevent unnecessary treatment. In the differential diagnosis of renal tumours, cases of chronic pyelonephritis developed in the background of chronic obstruction should also be considered.

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## Ethics

**Informed Consent:** An informed written consent was obtained from the patient for this case report.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Concept: S.Ş., Y.Ö., B.G., Design: S.Ş., K.C., Data Collection or Processing: K.C., Analysis or Interpretation: Y.Ö., Literature Search: C.C., K.C., Writing: S.Ş.

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# Primary Signet-ring Cell Adenocarcinoma of the Urinary Bladder That Invades the Pelvic Wall Treated with Partial Cystectomy and Adjuvant Chemotherapy: A Case Report and Review of the Literature

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## Abstract

Primary signet-ring cell carcinoma of the urinary bladder is an exceedingly rare entity associated with poor prognosis. Thus, it is essential to distinguish this carcinoma from gastrointestinal metastases, as different therapeutic strategies are often necessary. We report the case of a 23 year old female patient with primary signet-ring cell carcinoma of the bladder that invades the pelvic wall and treated with partial cystectomy and adjuvant chemotherapy. No metastatic spread or recurrence was detected in the patient after 12 months of follow-up. To our knowledge, this is the first youngest female patient reported in the English literature.

**Keywords:** Urinary bladder, adenocarcinoma, signet-ring cell carcinoma, partial cystectomy

## Introduction

Primary signet-ring cell carcinoma (PSRCC) of the urinary bladder, which was first reported by Saphir in 1955 (1), is a rare variant of adenocarcinoma and comprises only 0.24% to 2% of all primary epithelial urinary bladder tumours. It is associated with a poor prognosis and is generally resistant to chemotherapy and radiotherapy (2,3,4).

Herein, we report the case of 23 year old female patient with PSRCC of the urinary bladder that invades the pelvic wall and treated with partial cystectomy and adjuvant chemotherapy. To our knowledge, this is the second case and the first youngest female patient reported in the English literature.

## Case Presentation

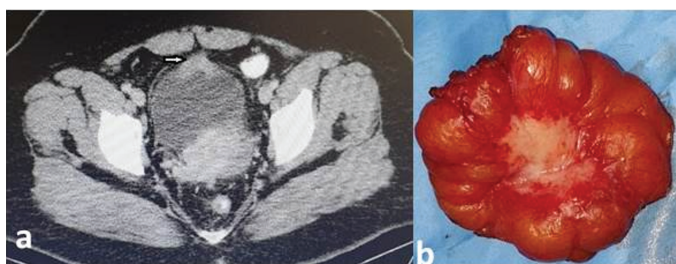
A 23 year old female patient presented with lower abdominal pain, dysuria, intermittent episodes of painless haematuria with amorphous clots of 3 months duration. The medical and familial histories were unremarkable. The general and abdominal physical examination, gynaecologic and breast examinations, gynecologic and breast examinations urine analysis and

blood tests were normal. Ultrasound evaluations revealed a polypoidal vesical mass measuring 30×32 mm arising from the posterolateral wall of the bladder dome. Both kidneys and upper urinary tracts appeared normal. Computed tomography (CT) with and without intravenous contrast administration demonstrated a solid lesion with a diameter of 3 cm leading to a filling defect in the dome of the bladder without distant metastasis (Figure 1a).

After clinical examination, the patient underwent a transurethral resection of the bladder tumour (TURBT) that revealed a white, calcified, solid, papillary tumour extending from the posterior bladder wall to the dome. Biopsy specimens were sent for histopathological examination.

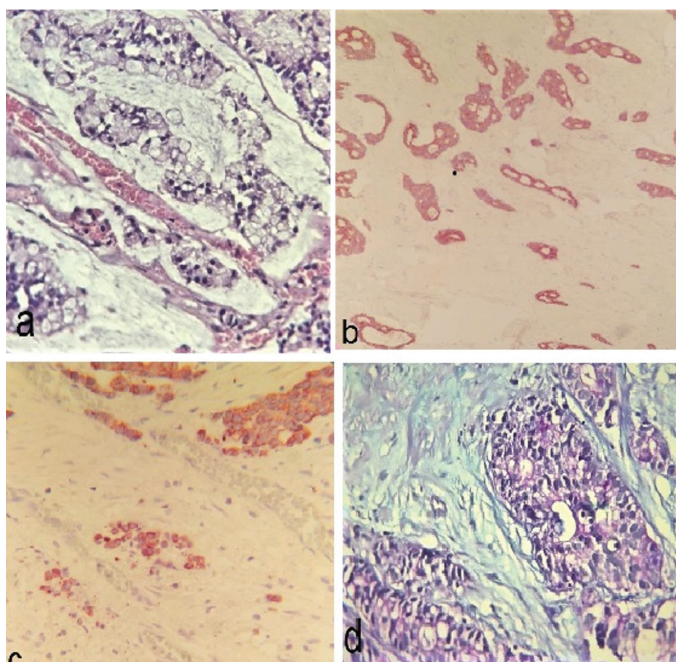
Histological findings were consistent with poorly differentiated mixed mucinous and signet-ring cell adenocarcinoma. The tumour was seen infiltrating the underlying stroma and deep muscle (Figure 2a). Immunohistochemical studies demonstrated strong positivity for CK7 and CK20 (Figure 2b and 2c), and prostate-specific antigen was negative. Periodic acid-Schiff (PAS) stain showed intense pink stain of the cytoplasmic vacuoles of the tumour cells (Figure 2d).

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**Figure 1.** (a). Computed tomography image showing a solid lesion with a diameter of 3 cm leading to a filling defect in the dome of the bladder (arrow) without distant metastasis.

(b). Macroscopic appearance of partial cystectomy specimen



**Figure 2.** Histopathology of transurethral resection of the bladder tumour: poorly differentiated mixed mucinous and signet-ring cell adenocarcinoma (haematoxylin and eosin staining,  $\times 200$ ) (a). Immunohistochemical studies demonstrated strong positivity for CK7 and (b) CK20 (c), and periodic acid-Schiff staining showed intense pink stain of the cytoplasmic vacuoles of the tumour cells (d)

After this pathology report, gastrointestinal tract workup was carried out. Metastasis from a primary gastrointestinal tumour was considered, but gastroduodenoscopy and colonoscopy did not reveal a primary malignancy. Thorax CT and tumour markers such as alpha fetoprotein, cancer antigen (CA)-125, CA15-3, CA19-9 and carcinoembryonic antigen were normal. Fluorodeoxyglucose-positron emission tomography (FDG-PET) scan revealed a 30-mm nodular lesion with increased FDG involvement in the bladder anterosuperior wall extending to the perivesical area. No pathologic FDG involvement was detected in other organs and lymph nodes. Radical cystectomy was recommended to the patient, but partial cystectomy was planned because the patient refused. Partial cystectomy and pelvic lymph node dissection were performed through a Phannenstiel incision. The peritoneum was opened, and generous margin of excision was achieved. No obvious pelvic lymphadenopathy was

noted. Tumour metastasis was detected in the bilateral pelvic side wall and then resected. Pelvic lymphadenectomy to the bifurcation of the aorta was performed. The recovery following surgery was uneventful.

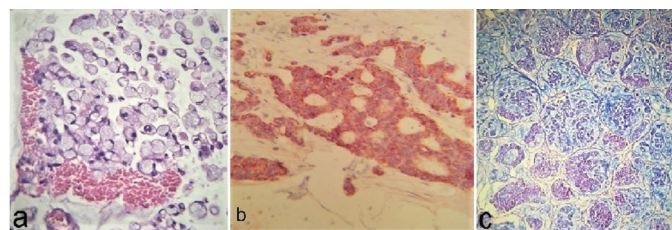
Macroscopic examination of the partial cystectomy specimen revealed an ulcerated mucosa, cut surface revealed a solid tumour measuring  $30 \times 25 \times 20$  mm, infiltrating the bladder wall, and perivesical soft tissue (Figure 1b).

Histopathological evaluation revealed a primary bladder carcinoma composed of mucinous and signet-ring cell components, showing nests of columnar cells and signet-ring cells floating in pools of extracellular mucin. The columnar cells contained pleomorphic hyperchromatic nuclei. Signet-ring cells contained intracytoplasmic mucin (Figure 3a) and strongly positive for CDX-2 and PAS (Figure 3b and Figure 3c). The epithelium was ulcerated and inflamed and was focally continuous with the tumour. The tumour involved muscularis propria. Lymphovascular and perineural invasion was positive and surgical margin was negative.

Pelvic lymph node metastasis was not observed, but metastasis was detected in the specimen of the pelvic side wall material bilaterally.

After 1 month, the patient was given eight cycles of gemcitabine/cisplatin. CT and PET scans showed no pathologic evidence 3 months after the last cycle of chemotherapy. Cystoscopy was performed 6 and 12 months after the last cycle of chemotherapy, and no tumour was detected.

The patient provided written informed consent which includes the case details, operation and agreed to the publication of histopathological images.



**Figure 3.** Histopathology of partial cystectomy. Multiple signet-ring cells (haematoxylin and eosin staining,  $\times 200$ ) (a). Immunohistochemical studies demonstrated positive staining for CDX-2 (b) and periodic acid-Schiff staining (c)

## Discussion

PSRCC of the bladder is a rare type of adenocarcinoma of the bladder. Most of the patients were in their seventh to eighth decades of life, there was male predominance and they were usually diagnosed at an advanced stage, usually demonstrating a subsequently poor prognosis (1).

To our knowledge, this is the youngest female patient reported in the English literature. An 18 year old male patient with PSRCC of the bladder treated with radical cystectomy was reported in 2017 (5).

Primary adenocarcinoma of the urinary bladder is derived from the urothelium that underwent glandular metaplasia, often



in the context of chronic irritation of the vesical mucosa. The histologic diagnosis is based on the presence of characteristic signet-ring cells filled with cytoplasmic mucin-containing vacuoles compressing and displacing the nucleus into a peripheral crescent alongside the cell wall. The component of signet-ring cells in the tumour is variable, and it was reported as greater than 75% in almost half of the cases (6). In our patient, clinical imaging and immunohistochemistry were compatible with PSRCC of the bladder and the tumour tissue stained positive for CK7, CK20 and CDX-2.

Most adenocarcinomas of the urinary bladder result from direct extension from adjacent organs (e.g. colon and prostate). In a female patient, possible primary tumours include tumour from the colon, breast and genital system that should be considered differential diagnosis (7).

The variant signet-ring cell is poorly differentiated and is exceptionally described, and it is seen in approximately 0.24% of bladder cancers (8).

Clinical presentation of PSRCC of the bladder is similar to other bladder malignancies, and haematuria is the most common presenting symptom. Another rare presentation in the literature is mucinuria, which is reported in 3-12% of the patients (9). Our patient had a history of 3 months of intermittent painless haematuria with clot as the presenting symptom.

One of the main problems in cases of PSRCC of the bladder is to exclude metastatic adenocarcinoma from other sites of the body. It is essential to distinguish this carcinoma from metastases as different therapeutic strategies are often necessary. In our case, the gastrointestinal evaluation included esophagogastroduodenoscopy and colonoscopy, but no other tumour lesions were found.

SRCC is known to be associated with poor prognosis. On diagnosis, distant metastases are seen in approximately 25% of patients, and stage IV disease was found in almost half of the patients. This is due to the insidious progression of the disease (10). Its treatment is challenging, especially when diagnosed at an advanced stage. Surgery is the mainstay of treatment, and radical cystectomy is usually performed. Considering the rarity of this histologic type of tumour, there is no consensus regarding the management after surgical care. Chemotherapy and radiation therapy are discussed. Jayarajah et al. (11) reported a 71-year-old female patient with localised tumour treated with partial cystectomy. Wang and Wang (12) reported that 230 patients with pathologically confirmed PSRCC of the bladder were identified between 1973 and 2004. Overall, 26.5% presented with metastatic disease, 25.7% underwent TURBT only and 46.5% had partial or radical cystectomy. The 1-, 3- and 10-year cancer-specific survival rates were 66.8, 40.6 and 25.8%, respectively. Cystectomy was strongly associated with improved survival in patients with localised tumours that did not receive potentially curative cystectomy.

However, in our case, because the patient refused radical cystectomy, partial cystectomy and adjuvant chemotherapy (gemcitabine/cisplatin) was given following a deep TURBT. Follow-up cystoscopy, CT and PET scan at 6 and 12 months have

shown no evidence of tumour recurrence. Partial cystectomy and adjuvant chemotherapy may be considered in selected young patients with stage IV disease who refused radical cystectomy.

## Conclusion

PSRCC of the bladder is a rare tumour known to be associated with poor prognosis. However, partial cystectomy and adjuvant chemotherapy may be considered in selected young patients with stage IV disease without evidence of distant metastasis who cannot undergo radical cystectomy or refuse radical cystectomy.

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

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

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## Ethics

**Informed Consent:** The patient provided written informed consent which includes the case details, operation and agreed to the publication of histopathological images.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Concept: Ç.Y., Design: Ç.Y., Data Collection or Processing: Ç.Y., Analysis or Interpretation: A.H., Literature Search: A.H., Writing: Ç.Y.

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