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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.

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Instructions to Authors

1. General Information

The Bulletin of Urooncology is the official scientific publication of the Turkish Association 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).

All submitted manuscripts are committed to rigorous peer review.

THE BULLETIN OF UROONCOLOGY DOES NOT CHARGE ANY ARTICLE SUBMISSION, PROCESSING OR PUBLICATION CHARGES, NOR DO AUTHORS RECEIVE ANY REMUNERATION OR COMPENSATION FOR THEIR MANUSCRIPTS.

Manuscripts must be written in English and must meet the requirements of the Bulletin. Articles are accepted for publication on the condition that they are original, are not under consideration by another journal, and have not been previously published. This requirement does not apply to papers presented in scientific meetings and whose summaries not exceeding 400 words have been published. In this case, however, the name, date, and place of the meeting in which the paper was presented should be stated. Direct quotations, tables, or illustrations taken from copyrighted material must be accompanied by written permission for their use from the copyright owner and authors.

The name of the journal is registered as "Bulletin of Urooncology" in international indices and databases and should be abbreviated as "Bull Urooncol" when referenced.

All manuscripts should comply with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" produced and updated by the International Committee of Medical Journals Editors (www.icmje.org).

It is the authors' responsibility to ensure their manuscript meets scientific criteria and complies with ethical requirements.

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The Bulletin adheres to the principles set forth in the Declaration of Helsinki 2016 version (http://www.wma.net/en/30publications/10policies/b3/index.html) and holds that all reported research involving human beings is conducted in accordance with such principles. Reports describing data obtained from research conducted in human participants must contain a statement in the "Materials and Methods" section indicating 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.

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Manuscripts are submitted online at www.uroonkolojibulteni.com. If you are unable to successfully upload the files, please contact the editorial office by e-mail or through the online submission system. Rejected manuscripts are not sent back to the authors except for art work.

All submissions must include "Copyright Transfer and Author Declaration Statement Form". All authors should sign this form declaring acceptance of full responsibility for the accuracy of all contents in accordance with the order of authors. They should also indicate whether there is a conflict of interest regarding manuscript. The names of the institutions, organizations, or pharmaceutical companies that funded or provided material support for the research work, even in the form of partial support, should be declared and acknowledged in the footnote of the article. Copyright Transfer and Author Declaration Statement Form must also indicate that "Patient Consent Statement" is obtained for human studies particularly prospective clinical trials, surgery videos (Video-urooncology) and case reports. All manuscripts submitted must also be accompanied by an "Acknowledgements Form" which is available at www.uroonkolojibulteni.com.

The ORCID (Open Researcher and Contributor ID) number of the all authors should be provided while sending the manuscript. Free registration can be done at http://orcid.org.

3. Peer-Review Process

The Bulletin of Urooncology is an independent international journal based on double-blind peer-review principles. All articles are subject to review by the editors and peer reviewers. All manuscripts are reviewed by the editor, associate editors, and at least two expert referees. The scientific board guiding the selection of papers to be published in the 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.

The editor and editorial board is the sole authority regarding reviewer selection. The reviewers are mainly selected from a national and international advisory board. The editorial board may decide to send the manuscript to independent national or international reviewers according to the subject.

Authors of accepted manuscripts accept that the editor and associate editors can make corrections without changing the main text of the paper.

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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).

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

-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). 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). 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
- Study Limitations
- Conclusions
- 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.

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.

- First page: Title -Abstract (maximum 250 words; without structural divisions - Keywords (List 3-5 key words using Medical Subjects Headings [MeSH]).

-Introduction

- 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:

1) Copyright Transfer and Author Declaration Statement Form: This form must indicate that "Patients' Informed Consent Statement" is obtained.

2) Title Page

3) Summary: Summary should point out critical steps in the surgery up to 500 worlds. This part was published as an abstract to summarize the significance of the video and surgical techniques. The author(s) may add references if it is required.

5) Video: Please upload your video to www.uroonkolojibulteni.com using online submission system. Accepted video formats are Windows Media Video (WMV), AVI, or MPEG (MPG, MPEG, MP4). High-Definition (HD) video is preferred.

6) "Acknowledgements From" 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.

6. Manuscript Preparation

Manuscripts should be prepared following sequence according to article type:

A. Copyright Transfer and Author Declaration Statement Form

All manuscripts submitted must be accompanied by this form which is available at www.uroonkolojibulteni.com. All of the authors must sign this form. This form must indicate that "Patient Consent Statement" is obtained for prospective trials, surgery videos (Video-oncology) and case reports. By signing this form the authors declare that they obtained the Ethic Committee approval document regarding all experimental, clinical and drug human studies. By signing this form authors also state that the work has not been published nor is under evaluation process for other journals, and they accept the scientific contributions and responsibilities. No author will be added or the order of authors will be changed after this stage. Any funding and/or potential conflict of interest must be declared in this form.

B. Title Page

The title page should include the following:

-Full title

-Running title

-Authors' names and institutions

-The ORCID (Open Researcher and Contributor ID) number of all authors should be provided

-Corresponding author's e-mail and postal address, telephone, and fax numbers

C. Main Text (without authors' credentials)

Each section of the main text should be started on a new page and abide to the following sequence according to article type:

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

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

-Materials and Methods: This section should describe the study plan, indicating whether the study was randomized or nonrandomized, retrospective or prospective, the number of trials, the characteristics, and statistical methods used. If applicable, it should be indicated that the results should be scrutinized.

-Results: This part should summarize the results of the study, with tables and figures presented in numerical order; results should be indicated in accordance with statistical analysis methods used.

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

-Study Limitations: Limitations of the study should be discussed for only original articles. In addition, an evaluation of the implications of the obtained findings/results for future research should be outlined.

-Conclusions: The conclusion of the manuscript should be highlighted.

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

Examples for writing references:

Format for journal articles: initials of author's names and surnames. title of article. journal name date; volume: inclusive pages.

Example:

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

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

Example:

Book Chapters: Lang TF, Duryea J. Peripheral Bone Mineral Assessment of the Axial Skeleton: Technical Aspects. In: Orwoll ES, Bliziotes M, eds. Osteoporosis: Pathophysiology and Clinical Management. New Jersey, Humana Pres Inc, 2003;83-104.Books: Greenspan A. Orthopaedic Radiology a Practical Approach. 3rd ed. Philadelphia: Lippincott Williams Wilkins; 2000. p. 295-330.

-Figure legends: These should be included in main text on a separate page after the references.

-Short Quiz: A list of 3-5 questions as the last page about the context of article for CME credit only for review articles.

D. Tables and Figures

If you use data from another published or unpublished source, obtain permission and fully acknowledge that source. Number of figure/tables is restricted to five for original article and reviews and three for case reports. Authors should contact the editor prior to submission regarding any manuscript exceeding these figure/table limitations.

Direct quotations, tables, or illustrations taken from copyrighted material must be accompanied by written permission for their use from the copyright owner and authors.

Tables: Supply each table in a separate file. Number tables according to the order in which they appear in the text, and supply a brief caption for each. Give each column a short or abbreviated heading. Write explanatory statistical measures of variation, such as standard deviation or standard error of mean. Be sure that each table is cited in the text.

Figures: Supply each figure in a separate file. Authors should number figures according to the order in which they appear in the text. Figures include graphs, charts, photographs, and illustrations. Each figure should be accompanied by a legend. Figures should be submitted as separate files, not in the text file. Image files must be cropped as close to the actual image as possible. Pictures/photographs must be in color, clear and with appropriate contrast to distinguish details. Figures, pictures/photographs must be uploaded as separate .jpg or .gif files (approximately 500x400 pixels, 8 cm in width and scanned at 300 resolution). Figure legends should be included in main text on a separate page after the references.

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All manuscripts submitted must be accompanied by an "Acknowledgements Form" which is available at www.uroonkolojibulteni.com. The information in this document will be published as a footnote of the article.

If the manuscript presented as an abstract previously; the name, date, and place of the meeting should be mentioned.

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7. Manuscript Submission

As part of the submission process, authors are advised to complete a check-list designed to ensure their submission complies with the instructions for authors, and submissions may be returned to authors who do not adhere to these guidelines.

The Bulletin of Urooncology only accepts electronic manuscript submission at the web site www.uroonkolojibulteni.com.

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.

Submissions must include according to the following sequence:

A-Original Article

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3) Main text (without authors' credentials): Each part should start on a new page.

First page (Title- structured abstract – keywords), Introduction, Materials and Methods, Results, Discussion, Study Limitations, Conclusions, References, Figure legends

4) Table(s)

5) Figure(s)

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B. Case Reports

1) Copyright Transfer and Author Declaration Statement Form

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3) Main text (without authors' credentials): Each part should start on a new page.

First page (Title- abstract – keywords), Introduction, Case Presentation, Discussion, References, Figure legends

4) Table(s)

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C-Review Article

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3) Main text (without authors' credentials): Each part should start on a new page.

First page (Title- abstract – keywords), Introduction, Text (appropriate headings and subheadings), Conclusions, References, Figure legends, Short Quiz

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First page (Title- abstract – keywords), Introduction, Text (Appropriate headings and subheadings), Conclusions, References, Figure legends

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Testis-sparing Surgery in the Treatment of the Normal Contralateral Testicle: A Prospective Multicenter Bench Study Following Radical Orchiectomy

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Abstract

Objective: Testicular tumors can be seen bilaterally in 2-3% of cases as synchronous or metachronous. The long cancer-specific survival in early-stage testicular cancer requires consideration for fertility and quality of life issues because of organ loss in these patients. In the present case series, the surgical outcome and histopathological features of testis-sparing surgery were evaluated using bench work after a standard radical orchiectomy in testicular tumor patients with normal contralateral testis.

Materials and Methods: Patients with a testicular mass confirmed by ultrasonography and/or magnetic resonance imaging and normal contralateral testis were included in the study. All patients underwent standard radical orchiectomy. Partial orchiectomy was performed on a separate operating table (bench) following radical orchiectomy. After visual evaluation of the removed tumor mass, seven biopsies were taken from the tumor bed for frozen section examination (FSE). If a residual tumor was found in the tumor bed because of FSE, parenchymal resection was performed until a negative margin was achieved. The patients' age, tumor marker levels, tumor type, tumor diameter, rete testis invasion, epididymis and spermatic cord invasion, necrosis, and presence of lymphatic-vascular invasion were recorded.

Results: Sixteen patients were included in the study. The mean age of the patients was 31.6±11.6 years. The mean tumor diameter was 26.9±15.3 mm, and the mean tumor-testicular-volume ratio was 33.2±24.9 percentage. The surgical margin was positive in 12.5% (n=2/16) patients in the FSE. In these two patients, the tumor-testicular volume ratio was above 50%, the tumor diameter was greater than 50 mm, and necrosis and invasion of the tunica albuginea were observed in the final histopathology. The tumor histopathology of patients was pure seminoma, non-seminomatous germ cell tumors, mixed germ cell tumor, sex cord stromal tumor, and fibrosis in 50% (n=8/16), 12.5% (n=2/16), 25% (n=4/16) 6.5% (n=1/16) and 6.5% (n=1/16) of the cases, respectively. Histopathological examination revealed 37.5% (n=6/16) intratubular germ cell neoplasia in the adjacent testicular tissue.

Conclusion: Our experience in the present case series shows that testis-sparing surgery is technically straightforward. Surgical margin positivity can be detected in patients with a large tumor or a high tumor-testicular-volume ratio. FSE is useful for detecting surgical margin positivity.

Keywords: Organ-sparing surgery, testicular cancer, partial orchiectomy

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Introduction

Testicular tumors are one of the most common malignant tumors that appear in the young age group. Testicular tumors can be bilaterally seen in 2-3% of cases as synchronous or metachronous (1). Currently, the standard treatment for a testicular mass with a suspicion of malignancy is radical orchiectomy.

Urologists are well aware of the complications caused by organ loss because of other urologic tumor treatments. For example, organ-sparing surgery has claimed its place as a standard practice in urological practice in kidney tumors. The long cancer-specific survival in early-stage testicular cancer requires special consideration for the consequences of organ loss in these patients. The problems caused by testicular loss are not limited to infertility. These may include cosmetic deficiency, erectile dysfunction, loss of muscle strength, and psychological problems due to testosterone deficiency. Therefore, organ-sparing surgery in testicular tumors should be considered, although testis-sparing surgery is recommended only for selected patients treated by clinicians and facilities with experience in this approach (2).

Thus, in the presence of solitary testis or bilateral synchronous testis cancer, testis-sparing surgery may be performed to prevent problems associated with fertility and adverse effects on testosterone hormonal imbalance (3,4).

Usually, small testicular masses are deemed suitable for organ preservation, which may provide a foundation for this particular approach. Small masses are thought to be less capable of invasion and migration. They may be either benign or early lesions during malignancy (3). Nevertheless, there has not been enough experience with testis-sparing surgery to recommend it in an individual with a normal contralateral testis until now, nor is there enough prospective literature data to support this approach in such patients. At present, there is no clear recommendation for testis-sparing surgery in the European Urology guidelines.

Data obtained from the results of retrospective studies showed that testis-sparing surgery may be an alternative in carefully selected cases (5). In the present case series, the surgical outcome and histopathological features of testis-sparing surgery were evaluated with bench work mimicking the in situ surgical procedure after a standard radical orchiectomy in testicular tumor patients with normal contralateral testis.

Materials and Methods

This study was planned and conducted by the Turkish Urooncology Association, Kidney and the Testicular Cancers study group. The patients with a testicular mass confirmed by ultrasonography and/or magnetic resonance imaging with normal contralateral testis were included in the study.

"Bench" Procedure

All patients underwent standard radical orchiectomy. The specimen was immediately placed in ice water and monitored by a 15-19 °C heat probe on a separate operating table (bench). After the procedure, partial orchiectomy was initiated. Localization of the tumor was defined by palpation or, in small nonpalpable tumors by intraoperative ultrasonography. The mass location was evaluated, and the tunica albuginea was opened. The tumor and its surrounding fibrous pseudocapsule were resected along with approximately 3 mm of healthy-appearing testicular tissue. After visual evaluation of the removed tumor mass, seven biopsies were taken from the tumor bed two anterior, two posterior, one medial, one lateral, and one central and sent for frozen section examination (FSE). If a residual tumor was found in the tumor bed because of FSE, parenchymal resection was performed until a negative margin was achieved. Following the bench procedure, the tunica albuginea was closed with a 5/0 monofilament polyclecaprone suture. The remaining surgical specimens were fixed in 10% buffered formalin and sent for histopathological examination.

For pathological examination, serial sections were taken at 5 mm intervals from the testicular tumor and remaining testicular tissue that underwent partial orchiectomy on the bench, and macroscopic examination was performed. The rete testis was sampled in a separate cassette. Tissue samples were fixed in 10% buffered formalin, and 5-micron-thick sections were taken, stained with hematoxylin-eosin, and evaluated under a microscope. The tumor type, tumor diameter, rete testis invasion, epididymis and spermatic cord invasion, necrosis, and lymphatic-vascular invasion were recorded. Intratubular germ cell neoplasia (ITGCN) was evaluated by applying placental alkaline phosphatase for immunohistochemical evaluation of sections close to the tumor and rete testis samples.

Ethics committee approval of the study was received from Osmangazi University on June 26, 2013 in a letter numbered 80558721/213. Informed consent was obtained from all participants.

Statistical Analysis

Study data were collected and managed using esearch Electronic Data Capture) tools hosted at the Urologic Cancer Database - Testis, Turkish Urooncology Association (UroCaD-T) (6,7). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

Results

Sixteen patients from three centers were included in the study. The mean age of the patients was 31.6±11.6 years. The median AFP was 2.84 ng/mL (range 1-897.8), beta hCG 1.28 range 0-100.7 mU/L. The mean LDH was 216.6±100.7 U/L. The mean tumor diameter was 26.9±15.3 mm, and the mean tumor/testicular-volume ratio was 33.2±24.9 percentage (Table 1). Intraoperative ultrasonography was not required for tumor localization in any of the patients.

After partial orchiectomy on the bench, the surgical margin was positive in 12.5% (n=2/16) patients in the FSE. A negative surgical margin was obtained by widening the margin of the partial orchiectomy. In these two patients with positive surgical margins, the tumor-testicular volume ratio was above 50%, the

Table 1. Demographic, laboratory and pathological data of the patients included in the study

Nr.	Age	AFP	bHCG	LDH	TTV (%)	FSE-SM	Tumor type	Tumor diameter (mm)	Tunica albuginea inv.	Tunica vaginalis inv.	Rete testis inv.	Necrosis	LVI	ITGCN	Multifocality
1	34.8	5.8	2	243	50	Positive	Seminoma	50	Yes	No	No	Yes	No	No	No
2	38.9	2.52	1.28	195	30	Negative	Seminoma	37	No	No	No	Yes	No	No	No
3	37.9	2.84	1.2	133	6	Negative	Seminoma	40	No	No	No	No	No	No	No
4	31.5	49.8	20.1	139	25	Negative	Mixt Germ Cell Tumor	30	No	No	No	No	No	No	No
5	62	5.2	2	191	25	Negative	Benign	14	-	-	-	-	-	-	-
6	35.4	5.0	0.1	368	26	Negative	Mixt Germ Cell Tumor	13	No	No	No	Yes	No	No	No
7	16.5	*	*	*	11	Negative	Mixt Germ Cell Tumor	27	No	No	No	Yes	No	Yes	No
8	17.7	897.8	47.71	205	26	Negative	Mixt Germ Cell Tumor	25	No	No	No	Yes	Yes	Yes	No
9	37.1	1.11	0.1	345	15	Negative	Seminoma	10	No	No	No	No	No	Yes	No
10	32	2.59	0.1	362	30	Negative	Seminoma	20	Yes	No	Yes	No	No	Yes	No
11	22.8	192.4	<0.01	38.4	20	Negative	NSGCN	10	No	No	No	No	No	Yes	No
12	20.9	1.3	2	153	57	Negative	Seminoma	30	No	No	Yes	No	Yes	No	No
13	43.5	3.7	21.20	252	95	Negative	NSGCN	55	Yes	No	Yes	Yes	Yes	No	No
14	35.3	1.2	100.7	139	20	Negative	Seminoma	20	Yes	No	No	Yes	No	No	No
15	16.6	1.08	1.00	138	2	Negative	Leydig Cell	4.5	No	No	No	No	No	No	No
16	24.8	1.00	1.00	348	80	Positive	Seminoma	65	Yes	No	No	Yes	No	Yes	Yes

AFP: Alpha-fetoprotein, bHCG: Beta-Human chorionic gonadotropin, LDH: Lactate dehydrogenase, TTV: Tumor-testis volume ratio, FSE-SM: Frozen section examination-surgical margin, LVI: Lymphovascular invasion, ITGCN: Intratubular germ cell neoplasms, NSGCN: Non-seminomatous germ cell neoplasia, *missing due to recording error

tumor diameter was greater than 50 mm, and necrosis and invasion of the tunica albuginea were observed in the final histopathology. In one of these two patients, ITGCN and multifocal millimetric tumor nodules with no preoperative imaging findings were detected in the remaining testicular tissue. Both of these patients' final histopathological examinations were reported as seminoma.

The tumor histopathology rates of patients' pure seminoma, non-seminomatous germ cell tumors, mixed germ cell tumor, sex cord stromal tumor, and fibrosis were 50% (n=8/16), 12.5% (n=2/16), 25% (n=4/16) 6.5% (n=1/16) and 6.5% (n=1/16), respectively. Histopathological examination revealed 37.5% (n=6/16) ITGCN in the adjacent testicular tissue.

Discussion

Leaving aside the oncological consequences, testicular cancer patients are exposed to the adverse functional effects of radical orchiectomy because of its long survival time. Psychological/cosmetic problems that may arise following orchiectomy can be prevented primarily with a testicular prosthesis. However, the management of the effects of infertility and hypogonadism, especially those caused by bilateral synchronous or metachronal tumor conditions, may be more difficult (2). In theory, testis-sparing surgery appears ideal for the management of these unfavorable effects. Furthermore, at least some of these masses may be benign in relation to their size (8). Nevertheless, the fear of compromising oncological control in a patient with a normal contralateral testis seems to be an obstacle to the widespread adaptation of testis-sparing surgery. Thus, organ-sparing surgery in testicular cancer is currently recommended only in selected patients with bilateral synchronous and metachronous tumors and intraoperative FSE (3).

Intraoperative FSE evaluation has high sensitivity for the differentiation of malignancies and correlates well with the final histopathology. Therefore, FSE can also be used during testis-sparing surgery for malignant/benign discrimination, especially in small, nonpalpable, and/or multiple testicular masses (9). In this case series, FSE was used only for surgical margin control. A positive surgical margin was detected in two patients in whom both had a tumor size over 50 mm with a tumor/testicular-volume ratio more than 50%. These findings suggest that adverse pathological features, such as mass size, invasion of the tunica albuginea, and ITGCN, may be associated with positive surgical margins in the two patients with germ cell tumors. In cases where testis-sparing surgery is planned for imperative indications such as a solitary testis, in the presence of masses with tumor size over 50 mm or with a high tumor-testicular volume ratio, FSE may be useful for preventing a final positive surgical margin.

For treating germ cell tumors, testis-sparing surgery is recommended for tumors 25 mm in the presence of synchronous bilateral tumors or metachronous

contralateral tumors (10). With the selection of small-sized tumors, surgical margin positivity can be avoided. Moreover, the remaining testicular volume will be greater, and better functional outcomes may be achieved in terms of fertility and hormonal activity.

It is important to determine the location of the mass using pre-operative imaging. This allows the surgeon to access the tumor with less tissue trauma. However, testicular tumors can be easily located with palpation because of the prominent capsule and testicular tissue features, such as the softness and elasticity of the seminiferous tubules. Because of these tissue properties, the localization and surgical margins of the mass can be easily determined after incision of the tunica albuginea without the need for intraoperative imaging. Enucleation is possible when the tumor must be completely separated from the surrounding tissue. Therefore, it can be performed relatively easily compared with the surgical technique used in the partial surgery of other urological cancers.

There may be multifocality in testicular tumors (11,12). If a radiological diagnosis has not been made, we may not be able to pathologically detect the multifocal testicular tumor (13).

In this case series, pathologically detected multifocal tumors were observed without a radiological finding. Ultrasonographic archive images of this case were re-evaluated without any change in the radiological conclusion. The reason for this may be the images chosen by the radiologist for archiving, the small size of the mass, or the radiological echogenicity characteristics. Whatever the reason, it should not be forgotten that, while rare, such a situation may occur and can be a source of recurrence and progression.

Although testicular tumors can be surgically removed, the size of the mass, fixation of the tunica albuginea, or unfavorable location of the mass may adversely affect the remaining functional testicular tissue. In the resection of these masses, FSE should be used for testis-sparing surgery and for oncological control, and the amount of remaining functional tissue should be considered. The fact that it is possible to perform this surgical procedure does not allow us to abandon the basic oncological principles.

Study Limitations

This study has some limitations. First it is a patient series with a limited number of cases. Because of the nature of the bench study, there is a lack of information about the changes that may occur in sertoli and leading cells due to ischemia, and no further follow-up was possible for that testis. In addition, pre-operative and postoperative hormonal functional evaluation of patients in this setting would not reflect the contribution of the preserved testicular tissue.

Conclusion

Our experience in the present case series indicates the technical feasibility of testis-sparing surgery as a straightforward procedure, especially in small testicular tumors. Testis-sparing surgery may prove to be a valuable technique, especially in benign masses, to prevent long-term negative results.

Surgical margin positivity can be detected in patients with a large tumor or a high tumor-testicular-volume ratio. FSE is useful for detecting surgical margin positivity. Further studies may focus on the effect of unfavorable histopathological findings, such as the invasion of the tunica albuginea, ITGCN, and necrosis, on surgical margin positivity. Further studies would help to identify factors that may determine the best candidate for testis-sparing surgery, including oncological risk, fertility outcomes, and hormonal functions.

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Surgical and Medical Practices: T.A.Ö., A.Ö., C.C., A.T.E., M.A., Concept: Ş.K., S.E., L.T., Design: Ş.K., S.E., L.T., Data Collection or Processing: T.A.Ö., A.Ö., C.C., Analysis or Interpretation: T.A.Ö., A.Ö., Literature Search: T.A.Ö., A.Ö., C.C., Writing: T.A.Ö., A.Ö.

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Original Article

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Comparison of Laparoscopic Partial Nephrectomy vs. Radical Nephrectomy for Renal Tumors with a Renal Nephrometry Score ≥10: A Propensity Score Matched Analysis

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Abstract

Objective: The aim of this study was to assess the oncologic and functional outcomes associated with laparoscopic partial nephrectomy (LPN) in patients diagnosed with high-complexity renal tumors.

Materials and Methods: From November 2009 to October 2018, 399 patients underwent LPN, while 307 patients underwent laparoscopic radical nephrectomy (LRN). Employing propensity score matching to mitigate potential selection bias, individuals were matched on the basis of age, gender, clinical tumor stage, tumor size, baseline renal function, comorbidities, and final tumor pathology. A comparative analysis of functional and oncological outcomes was subsequently conducted across the two groups.

Results: After conducting propensity score analysis, a cohort of 39 patients who underwent LPN was meticulously matched with an equivalent number from the LRN group. The LPN group exhibited a postoperative major complication rate of 10.3%. In the year following surgery, the LRN group demonstrated a notably higher relative decline in renal function compared with the LPN group (-26% vs. -11%, p=0.001). Nevertheless, the two groups displayed similar levels of overall survival (94.9% vs. 82.1%, p=0.545) and recurrence-free survival (97.4% vs. 87.2%, p=0.227).

Conclusions: Although LPN is linked to heightened postoperative complication risks, it may yield superior functional outcomes and maintain comparable oncological outcomes, particularly within proficient medical institutions, for patients grappling with high-complexity renal tumors.

Keywords: Laparoscopic surgery, nephrectomy, patient outcome, propensity score, renal tumor

Introduction

Given the expanding use of cross-sectional imaging for assessing nonspecific issues, a significant proportion of renal tumors are incidentally detected (1).

While partial nephrectomy (PN) remains the preferred approach for patients with clinical T1a tumors, the inclination toward radical nephrectomy (RN) is progressively growing because of the escalation in tumor size and/or complexity in the management of such cases (2). Significant factors that impact treatment decisions encompass the surgeon's proficiency, the clinic's annual case volume, and the effective and widespread use of minimally invasive interventions. Although laparoscopic radical nephrectomy (LRN) has established its efficacy in addressing intricate renal tumors, the existing literature offers only a limited selection of retrospective studies on robotic-assisted PN for this patient cohort (2,3). Conversely, the safety and efficacy of laparoscopic partial nephrectomy (LPN) for high-complexity renal tumors remain inadequately elucidated.

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This study explored the justification for employing LPN in patients diagnosed with high-complexity renal tumors, with a particular focus on assessing both oncological and functional outcomes.

Materials and Methods

The study protocol received scrutiny and approval from the Ondokuz Mayıs University Clinical Research Ethics Committee (decision no: KAEK 2019/538, date: 11.07.2019). All participants provided informed consent upon enrollment and adhered to the tenets of the Declaration of Helsinki. Furthermore, the study has been registered under the identifier NCT04933604 on ClinicalTrials.gov.

We retrospectively analyzed prospectively collected data encompassing 399 cases of LPN and 307 cases of LRN performed between November 2009 and October 2018. Among the LPN group, 41 patients (10.2%) had complete data and each had a radius of the tumor size, exophytic, nearness to collecting system, anterior, location (RENAL) nephrometry score (RNS) of ≥10. In the LRN group, 265 patients (86.3%) had complete data and were consecutively included, with a minimum follow-up period of one year.

To mitigate selection bias, a meticulous 1:1 propensity score-matched analysis was conducted, aligning variables including age, gender, clinical tumor stage, tumor size, baseline renal function, American Society of Anesthesiologists (ASA) score, and pertinent comorbidities such as diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), and final tumor pathology of renal cell carcinoma (RCC) (4,5). The final analysis comprised 78 patients, evenly divided into 39 in the LPN group and 39 in the LRN group.

Clinical diagnoses and tumor anatomical characteristics were established using magnetic resonance imaging and/or contrast-enhanced computed tomography. The Urology Review Board was responsible for determining the treatment modality and specific surgical approach for all patients. Both LPNs and LRNs were conducted exclusively by a single surgeon (EO). Pertinent preoperative variables including age, gender, body mass index, hemoglobin levels, serum creatinine, estimated glomerular filtration rate (eGFR), and comorbidities such as DM, HT, CAD, and tumor size were meticulously documented. The complexity of tumors in both cohorts was evaluated using the RNS score (6).

Intraoperative and postoperative variables encompassing operation time (OT), estimated blood loss (EBL), warm ischemia time (WIT) in the LPN group, perioperative complications, postoperative complications, hospitalization duration, renal functional advancements, ultimate tumor pathology, follow-up duration, and the occurrence of metastatic recurrence were meticulously documented. Postoperative complications were stratified using the modified Clavien-Dindo classification system (Grades 1-5) (7). The evaluation of renal function involved the application of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to eGFR both before and one year following the surgical procedure (8). The achievement of optimal surgical outcomes in the LPN group was evaluated through the application of trifecta criteria, which encompassed negative surgical margins, WIT of 20 min, and the absence of major complications (≥ Clavien grade 3) (9).

Statistical Analysis

The dataset was subjected to analysis using IBM SPSS Statistics Package version 24 (IBM SPSS®, Armonk, NY). Normal distribution conformity was assessed using the Shapiro-Wilk test, with the comparison of normally distributed data performed using the independent samples t-test. In cases where the normal distribution was not met, the Mann-Whitney U test was employed. For categorical data, the chi-square test was applied, and Fisher's exact test was used when cell counts were less than 5. Analytical outcomes are presented as mean ± standard deviation for quantitative data, and categorical data are expressed as frequency (percentage). A significance level of $p<0.05$ was considered significant. The computation of overall survival and recurrence-free survival was conducted using Kaplan-Meier analysis.

Results

In the LPN group, RNS exhibited a mean of 10.23±0.42 (range: 10-11), indicating that 17 tumors (43.6%) were entirely endophytic, 13 tumors (33.3%) were less than 50% exophytic, and 9 tumors (23.1%) were more than 50% exophytic. The mean WIT was 18.28±5.48 min (range: 8-28). Table 1 presents the preoperative demographics and clinical characteristics of the tumors, both before and after propensity score matching.

The LPN group displayed significantly longer mean operation time (111 vs. 88 min., p=0.001), greater mean EBL (166 vs. 124 mL, p=0.020), and elevated rates of postoperative complications (23.1% vs. 10.3%, p=0.045). Each group had one patient who required postoperative transfusion (Clavien grade 2). Additionally, within the LPN group, two patients experienced pseudoaneurysms, leading to angioembolization (Clavien grade 3a) at 2 and 3 weeks post-LPN, respectively. Likewise, two other LPN patients required double J stenting (Clavien grade 3a) because of urine leakage.

Consequently, patients who underwent LPN exhibited superior preservation of renal function. Specifically, the LPN group demonstrated a mean decrease in the eGFR of 11.18±10.77 mL/min/1.73 m^2 one year post-surgery, in contrast to 26.46±18.11 mL/min/1.73 m^2 in the LRN group (p=0.001). The LPN group also displayed a notably lower relative change in renal function (ΔeGFR) compared to the LRN group (-11% vs. -26%, p=0.001). Furthermore, patients who underwent LRN experienced a substantially higher rate of CKD stage-upgradation 1year post-surgery. A detailed overview of the intraoperative and postoperative outcomes is presented in Table 2.

The mean duration of follow-up in the LPN and LRN groups was 28.43±15.95 months and 56.05±31.72 months, respectively. Among patients who underwent LPN, favorable outcomes were observed, with 97.4% achieving negative surgical margins, 89.7% experiencing no major complications, 66.7% having a WIT of 20 min, and 56.4% meeting the criteria for trifecta success. Additionally, within the same LPN cohort, 38.5% exhibited an upgrade in their CKD stage and 48.5% preserved ≥90% of their eGFR.

The analysis of overall survival revealed comparable rates between the LPN and LRN groups, with values of 94.9% and 82.1% respectively (p=0.545). Similarly, recurrence-free survival demonstrated comparable outcomes, with rates of 97.4% in the LPN group and 87.2% in the LRN group (p=0.227). A graphical representation of overall survival is presented in Figure 1, along with additional details in Table 3. Similarly, Figure 2 illustrates recurrence-free survival, which is complemented by supporting information in Table 4.

Discussion

This study demonstrates that LPN yields comparable oncological outcomes and superior functional outcomes compared with LRN for patients afflicted with high complexity renal tumors (RNS ≥10).

Within the decision-making framework for PN in patients with complex renal tumors, tumor size alone does not inherently serve as a definitive constraint. The interplay of patient demographics, clinical tumor attributes, and surgeon proficiency collectively influences the choice of pursuing PN. Of these factors, tumor complexity is potentially the most influential determinant (10). Although the proportion of patients with cT1a tumors was consistent at 59% in both groups within this study, those patients exhibited a higher RNS. Additionally, the tumors displayed distinct characteristics, with 43.6% (n=17) being entirely endophytic and 69.2% (n=27) located centrally.

Moreover, several nephrometry scoring systems, such as RENAL, PADUA, and C-index, which provide comprehensive insights into tumor anatomy based on preoperative imaging, serve as valuable instruments for anticipating surgical challenges, predicting complications, and informing the decision-making process (11). Correlative investigations have consistently revealed a direct relationship between elevated nephrometry scores and increased risks of prolonged WIT, extended OT, greater EBL, heightened complication rates, and the potential for conversion to RN (12,13). A study conducted by Borgmann et al. (14) proposed that RNS exhibited a stronger association with favorable surgical outcomes and perioperative variables, including OT, EBL, WIT, and LOS. Furthermore, it has been observed that patients with higher nephrometry scores are likely to achieve optimal surgical outcomes at a comparatively

Table 1. Pre-operative clinical and demographic characteristics

	Before propensity score matching			After propensity score matching		
Variables*	**LPN (n=41)**	**LRN (n=265)**	**p value**	**LPN (n=39)**	**LRN (n=39)**	**p-value**
Age, year	51.34±14.41	59.32±13.0	0.001	52.26±13.97	54.15±15.33	0.570[a]
Sex, n (%)			0.164			0.591[b]
Male	24 (58.5)	184 (69.4)		23 (59)	23 (59)	
Female	17 (41.5)	81 (30.6)		16 (41)	16 (41)	
DM, n (%)	5 (12.2)	55 (20.8)	0.199	5 (12.8)	8 (20.5)	0.362[b]
HT, n (%)	13 (31.7)	126 (47.5)	0.058	13 (33.3)	14 (35.9)	0.812[b]
CAD, n (%)	2 (4.9)	27 (10.2)	0.280	2 (5.1)	2 (5.1)	0.692[b]
BMI, kg/m²	28.12±4.56	26.95±3.75	0.129	28.36±4.61	27.27±3.79	0.339[a]
ASA score			0.001			0.517
1	22 (53.7)	68 (25.7)		20 (51.3)	16 (41)	
2	16 (39)	161 (60.8)		16 (41)	21 (53.8)	
3	3 (7.3)	36 (13.6)		3 (7.7)	2 (5.1)	
Baseline Cr, mg/dL	0.83±0.20	1.21±1.19	0.043	0.83±0.21	0.94±0.61	0.316[a]
Baseline eGFR	99.73±28.37	80.83±30.99	0.001	94.55±17.98	89.85±23.63	0.326[a]
Tumor size	38.71±16.0	62.65±28.9	0.001	38.90±16.27	44.44±22.74	0.220[a]
RENAL score	10.21±0.41	10.72±1.07	0.003	10.23±0.42	10.46±0.68	0.77[a]
Tumor stage			0.001			0.386[b]
T1a	25 (61)	54 (20.5)		23 (59)	23 (59)	
T1b	15 (36.6)	88 (33.3)		15 (38.5)	14 (35.9)	
T2a	1 (2.4)	50 (18.9)		1 (2.6)	2 (5.1)	
T2b	0	27 (10.2)		0	0	
T3a	0	30 (11.4)		0	0	
T3b	0	5 (1.9)		0	0	
T4	0	10 (3.8)		0	0	

ASA: American Society of Anesthesiologists, BMI: Body mass index, CAD: Coronary artery disease, Cr: Serum creatinine, DM: Diabetes mellitus, eGFR: Estimated glomerular filtration rate, LPN: Laparoscopic partial nephrectomy, LRN: Laparoscopic radical nephrectomy, n: Number
*Continuous variables are presented as the mean ± standard deviation, categorical variables as number (%)
[a]t-test, [b]chi-square test

lower rate than individuals with tumors characterized by lower complexity (9).

It has been reported that almost 80% of patients with T1b renal tumor undergo RN or only robotic PN in high-volume centers by experienced surgeons (2,9). Conversely, the sole randomized clinical trial, EORTC 30904, did not establish an overall survival advantage, despite observing improved functional and comparable oncological outcomes with PN in contrast to RN for patients with localized, solitary renal tumors measuring less than 5 cm (15). While the present guidelines recommend considering PN when technically viable for patients with renal tumors, the impact of renal mass size and complexity on post-PN functional outcomes remains a subject of debate, primarily due to the diversity inherent in retrospective studies (16).

Table 2. Perioperative and postoperative variables

Variables*	LPN (n=39)	LRN (n=39)	p-value
Operation time, min	111.15±35.99	88.08±24.21	0.001[a]
Blood loss, mL	166.15±78.99	124.62±74.75	0.020[a]
Hospital stays, day	4.05±2.60	4.29±6.45	0.832[a]
Positive surgical margin, n (%)	1 (2.6)	0	
ΔeGFR	11.18±10.77	26.46±18.11	0.001[a]
%ΔeGFR	-11	-26	0.001[a]
Postoperative complication rate			0.045[b]
Clavien 1	3(7.7)	0	
Clavien 2	2 (5.1)	4 (10.3)	
Clavien 3a	4 (10.3)	0	
Total	9 (23.1)	4 (10.3)	
Baseline CKD stage			0.296[b]
1	30 (76.9)	22 (56.4)	
2	7 (17.9)	13 (33.3)	
3a	1 (2.6)	2 (5.1)	
3b	1 (2.6)	2 (5.1)	
CKD stage 1 year after surgery			0.001[b]
1	16 (41)	2 (5.1)	
2	20 (51.3)	17 (43.6)	
3a	2 (5.1)	12 (30.8)	
3b	1 (2.6)	6 (15.4)	
4	0	1 (2.6)	
5	0	1 (2.6)	
RCC grade			0.530[b]
Low (1-2)	34 (87.2)	32 (82.1)	
High (3-4)	5 (12.8)	7 (17.9)	
Follow-up, month	28.43±15.95	56.05±31.72	0.001[a]

CKD: Chronic kidney disease, EBL: Estimated blood loss, eGFR: Estimated glomerular filtration rate, LOS: Length of hospital stay, LPN: Laparoscopic partial nephrectomy, LRN: Laparoscopic radical nephrectomy, PSM: Positive surgical margin, RCC: Renal cell carcinoma
*Continuous variables are presented as the mean ± standard deviation, categorical variables as number (%)
[a]t-test, [b]chi-square test

Recent literature has revealed the comparability of PN and RN in relation to oncological and functional outcomes, even in cases of complex tumors. Yang et al.'s (17) recent study suggested that patients undergoing LPN exhibited superior renal functional and oncological outcomes when compared with those who underwent LRN. In line with this, a recent meta-analysis encompassing 21 case-control studies underscores that PN provides comparable oncological outcomes while affording enhanced functional preservation in contrast to RN. The analysis further observed a correlation between increased tumor size, heightened risk of bleeding and complications, and reduced disease recurrence and cancer-specific mortality among patients with PN (18). Our results are consistent with those of the existing literature, demonstrating that OT, EBL, and the rate of complications were elevated in the LPN group. It is important to note that the current study design does not pertain to a specific subgroup within the PN patients, but rather compares the perioperative variables of patients who underwent RN. As anticipated, the extended surgical duration and increased blood loss observed in the LPN group were inherent to the need for

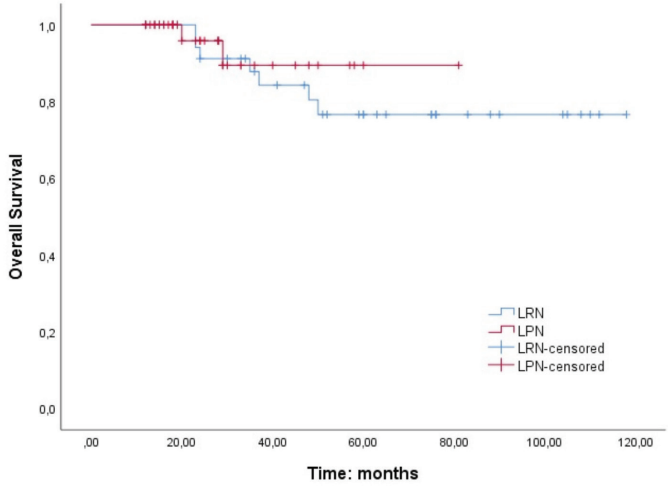

Figure 1. Kaplan-Meier analysis for overall survival

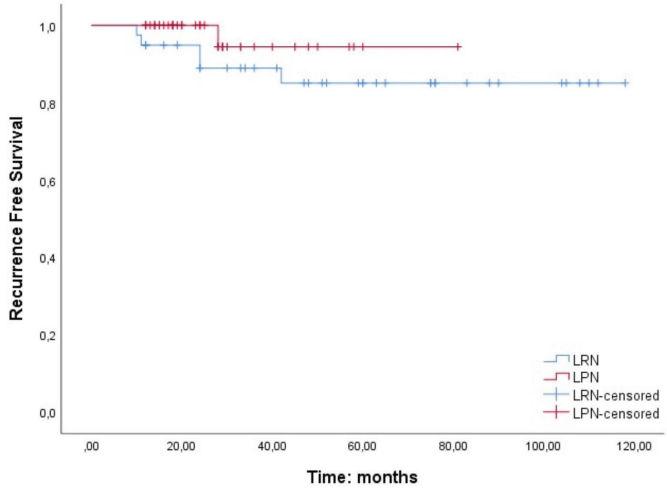

Figure 2. Kaplan-Meier analysis for recurrence free survival

Table 3. Kaplan-Meier analysis for overall survival		
	Mean (95% CI)	**p-value***
LRN	98.7 (86.1-111.3)	0.545
LPN	75.1 (67.3-82.9)	
Overall	100.9 (90.7-111.1)	
*Log rank, LRN: Laparoscopic radical nephrectomy, LPN: Laparoscopic partial nephrectomy, CI: Confidential intervals		

Table 4. Kaplan-Meier analysis for recurrence free survival		
	Mean (95% CI)	**p-value***
LRN	104 (92.6-115.4)	0.227
LPN	78.1 (72.4-83.7)	
Overall	107.6 (99.6-115.6)	
*Log rank, LRN: Laparoscopic radical nephrectomy, LPN: Laparoscopic partial nephrectomy, CI: Confidential intervals		

vascular control, tumor excision, and renorrhaphy during the procedure.

Contemporary literature presents limited evidence regarding LPN for high-complexity renal tumors. This scarcity can be attributed to the increasing adoption of robotic-assisted PN, even for intricate renal tumors, alongside the challenging learning curve associated with pure LPN. In our study, the substantial difference in follow-up duration between the two groups stems from the requisite learning curve for acquiring experience in LPN for patients with complex renal tumors. Nonetheless, our analysis reveals that perioperative outcomes within the LPN cohort, encompassing variables such as OT, WIT, EBL, and rates of postoperative complications, align closely with outcomes reported in prior robotic series (19,20,21).

Even though most complications were minor, tumors with a high-complexity rating have been reported to be directly related to the likelihood of development of increased postoperative complication rates in previous studies (22). In a retrospective cohort study across multiple institutions, Tanagho et al. (23) demonstrated that anatomically classified low-complexity tumors (RNS: 4-6), intermediate-complexity tumors (RNS: 7-9), and high-complexity tumors (RNS: 10-12) exhibited escalating rates of postoperative complications (9%, 15.8%, and 18%, p=0.016, respectively). Similarly, Volpe et al. (19) documented comparable findings, with the reported rates of 22.7% for overall complications and 9.1% for major complications. Our findings are consistent with these investigations. Within our study cohort, the aggregate rate of postoperative complications was 21%. Among these, instances necessitating angioembolization due to bleeding (n=2, grade 3a) and cases requiring double-J stent placement to address urine leakage (n=2, grade 3b) accounted for 10.3% (n=4) of the cases.

Study Limitation

This study was constrained by its retrospective design, a relatively modest patient population representing the experience of a EO, and variations in follow-up durations. Given the necessity for an increased depth of experience in the realm of LPN for complex renal tumors, a disparity in follow-up durations emerged between the LPN and LRN cohorts. The similarity in patients with renal cell carcinoma in the final pathology contributes to the relatively modest sample size. Non-etheless, this study employed a propensity score-matched analysis to mitigate potential selection bias.

Conclusion

Although LPN carries a heightened risk of postoperative complications, it demonstrates the potential for improved functional outcomes and comparable oncological results, particularly within experienced medical centers for patients with high-complexity renal tumors. Vigilant postoperative monitoring is advised, with special attention to potential bleeding and urine leakage.

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Ethics

Ethics Committee Approval: The study protocol received scrutiny and approval from the Ondokuz Mayıs University Clinical Research Ethics Committee (decision no: KAEK 2019/538, date: 11.07.2019).

Informed Consent: All participants provided informed consent upon enrollment.

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Original Article

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Determination of the PSA Cut-off Value to Predict the Clinically Significant Prostate Cancer in Patients with Positive Multiparametric MRI: A Population-based Study

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Abstract

Objective: In this study, we investigated the correlation between prostate imaging reporting and data scoring system (PIRADS) grades of patients' prostate lesions detected by multiparametric prostate magnetic resonance imaging (MpMRI) and prostate specific antigen (PSA) values obtained before prostate biopsy and its role in predicting clinically significant cancer in prostatectomy specimens.

Materials and Methods: Patients who underwent biopsy and were diagnosed with prostate cancer (PCa) because of positive or negative MpMRI were evaluated. Histopathological factors were recorded, and the relationship between the PIRADS grading system and PSA values was analyzed in patients who underwent radical prostatectomy and preoperative MpMRI. PSA cut-off values predicting clinically significant PCa (CSPCa) in MpMRI were calculated.

Results: A total of 1,319 patients were included in the study. MR-fusion biopsy was performed in 58% of the patients, and malignant histopathology was detected in 49% of the patients. While 87% of the patients had CSPCa, 13% had clinically insignificant PCa. The sensitivity and specificity of the PSA 4 ng/mL cut-off value were 88.6% and 15.1% in all patient groups, respectively. In predicting CSPCa, sensitivity was 88.9% and specificity was 18.8% for PSA 4 ng/mL cut-off value in MpMRI-negative patients. If PSA >4 ng/mL in MpMRI-negative patients, there is a >45% PCa detection rate in biopsy, but biopsy is more appropriate for PSA >10 ng/mL for CSPCa. In MpMRI-positive patients, if PSA is >2.5 ng/mL, biopsy provides a >50% PCa and >30% CSPCa diagnosis. If there are PIRADS 5 lesions and PSA is >2.5 ng/mL, biopsy has a >70% PCa and >60% CSPCa detection rate.

Conclusions: It may be appropriate to consider higher PSA cut-off values (PSA >10 ng/mL) to make a biopsy decision in patients with negative MpMRI, whereas it may be possible to detect CSPCa at lower PSA values in patients with positive MpMRI findings and high PIRADS grade.

Keywords: Multiparametric magnetic resonance imaging, prostate specific antigen, prostate cancer, prostate biopsy

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Introduction

Prostate cancer (PCa) is the second most common cancer in men and is responsible for approximately 15% of all male cancers (1). Risk calculators, urine-based tests, and sophisticated imaging methods for PCa diagnosis have been developed in recent years (2,3,4,5). However, none of these devices can replace a suspected digital rectal examination and/or elevated prostate specific antigen (PSA) level for prostate biopsy at the level of guideline recommendation (6). Although there is no definite threshold value for the PSA test, which has revolutionized the diagnosis of PCa, higher values predict higher rates of cancer and clinically significant cancer (7,8,9).

Multiparametric prostate magnetic resonance imaging (MpMRI), which is a breakthrough in PCa imaging, should be performed before prostate biopsy (6). In particular, it is correlated with radical prostatectomy specimens that MpMRI has high sensitivity in detecting and localizing ISUP grade 2 cancers (10). Prostate ımaging reporting and data scoring system (PIRADS) version 2 is a system created for the international interpretation and reporting of lesions in MpMRI (11). The correlation of the PIRADS scoring system with the histopathology of prostatectomy specimens has been investigated, and we demonstrated that high PIRADS scores may be a poor prognostic criterion in our previous multicenter study (12). PCa risk continues in the case of negative MpMRI findings. In this case, the importance of PSA and digital rectal examination, which are classical diagnostic tools, is increasing. Calculation of a PSA cut-off value that can differentiate PCa from clinically significant cancer in MpMRI-negative patients may provide clinical benefit and prevent unnecessary biopsies. There are very limited data in the literature on PSA values predicting MpMRI findings and clinically significant prostate cancer (CSPCa) diagnosis. Some retrospective series conducted with a limited number of patients focused specifically on PSA values in the gray zone (4-10 ng/mL) and evaluated its correlation with high-risk cancers (13,14).

Although there is no clear threshold value and it is not a disease-specific marker, PSA is the first test to be used in PCa suspicion. Therefore, we evaluated the correlation of PSA levels with prostatectomy cancer rates in patients grouped according to PIRADS grades on MpMRI in a population-based multicenter study.

Materials and Methods

The study was conducted retrospectively with the introduction of MpMRI data into the Urologic Cancer Database-Prostate, the Urooncology Association, Turkey. Study data were collected and managed using research electronic data capture (REDCap) electronic data capture tools hosted at our institutions (15,16). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. A total of 1,319 patients from 15 different centers were included in the study. The data from each participating center were anonymized and entered into the database. Patients who underwent prostate biopsy and were found to have PCa because of positive or negative MpMRI were evaluated. The PSA cut-off value was investigated for positive MpMRI before biopsy. After the MpMRI findings were positive, clinically significant and clinically insignificant disease were evaluated after radical prostatectomy. The PSA cut-off value for predicting a clinically significant disease in MpMRI-positive patients was investigated.

Diagnosing lesions with clinical significance in disease management, evaluating the extent of the disease at the time of diagnosis, and determining the risk of progression are important goals. Thus, this study aims to prevent unnecessary treatments in patients with a low risk of progression. Patients who underwent 1.5 or 3 tesla MpMRI and radical prostatectomy were included in the study.

We accepted patients with PIRADS 1 and 2 lesions as potential candidates for active surveillance and these lesions as negative, and PIRADS 3-5 lesions as patients who may require active treatment, and we accepted these lesions as positive (17). Clinically significant cancer in radical prostatectomy was defined as a tumor with a volume of >0.2 cm^3, Gleason grade >7, or extracapsular extension, according to the Johns Hopkins-based definition (18). First the primary endpoint of our study was to evaluate the rates of PCa detection in MpMRI -negative and -positive patients and the change in these rates according to PSA values. Therefore, determining the PSA threshold values predicting this distinction by distinguishing clinically significant and clinically insignificant cancers in radical prostatectomy was the secondary endpoint of our study. A flowchart of the study is shown in Figure 1.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The Urooncology Association study protocol number is TUO-PR-19-02.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS, Version 20.0; SPSS, Chicago, III) was used for statistical analysis. ROC curve

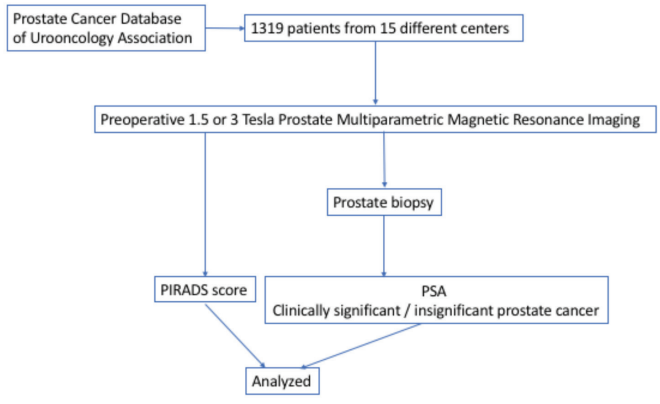

Figure 1. Flowchart of the study

PIRADS: Prostate imaging Reporting and Data Scoring System, PSA: Prostate-specific antigen

analysis was used to predict PSA levels according to preoperative MpMRI findings detecting PCa in biopsy and CSPCa in radical prostetectomy. PSA intervals were evaluated to detect the best predictive PSA cut-off in MpMRI-negative and MpMRI-positive patients for predicting PCa and CSPCa. In parallel, it was also assessed according to the PIRADS lesions in MpMRI-positive patients. Statistical significance was accepted as p-value<0.05 for all analyzes.

Results

A total of 1,319 patients who met the study criteria were included in the study. The mean PSA level was 9.1 ng/mL. Three-tesla MRI was applied to the majority of patients (82% vs. 12%). Approximately three quarters of the patients had PIRADS 4 and 5 lesions on MRI, and more than half of the patients had undergone MR-fusion biopsy. Approximately half of the patients had malignant histopathology on biopsy, and ISUP grades were mostly 1 and 2. Radical prostatectomy was performed in 656 patients, and the histopathology of the prostatectomy specimens was mostly in the ISUP grade 1-3 group, consistent with the biopsy. Surgical margins were positive in approximately one-third of the patients, and extraprostatic spread was in another third. Approximately 1 of 10 patients had lymph node metastasis and seminal vesicle invasion. Most patients had CSPCa (87% vs. 13%). The demographic and clinicalopathological characteristics of the patients are summarized in Table 1.

The sensitivity and specificity of the PSA 4 ng/mL cut-off value were 88.6% and 15.1% in all patient groups [area under the curve (AUC): 565, p<0.001]. In the analysis of 321 patients with negative MpMRI, the sensitivity of the PSA 4 ng/mL cut-off value was 87.7% and the specificity was 19.9% (AUC: 0.575, p=0.02); In the analysis of 998 patients with positive MpMRI, the sensitivity of the PSA 4 ng/mL cut-off value was 88.8% and the specificity was 13.5% (AUC: 0.560, p=0.001). The sensitivity for PSA 4 ng/mL value of those with PIRADS 5 lesions was 93.2% and the specificity was 17.9% (AUC: 0.627, p=0.004). To predict CSPCa, the sensitivity was 88.9% and specificity was 18.8% for the PSA cut-off value of 4 ng/mL in MpMRI-negative patients (AUC: 0.571, p=0.039). The ROC curve of the PSA value for patients with negative MpMRI findings (PIRADS 1-2) is shown in Figure 2. In patients with positive MpMRI, the sensitivity for PSA 4 ng/mL cut-off value was 90% and the specificity was 14% (AUC: 0.583, p<0.001). Figure 3 shows the ROC curve of PSA values for patients with positive MpMRI findings (PIRADS 3-5).

In patients with PIRADS 5 lesions, the sensitivity for PSA cut-off value of 4 ng/mL was 92.5% and the specificity was 17.5% for predicting CSPCa (AUC: 0.607, p=0.018). The relationship between PSA values, MpMRI findings, and PIRADS grades in all patient groups and patients with CSPCa is presented in Table 2.

Discussion

Various serum, urine, and imaging-based diagnostic methods are being developed for the diagnosis of PCa, which is one of the most common cancers in men. However, none of these methods can replace the gold standard diagnosis with biopsy and histopathological examination. Various modifications are being studied and different nomograms are developed to increase the accuracy of these methods and to identify only the necessary biopsies, which is an invasive and complicated procedure. For these modifications, one or more of these items are often used together. Among these, the simple and rapidly accessible PSA serum test and MpMRI, which have been used with increasing frequency in recent years, are two important diagnostic tools. We believe that determining the threshold values that can predict high PIRADS-grade lesions and associated CSPCa for PSA, which is the first diagnostic method used, may prevent overdiagnosis and overtreatment. In this multicenter study, we aimed to investigate the correlation between PIRADS grades of prostate lesions detected by MpMRI and PSA values

Table 1. Demographic and clinicopathological data

Variables		**n=1319**
Age		
PSA		9.1±12.2 (0.5-335.3)
MpMRI (tesla)	**1.5**	162 (12.3)
	3	1089 (82.6)
	N/A	68 (5.2)
Lesion in the MpMRI	**Negative**	321 (24.3)
	Positive	998 (75.7)
PIRADS grade (n=998)	**PIRADS 3**	263 (26.4)
	PIRADS 4	489 (49)
	PIRADS 5	246 (24.6)
Biopsy	**TRUS-Bx**	506 (38.4)
	MR-fusion	770 (58.4)
	Kognitive	43 (3.3)
Biopsy pathology	**Benign**	663 (50.3)
	Malign	656 (49.7)
Biopsy ISUP grade (n=656)	**ISUP 1**	294 (22.3)
	ISUP 2	195 (14.8)
	ISUP 3	81 (6.1)
	ISUP 4	42 (3.2)
	ISUP 5	44 (3.3)
Radical prostatectomy (n=656)		464 (70.7)
Radical prostatectomy ISUP grade (n=464)	**ISUP 1**	110 (23.7)
	ISUP 2	198 (42.7)
	ISUP 3	94 (20.3)
	ISUP 4	23 (5)
	ISUP 5	39 (8.4)
Surgical margin positivity (n=449)		132 (29.4)
Extraprostatic extension (n=450)		126 (28)
The seminal vesicle invasion (n=453)		45 (9.9)
Lymph node metastasis (n=219)		28 (12.8)
Clinically significant/ insignificant prostate cancer (n=464)	**Clinically insignificant**	62 (13.4)
	Clinically significant	402 (86.6)

ISUP: International Society of Urologic Pathologists, MpMRI: Multiparametric magnetic resonance ımaging, N/A: Not available, PIRADS: Prostate imaging reporting and data scoring system, PSA: Prostate-specific antigen

before prostate biopsy and to calculate PSA threshold values for predicting clinically significant cancer in prostatectomy specimens.

A diagnostic model, including MpMRI, has recently been developed to identify clinically significant and clinically insignificant PCa. In this retrospective study of 784 patients, PSA and MpMRI models for diagnostic accuracy were higher for clinically significant and insignificant PCa (19). Unlike our study, PSA derivatives were used in this study, and seminal vesicle and lymph node invasions were included in MpMRI instead of the PIRADS system. In addition, biopsy results were considered the prostate histopathology evaluated in this study. However, similar to our findings, it has been concluded that PSA and MpMRI are predictive factors for cancer aggressiveness. Very few studies in the literature have used the PIRADS system and PSA derivatives for prostate biopsy indication. In a retrospective analysis with a high number of cases reported from Korea, it was concluded that patients with a PIRADS score of ≤2 should not undergo unnecessary biopsy regardless of PSA density (PSAD), and patients with a PIRADS score of 3 should be decided according to the PSAD results (20). In this study, unlike others, biopsy-naïve and previously biopsied patients were evaluated in separate groups, and the results were confirmed in both groups. MpMRI assessments were performed by two different centers. Biopsy histopathology was also based on this study, which included several cases and most of which were clinically significant cancers. In another retrospective series, the PIRADS system and the classical parameters; PSA, prostate volume, and

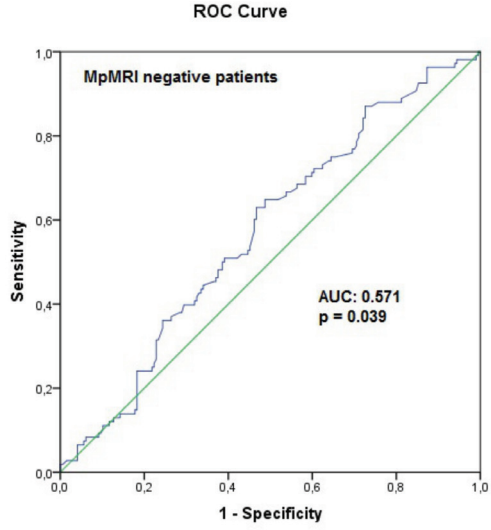

Figure 2. ROC curve analyzes of PSA values in patients with negative MpMRI findings

ROC: Receiver operating characteristics, PSA: Prostate specific antigen, MpMRI: MpMRI: Multiparametric magnetic resonance imaging, AUC: Area under the curve

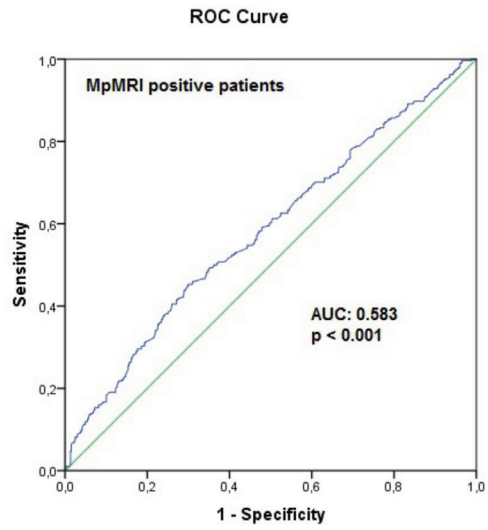

Figure 3. ROC curve analyzes of PSA values in patients with positive MpMRI findings

ROC: Receiver operating characteristics, PSA: Prostate specific antigen, MpMRI: MpMRI: Multiparametric magnetic resonance imaging, AUC: Area under the curve

Table 2. Relationship between PSA values, MpMRI findings, and PIRADS grades

	PCa (n)	PCa rates according to PSA levels (ng/mL)					p-value
		<2.5	2.5-3.99	4-9.99	10-19.99	>20	
MpMRI negative (n=321)	155	4 (33.3)	10 (30)	89 (46.8)	48 (60.8)	4 (40)	0.019
MpMRI positive (n=998)	501	8 (29.6)	48 (52.7)	302 (47.9)	95 (51.9)	48 (71.6)	0.001
PIRADS 3 (n=263)	73	2 (20)	11 (47.8)	45 (25.9)	14 (30.4)	1 (10)	0.138
PIRADS 4 (n=489)	238	4 (40)	26 (49.1)	162 (49.4)	35 (44.3)	11 (57.9)	0.805
PIRADS 5 (n=246)	190	2 (28.6)	11 (73.3)	95 (74.2)	46 (79.3)	36 (94.7)	0.002
	Clinically significant PCa (n)						
MpMRI negative (n=305)	108	2 (18.2)	8 (27.6)	61 (33.9)	34 (45.3)	3 (30)	0.054
MpMRI positive (n=822)	294	4 (19)	26 (35.1)	169 (32.9)	67 (41.9)	28 (57.1)	0.001
PIRADS 3 (n=237)	37	1 (10)	4 (23.5)	21 (13.2)	10 (23.8)	1 (10)	0.402
PIRADS 4 (n=402)	137	2 (20)	14 (31.8)	91 (34.6)	21 (30.9)	9 (52.9)	0.404
PIRADS 5 (n=183)	120	1 (16.7)	8 (61.5)	57 (62)	36 (72)	18 (81.8)	0.033

MpMRI: Multiparametric magnetic resonance imaging, PCa: Prostate cancer, PIRADS: Prostate imaging reporting and data scoring system, PSA: Prostate specific antigen

PSAD's predictive capacity for biopsy results were evaluated (21). Approximately half of the patients in this series were benign and the other half had a clinically significant cancer histopathology. In the multivariate analysis, it was concluded that the combination of PIRADS and PSAD would aid in decision making for prostate biopsy. It has been shown that PIRADS <3 and PSAD <0.15 ng/mL/mL can prevent unnecessary biopsies. Contrary to our study, the inclusion of benign histopathology may be the reason why PSA was not detected as a predictive factor in the logistic regression analysis

In another study describing factors predicting CSPCa in patients with PSA values in the gray zone (4-10 ng/mL), prostate volume, PSA density, and MpMRI were the independent factors that could define clinically significant cancer (22). tPSA appeared as a significant factor only in the univariate analysis. The small number of clinically important cancers in the gray zone (n=28) was an important limitation of this study. Most patients in our study had CSPCa. Most of this study group consisted of benign cases, and there were very few cancer cases (n=56). As a result, it is possible to expect a low mean PSA value and a limited role in distinguishing clinically important cancers. A noninvasive test that can predict a clinically insignificant or significant PCa diagnosis and reduce unnecessary biopsies is required. This requirement is a priority for patients with PSA levels in the gray zone. In another study including 104 patients in the gray zone, the PIRADS system had a high diagnostic performance in predicting CSPCa when PSA density-free PSA% was added (23). The PIRADS system, PSA, and PSAD were found to be independent predictors of PCa and CSPCa (24). Identification of the high-risk group is improved using a PIRADS system combined with PSA and PSAD. A detection rate of 96.1% was detected for high-risk PCa and 93.0% for CSPCa, and 6.1% for PCa and 2.2% for CSPCa for the low-risk group. We conclude that PIRADS v2 can be used as a reliable and independent predictor of PCa and CSPCa. The combination of the PI-RADS v2 score with PSA and PSAD can aid in the prediction and diagnosis of PCa and CSPCa and prevent unnecessary biopsies. An important aspect of the study that differentiated it from ours and others was that it divided the patients into groups as normal, gray zone, and high according to their PSA values, and differentiated clinically significant and insignificant cancer within each group separately. However, in this study, the cut-off value determined instead of PSA was the PIRADS score.

Four hundred ninety one patients were included in a study investigating the factors that would aid clinical decision-making to avoid unnecessary prostate scanning in patients with PIRADS v2 ≤3. In patients with a PIRADS score of 3, PSA and its derivatives appeared to be important factors for distinguishing clinically significant cancer, but in patients with a score ≤3, only age, PSAD, and the PIRADS system were predictive factors (25). These results reflected the results of a single center and lacked external validation. In addition, it was based on biopsy histopathology data instead of radical prostatectomy results. A nomogram that includes all these factors will differentiate clinically important cancer; therefore, studies should focus on this issue. As this study shows, the distinctive feature of PSA becomes more prominent in prostates with high PIRADS scores, which supports the results of our study.

Study Limitations

Its retrospective nature was the main limitation. One major limitation was the absence of centralization. PSA values were obtained from different laboratories, MpMRI images from different devices, and interpretations from different experts. Another limitation was that prostatectomy operations were performed in different centers by different surgeons using different methods. In addition, our study lacked new biomarkers, such as the 4 K score and PCA3. However, it is undeniable fact that this study reflects the real-life scenario better. However, being a multicenter study makes centralization and homogenization difficult. The fact that our study used PSA and MpMRI, two widely used and easily accessible devices in the diagnosis of PCA, stands out as a factor that facilitates its reproducibility and adaptation to clinical use. Another strength of our study was that prostatectomy histopathology was used as a reference instead of biopsy histopathology used in many studies.

Conclusion

In light of these results, it may be appropriate to base a biopsy decision on higher PSA values in MpMRI-negative patients, while it may be possible to detect CSPCa at lower PSA values in patients with MpMRI-positive and high PIRADS grades. Our study is a pioneering study in terms of suggesting a PSA cut-off value to distinguish clinically insignificant-significant cancer and prevent unnecessary biopsies by combining the historical diagnosis and screening tool of PSA with MpMRI PIRADS findings. Certainly, alternative prospective, multicenter studies are needed on this subject. Thus, it is possible to provide more consistent data by better demonstrating the correlation of PSA and its derivatives with the PIRADS system and their role in detecting clinically significant cancer.

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Ethics

Ethics Committee Approval: The study is structured as a database report and therefore, ethical committee approval was not sought.

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: F.K., S.Ç., F.N., S.S., H.Ö., B.A., G.A., L.T., V.İ., B.Ş., S.E., Concept: F.K., S.Ç., Design: F.K., S.Ç., F.N., S.S., H.Ö., B.A., G.A., L.T., V.İ., B.Ş., S.E., Data Collection or Processing: F.K., S.Ç., F.N., S.S., H.Ö., B.A., G.A., L.T., V.İ., B.Ş.,

S.E., Analysis or Interpretation: F.K., S.Ç., B.Ş., Literature Search: F.K., S.Ç., Writing: F.K.

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Original Article

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Transrectal Prostate Biopsy Prophylaxis in Elderly Patients: Comparison of Two Different Prophylaxis Regimens, Seven Years of Experience

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Abstract

Objective: Recent studies have identified increased fluoroquinolone (FQ) resistance; therefore, alternative prophylactic agents such as fosfomycin have begun to be applied to prevent infectious complications of transrectal prostate biopsy. This study compared the use of FQ and fosfomycin for antibiotic prophylaxis in transrectal prostate biopsy in elderly patients.

Materials and Methods: This study was conducted between January 2011 and December 2017. There were 182 patients over the age of 65 years. Group 1 included 97 patients who received oral FQ twice daily for five days, starting 1 h before the procedure, between January 1, 2011 and January 1, 2014. Group 2 included 85 patients who received a single oral dose of fosfomycin the night before the procedure between January 1, 2014 and December 31, 2017.

Results: The average ages of groups 1 and 2 were 69.90±3,906 years and 70.08±3,566 years, respectively. Afebrile urinary tract infection (UTI) was observed in 10 patients and febrile UTI was observed in 11 patients. Of the 10 patients with afebrile UTI, three received fosfomycin and 7 received FQ treatment. Of the 11 patients with febrile UTI, one received fosfomycin and 10 received FQ therapy. There were 20 FQ-resistant infections, 16 of which were observed after the administration of ciprofloxacin and 4 of which were observed after the administration of fosfomycin.

Conclusions: High resistance to routinely applied drugs such as FQs is a worrying concern. One alternative method to decrease FQ-resistant infection and associated hospitalizations is the use of fosfomycin. It seems to be an option and potent agent for prophylaxis in transrectal prostate biopsy for geriatric patients.

Keywords: Aged, fluoroquinolone, fosfomycin, prostate biopsy, prophylaxis

Introduction

Aging is unavoidable status with chronological, biological, and personal conditions. Because of the prolongation of life expectancy and the increase in the geriatric population, the approach to care for the elderly population has become more important. The number of medical problems associated with the geriatric population is also increasing. Significant advances in medical technology and healthcare are causing an increasing number of elderly patients to benefit from complex surgical procedures. With increasing age, physiological and anatomical changes inevitably emerge. Immune function decreases with age with chronic diseases such as carcinoma affecting human resistance (1). Prostate cancer (PC) is the most common malignant tumor in older men. PC has emerged as the most common cancer in men, and its incidence has been increasing rapidly in Europe over the past two decades (2). PC is one of several urological problems that make up a significant part of the problems that affect the elderly and reduce their quality of life. PC diagnosed early can be successfully treated with radical prostatectomy and radiotherapy (3). Abnormal digital rectal examination (DRE) and serum prostate specific antigen (PSA) levels are associated to the risk of PC (4). Transrectal ultrasonography-guided prostate biopsy (TRUS-Bx) is a commonly used canonical method to diagnose PC. The urinary tract infection (UTI) is the most important complication of TRUS-Bx. Although afebrile or non-complicated UTIs mostly occur after TRUS-Bx (1.2-11.3%), febrile or complicated UTIs are also not rare (1.4-4.5%) (5). It can lead to severe sepsis (0.3-3%), require hospitalization, and cause life -minimum status (5). The European Association of Urology guidelines recommend the

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use of antimicrobial prophylaxis in men before TRUS-Bx (6). The most broadly used antibiotics for prophylaxis are fluoroquinolone (FQ) and trimethoprim-sulfamethoxazole. However, recent studies have identified increased FQ resistance (7). Overuse and misuse of antibiotics is an important factor leading to antibiotic resistance (7). Therefore, alternative prophylactic agents such as fosfomycin (single or double dose) have been applied to prevent infectious complications of TRUS-Bx (8,9). Fosfomycin is an oral, broad-spectrum, bactericidal antibiotic that is opposed to the most general Gram-positive (Gr+) and Gram-negative (Gr-) bacterias (10). Owing to its effectiveness, ease of administration, and safety, fosfomycin is highly recommended and practiced for treating uncomplicated UTI (10). UTI is one of several urological problems affecting the elderly and constitutes an important part of the problems that decrease their quality of life. Here, we aimed to compare the effectiveness and reliability of a single-dose fosfomycin with 5 day administration of 500 mg oral ciprofloxacin (FQ) for prophylaxis in TRUS-Bx. To the best of our knowledge, the use of fosfomycin for prophylaxis in TRUS-Bx has not been reported in elderly patients.

Materials and Methods

We conducted this study at Diyarbakır Gazi Yaşargil Training and Research Hospital, Turkey, between January 2011 and December 2017. A total of 182 patients over the age of 65 years were enrolled in this study. The medical records of the patients were retrieved from the hospital database and retrospectively reviewed. Diyarbakır Gazi Yaşargil Research and Training Hospitals Ethical Board confirmed our study (decision number: 12/27, date: 12.02.2018), and all patients signed consent forms. Our study also complied with the principles of the Declaration of Helsinki. TRUS-Bx indications included an elevated PSA level (>2.5 ng/mL), abnormal findings on DRE, and prior prostate biopsy pathology. Urine analysis and urine cultures were negative for infection in all cases. We excluded those who had used antibiotics in the past four weeks, had UTI anamnesis, and had permanent urethral foley. In group 1, there were 97 patients who received oral FQ for 5 days twice daily starting 1 h before the process, between January 1, 2011 and January 1, 2014. FQ resistance was detected in urine culture antibiograms in 33% of patients (in all age group) who applied to our urology department between January 1, 2012 and January 1, 2014. Therefore, as of January 1, 2014, we started using fosfomycin (oral, 3 g) for antibiotic prophylaxis to prevent infectious complications of TRUS-Bx. In group 2, there were 85 patients who received a single dose of fosfomycin (oral, 3 g) the night before the biopsy between January 1, 2014 and December 31, 2017. Acetylsalicylic acid or anticoagulant drugs were administered 5-7 days before TRUS-Bx. All patients received a fleet enema the night before the biopsy. Rectal cleaning was performed using povidone-iodine (10% solution of povidone iodine) just before biopsy during the entire study period. We performed TRUS in the left lateral decubitus position. Local anesthesia was administered transrectally before prostate biopsy. Standard prostate biopsies (12 cores) were obtained using a biopsy device with a disposable 16-gauge 25-cm needle. Prostate volume was measured using the prostate ellipsoid formula: volume=0.52 (HxLxW) where H is the anteroposterior diameter, L is the cephalocaudal diameter, and W is the width. We informed all patients about possible complications after biopsy. All cases were informed to be admitted to the emergency clinic of our hospital in the event of chills, 38.0 °C fever, macroscopic hematuria, and/or serious voiding symptoms. All patients were instructed to visit the controls at 1 and 4 weeks after TRUS-Bx. We planned visits within 4 weeks after TRUS-Bx as a cut-off to conquer infections that could have been linked to TRUS-Bx. Any event that occurred 1 month after prostate biopsy was not considered to be associated with TRUS-Bx. Physical examination, urinalysis, and urine culture were performed in all cases at the 1st week and 1st month after TRUS-Bx. We hospitalized cases with febrile UTI and cured them with intravenous antibiotics, and the drug was altered to an oral type when the patients were discharged. Oral antibiotics were administered to all afebrile UTI patients based on culture results. We evaluated the infectious complications of two antibiotic prophylaxis regimens after TRUS-Bx.

Statistical Analysis

Statistical analyzes were performed using SPSS version 24.0 (Chicago, IL) statistical software package. In the comparison of continuous variables between the groups, it was determined whether they were parametric or non-parametric by the Shapiro-Wilk test. Categorical features were given as numbers, continuous measurements were given as mean ± standard deviation and median IQR. Chi-square test was used to collate categorical variables. The Mann-Whitney U test was used for continuous variables. A p-value of <0.05 was considered statistically significant in all tests.

Results

A total of 182 patients who had received TRUS-Bx were enrolled in this retrospective study. Between January 1, 2011 and January 1, 2014, 97 patients were administered FQ prophylaxis (group 1). Between January 1, 2014 and December 31, 2017, 85 patients were administered fosfomycin prophylaxis (group 2). Patient characteristics are summarized in Table 1 for both the groups. There was no statistically significant difference in terms of age, total PSA level, prostate volume, or previous biopsy for both groups. The mean ages of groups 1 and 2 were 69.90±3,906 years and 70.08±3,566 years, respectively, (p=0.630). The microbiological features and culture findings of cases with afebrile and febrile UTIs are summarized in Table 2. Afebrile UTI was seen in 7 patients in group 1 and 3 patients in group 2 (p=0.318). Febrile UTI was observed in 10 patients in group 1 and in 1 patient in group 2 ($p<0.05$). Positive urine culture was detected in 11 patients with febrile UTI and in 10 patients with afebrile UTI in both groups. Febrile UTI ratio was significantly higher in group 1 (10 vs. 1, $p<0.05$). *E. coli* and *K. pneumoniae* were the most produced agents from urine cultures in all patients. FQ-resistant *E. coli/K. pneumoniae* was determined in 7 patients with afebrile UTI in group 1 and in 3 patients with afebrile UTI in group 2 (p=0,308). FQ-resistant *E. coli/K. pneumonia*e was determined in 9 patients with febrile UTI in group 1 and in 1 patient with febrile UTI in group 2 ($p<0,05$). No patient had experienced extended-spectrum beta-lactamase (ESBL) *E. coli* infection. None of the cases with febrile UTI had positive blood cultures.

Discussion

The aged population is rising worldwide. As a result of this, diseases and health problems have become more widespread. Age-linked variances in immunity, medical comorbidities, invasive interventions, prosthetic/urethral devices, and short- and long-term urinary catheterization increase the sensitivity to UTIs and hospitalization (11). UTI is common in older people and is generally misdiagnosed because of diffuse asymptomatic bacteriuria (11). Cancer incidence and mortality are higher in patients 65 years and older (12). In elderly patients, the procedure of treatment and interventions should be considered individually, based on the characteristics of each patient (13). PC is the most widespread malignancy among elderly men and has emerged as the most widespread cancer among men, with an evident increasing occurrence in Europe over the last two decades (2). PSA testing is performed to decrease and prevent death from PC (14). DRE and serum PSA screening are two ways for early detection of PC (14). The final diagnosis of prostate cancer is made with TRUS-Bx (15). Various antibiotics have been used to prevent the infectious complication of TRUS-Bx, however, standard antibiotic prophylaxis has not yet been described (15). FQs are the most generally used antibiotics because of their dense bioavailability in the prostate, ease of use, and pharmacological biography for TRUS-Bx prophylaxis (16). Unluckily, FQ-resistant *E. coli* derivatives are rising yearly in most countries all over the world (17). Resistance to FQs has been previously known to be related to the use of antibiotics, especially FQs, and previous reports have shown that underlying UTIs tend to expose patients to repeated UTIs and then to antibiotics such as FQs (17). We found FQ resistance in 33% of the patients revealed to our department between January 1, 2012 and January 1, 2014, parallel to the literature in TRUS-Bx (18,19). Numerous studies have recommended that FQ prophylaxis may not be adequate to avert infectious complications of TRUS-Bx (20,21). Some authors recommend rectal swab cultures before the procedure to guide the appropriate antibiotic selection to avert infectious complications of TRUS-Bx (22). Alternative prophylaxis forms, such as single- or double-dose fosfomycin, have been described to avert the infectious complications of TRUS-Bx. In this study, we administered a single dose of fosfomycin for TRUS-Bx prophylaxis. Fosfomycin has broad antibacterial activity against both Gr and Gr+ bacteria, which is known to attack bacteria with mucopeptide synthesis by inhibiting phosphoenolpyruvate transferase, the first enzyme related to the synthesis of peptidoglycan. Fosfomycin is very decently tolerated, and the side effects range is in 1-10% of patients (23). The main side effects of oral fosfomycin are headache, fatigue, and mild gastrointestinal discomfort. The fosfomycin resistance rate is currently considered low despite years of clinical use, and there is also no parallel and/or cross-resistance to fosfomycin and other commonly used agents (10). Shrestha and Tomford (24) reported only 1 case of pseudomembranous colitis observed in a post-marketing study that involved 35,481 patients over 6 years. Gardiner et al. (25) investigated the diffusion of fosfomycin into benign prostate tissue in patients undergoing transurethral resection of the prostate. They found that fosfomycin reached enough intraprostatic aggregations in the inflamed prostate after a single 3 g oral dosage and indicated that fosfomycin can be an effective choice for antibiotic prophylaxis before TRUS-Bx and likely for the medicament of multidrug robust Gr- bacteriuria prostatitis (25). Fosfomycin was first applied by Ongün et al. (8) for TRUS-Bx prophylaxis. Lista et al. (9) in their prospective randomized study collated double doses of fosfomycin with 500 mg oral ciprofloxacin twice daily dispensed for five days beginning one day before biopsy, and Ongün et al. (8) in their

Table 1. Patients characteristic

	Group 1	Group 2	p-value
Patients (n)	97	85	
Age (years) mean ± SD (range)	69.90±3,906 (65-78)	70.08±3,566 (65-77)	0.630
Total Psa (ng/mL) mean ± SD (range)	7.431±3,642 (2.5-20.3)	7,625±3,654 (2.5-20.1)	0.657
Prostate volume (cm^3) mean ± SD (range)	67.43±25,241 (30-156)	67.64±26,610 (33-156)	0.830
Previous biopsy (n)	22	15	0.380

SD: Standard deviation, PSA: Prostate specific antigen

Table 2. Microbiological characteristics and culture results of patients with afebrile and febrile UTIs

	Group 1	Group 2	p-value
Patients (n)	17/97 (17.5%)	4/85 (4.7%)	
Afebrile UTI (n)	7	3	0.308
Fluoroquinolone - resistant *E. coli/K. pneumoniae*	7	3	0.308
Fluoroquinolone - sensitive *E. coli/K. pneumoniae*	-	-	
Febrile UTI (n)	10	1	<0.05
Fluoroquinolone - resistant *E. coli/K. pneumoniae*	9	1	<0.05
Fluoroquinolone - sensitive *E. coli/K. pneumoniae*	1	0	0.149
ESBL *E. coli*[*]	-	-	

[*]Fluoroquinolone-resistant, ESBL: Extended-spectrum beta-lactamases; UTI: Urinary tract infection

retrospective study collated single-dose fosfomycin with 500 mg oral ciprofloxacin twice daily and single dose levofloxacin dispensed for 5 days beginning 1 day before biopsy (9). These two studies showed that fosfomycin is as effective and safe as levofloxacin and ciprofloxacin, indicating that fosfomycin can reduce FQ-resistant infections. Numerous studies have recommended that a single ciprofloxacin prophylaxis cannot be adequate to avert infectious complications of TRUS-Bx (18,20,21). Kehinde et al. (26) argued that combining aminoglycosides decreased infectious complications following TRUS-Bx (26). Marino et al. (27) declared that the combination regimen is more effective than single agents, such as ceftriaxone, ciprofloxacin, and gentamicin, alone for the prophylaxis of TRUS-Bx. Unnikrishnan et al. (28) reported that levofloxacin is more effective than ciprofloxacin when used in combination with aminoglycosides in averting serious infections after TRUS-Bx. Costelloe et al. (29) reported that longer periods and multiple sequences of administered antibiotics are linked with higher rates of bacterial resistance. Today, the prevalence of FQ-resistant and ESBL -positive coliforms is increasing worldwide (20). Bacterial resistance associated with fosfomycin use remains low (9). In the present study, FQ-resistant *E. coli/K. pneumoniae* were detected in 16 patients in group 1 and 4 patients in group 2. In our study, the febrile UTI ratio was significantly higher in group 1. Nowadays, the increase in the number of patients with prostate cancer in active surveillance is associated with recurrent biopsy rates and a higher risk of complications such as urinary infections than primary biopsies (30). Day after day, more infections are observed after TRUS-Bx, and more money is used for the treatment of infectious complications. Prospective common studies are required to decrease infectious complications after TRUS-Bx, including those that analyze selecting prophylactic antibiotics, customizing methods for the patient, and liable possible infection throughout biopsy. Fosfomycin can be used to prevent further development of resistance among elderly patients.

Our research is the first retrospective study collating single-dose fosfomycin with 5-day administration of 500 mg oral ciprofloxacin for prophylaxis in prostate biopsy in geriatric patients. To the best of our knowledge, the use of fosfomycin for prophylaxis in prostate biopsy has not been reported in elderly patients.

Study Limitations

The current study has some significant limitations. First, it's a retrospective nature. Second, as controls, we chose only patients with FQ prophylaxis to make the group as homogeneous as probable for comparison. However, the first study on the use of fosfomycin for TRUS-Bx prophylaxis in the elderly patient population is the strength of our study. The ease of use and low resistance rates are the advantages of fosfomycin. Prospective randomized trials with several cases of fosfomycin use for TRUS-Bx prophylaxis are required.

Conclusion

Antibiotic resistance is a serious issue for doctors and their patients. High levels of bacterial resistance to antibiotics require reassessment of empirical antimicrobial therapy in TRUS-Bx to prevent infectious complications in geriatric patients. Today, variable antibiotic resistance, increasing antibiotic charges, and the use of new antibiotics have made the choice of ideal antibiotic regimens harder than in the past. Fosfomycin can be safely used for TRUS-Bx prophylaxis, especially in geriatric men, because of its easy use, potent antibacterial activity, and low bacterial resistance. We believe that well- designed reports with a larger sample size are needed to confirm our results.

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Ethics

Ethics Committee Approval: Diyarbakır Gazi Yaşargil Research and Training Hospitals Ethical Board confirmed our study (decision number: 12/27, date:12.02.2018).

Informed Consent: All patients signed consent forms.

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Authorship Contributions

Surgical and Medical Practices: C.A., Concept: Z.B.A., C.A., Design: Z.B.A., C.A., Data Collection or Processing: Z.B.A., C.A., Analysis or Interpretation: Z.B.A., C.A., Literature Search: Z.B.A., C.A., Writing: Z.B.A., C.A.

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Original Article

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Are Clinically Significant Cancer Detection Rates Different in Peripheral Zone Lesions Undergoing Transrectal MR-TRUS Targeted Prostate Biopsy with Local Anesthesia and Sedoanalgesia?

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Abstract

Objective: We aimed to compare clinically significant prostate cancer (csPC) detection rates between patients who underwent targeted prostate biopsy under sedoanalgesia and those who underwent biopsy under local anesthesia with intrarectal local anesthetic instillation (IRLI).

Materials and Methods: We analyzed targeted biopsy data from 2015 to 2021 at our center. csPC detection rates of sedoanalgesia (n=56) and IRLI (n=257) groups in targeted biopsy in peripheral zone (PZ) lesions compared after Mahalanobis distance matching within the propensity score caliper method. Four variables-age, prostate specific antigen density, index lesion prostate imaging-reporting and data system score, and the number of lesions-were selected as covariates for the matching procedure.

Results: After matching, 96 patients from the IRLI group and 50 patients from the sedoanalgesia group were included in the analysis. In the IRLI group, csPC was detected in 33 (34.4%) patients, whereas in the sedoanalgesia group, it was detected in 21 (42%) patients. No statistically significant difference was found between the two groups (p=0.365).

Conclusions: csPC detection rates for local and sedoanalgesia are similar in PZ lesions while performing targeted transrectal biopsy.

Keywords: Prostate cancer, targeted biopsy, local, sedoanalgesia, anesthesia

Introduction

Transrectal or transperineal prostate biopsy performed under the guidance of transrectal ultrasound (TRUS) is the most commonly used method for diagnosing prostate cancer (1). The 2022 European Association of Urology (EAU) Prostate Cancer Guidelines state that biopsy with an 18 gauge needle and periprostatic block (PPB) is the standard practice; however, differing anesthesia techniques have been reported in the literature.

For men with a high prostate specific antigen (PSA) level or abnormal findings on digital rectal examination (DRE), 10 or 12 systematic biopsies guided by TRUS are recommended to diagnose suspected prostate cancer. Systematic biopsy without imaging has a low rate of detecting clinically significant prostate cancer (csPC) but a high rate of detecting clinically insignificant prostate cancer (2), which can lead to undertreatment in some patients and overtreatment in others (3,4). The current EAU guidelines strongly recommend performing multiparametric magnetic resonance imaging (mpMRI) before systematic biopsy (1). Performing mpMRI can prevent unnecessary biopsies in some patients and enable targeted biopsies in cases of suspicious lesions (5). The PRECISION study demonstrated that mpMRI is superior to standard systematic biopsies in detecting csPC in men who had not previously undergone prostate biopsy, regardless of whether a targeted biopsy was performed (6). However, the MRI-FIRST and 4M studies found that the difference in the success rate of csPC detection between the two methods was statistically insignificant (7,8). In the MRI-FIRST study, combined biopsy demonstrated a significantly higher success rate in diagnosing csPC than targeted or systematic biopsy alone (7). In the 4M study, the diagnostic rate of clinically insignificant

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prostate cancer was significantly lower with targeted biopsy (8). Current EAU guidelines recommend combined biopsy for patients with a suspicious lesion on mpMRI and targeted biopsy only for patients with a negative biopsy history (1).

Systematic prostate biopsy and transrectal MR-targeted prostate biopsy under TRUS guidance (TRUSG) are commonly performed under local anesthesia. Local anesthesia can be applied as intrarectal local anesthetic instillation (IRLI), PPB, or pudendal nerve block. Many studies in the literature have compared these techniques (9,10,11,12). Other studies have compared general anesthesia methods with local anesthesia or placebo methods, primarily based on pain scores (13,14).

In this study, we aimed to compare csPC detection rates between patients who underwent TRUS-MR targeted prostate biopsy under pseudoanalgesia and those who underwent biopsy under local anesthesia with IRLI. The gel used for local anesthesia contained 6 mL of 2% lidocaine and chlorhexidine.

Materials and Methods

Patients

This study consists of a retrospective analysis of data from patients who underwent MR-TRUS-targeted transrectal prostate biopsy at the Department of Urology, Gazi University Faculty of Medicine Hospital between December 2015 and October 2021. In this medical center, lesions located in the peripheral zone (PZ) are routinely biopsied under local anesthesia. However, lesions located in the transitional zone (TZ), central zone (CZ), and anterior fibromuscular stroma (AFS) are biopsied under sedoanalgesia. Biopsy-naïve patients and had lesions located in TZ and/or CZ and/or AFS underwent combined biopsy (targeted + systematic) under sedoanalgesia, and these patients were included in the study sample if they had a concurrent PZ lesion (n=56). Patients with only PZ lesions who underwent biopsy with IRLI were also included in the study sample (n=257). Biopsy results of lesions outside the PZ in the pseudoanalgesia group were excluded from the analyzes.

MRI and Targeted Biopsy

Patients with elevated PSA levels or abnormal DRE findings who were scheduled for a prostate biopsy underwent mpMRI, which was conducted before biopsy using a 3.0 Tesla (T) MRI device (Magnetom Verio; Siemens Health Care, Erlangen, Germany). All examinations were reported according to PI-RADS v2 or v2.1. Patients with PI-RADS ≥3 lesions underwent TRUSG-MR targeted biopsy. All PI-RADS ≥3 lesions were marked on T2 sequences by a radiologist with extensive experience in this field, and the lesions were outlined on the prostate boundaries and drawings made by a urologist using the BioJet fusion system (D&K Technologies, Barum, Germany) software in conjunction with the Flex Focus 500 ultrasound system (BK Medical, Herlev, Denmark). All targeted biopsies were performed by two experienced urologists. All patients also underwent a standard 12-core systematic biopsy simultaneously with the targeted biopsy. All biopsies were evaluated by the same pathologist. The csPC threshold was defined as International Society of Urological Pathology Grade Group ≥2.

Statistical Analysis

Statistical analyzes were performed using R version 4.0.4 and R Studio version 1.4.1106, with the MatchIt package used for matching analysis. Four variables-age, PSA density, index lesion PI-RADS score, and the number of lesions-were selected as covariates for the matching procedure. Propensity scores were calculated using logistic regression with biopsy technique (local vs. general anesthesia) as the dependent variable and the selected covariates as predictors. A matching caliper was created using propensity scores, and the nearest Mahalanobis distance was used for actual matching based on defined covariates. Before conducting this analysis, the treatment assignment, independence assumption, ignorability assumption, balance checking, overlap assumption, and caliper specification were met. The chi-square test was used to determine the statistical difference among categorical variables. All analyzes used a significance level of α=0.05.

The study protocol was approved by the Clinical Research Ethics Committee of Gazi University Faculty of Medicine (decision no: 104 , date: 07.02.2022).

Results

The clinical and radiological patient data are summarized in Table 1. Propensity distance matching was performed for homogenization for comparison (Table 2, Figure 1). After matching, 96 patients from the local anesthesia group and 50 patients from the sedoanalgesia group were included in the analysis. In the local anesthesia group, csPC was detected in 33 (34.4%) patients, whereas in the sedoanalgesia group, it was detected in 21 (42%) patients. No statistically significant difference was found between the two groups (p=0.365; Table 3). Regarding anesthesia complications, no adverse events were reported. However, some patients experienced fever within 48 h after the procedure. In the local anesthesia group, 3 patients (3.1%) developed fever, whereas in the sedoanalgesia group, 2 patients (4.0%) experienced the same symptoms. These patients were subsequently treated with parenteral antibiotics

Table 1. Clinical and radiological features of the patients

n	**313**
Age [median(range)] (years)	63 (58-68)
PIRADS n (%)	
3	91 (29.1%)
4	152 (48.6%)
5	70 (22.4%)
Total PSA [median(range)] (ng/dL)	6.4 (4.8-9.1)
MRI prostate volume [median(range)] (mm^3)	54 (40-175)
PSA density [median(range)] ($ng/dL/mm^3$)	0.116 (0.078-0.170)
Lesion length [median(range)] (mm)	12 (9-15)
The number of lesions n (%)	
Solitary	239 (76.4%)
Multiple	74 (23.6%)

PSA: Prostate specific antigen

Table 2. Before and after match analysis						
	Pre-match			Post-match		
	Local anesthesia (n=257)	Sedoanalgesia (n=56)	p-value	Local anesthesia (n=96)	Sedoanalgesia (n=50)	p-value
Age			0.75			0.735
Median	63	62.5		63.5	64	
Q1, Q3	57, 68	59, 67		59, 68	59, 68	
PSA density			0.015			0.449
Median	0.110	0.142		0.124	0.134	
Q1, Q3	0.077, 0.16	0.096, 0.202		0.087, 0.162	0.091, 0.183	
PI-RADS			0.182			0.909
3	80 (31.1%)	11 (19.6%)		15 (15.6%)	9 (18.0%)	
4	123 (47.9%)	29 (51.8%)		57 (59.4%)	28 (56.0%)	
5	54 (21.0%)	16 (28.6%)		24 (25.0%)	13 (26.0%)	
The number of lesions			0.192			0.710
Solitary	200 (77.8%)	39 (69.6%)		70 (72.9%)	35 (70.0%)	
Multiple	57 (22.2%)	17 (30.4%)		26 (27.1%)	15 (30.0%)	
PSA: Prostate specific antigen, PI-RADS: Prostate imaging-reporting and data system						

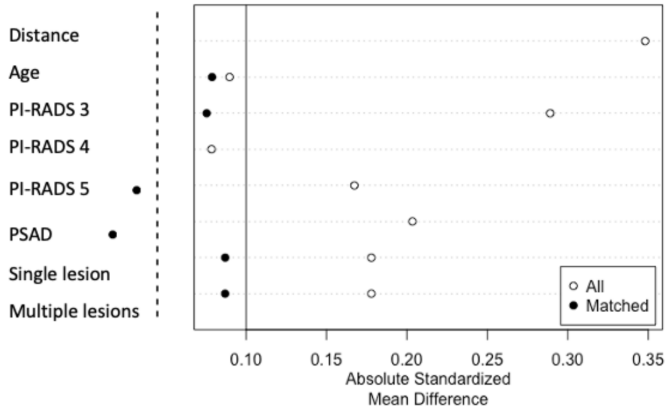

Figure 1. Distribution chart before and after the match

PI-RADS: Prostate imaging-reporting and data system, PSAD: Prostate specific antigen density

Table 3. csPC detection rates by anesthesia type			
	csPC	Benign	p-value
Local anesthesia n=96	33 (34.4%)	66 (65.6%)	0.365
Sedoanalgesia n=50	21 (42.0%)	29 (58.0%)	
csPC: Clinically significant prostate cancer			

after hospitalization. In addition, urinary retention occurred in 4 patients (4.1%) in the local anesthesia group and 2 patients (4.0%) in the sedoanalgesia group.

Discussion

Regardless of the application method (systematic/targeted), route (transrectal, transperineal), and anesthesia type, the most important goal of prostate biopsy is to determine the presence and degree of cancer. Although many studies have compared the detection rates of csPC for different application methods (7,8) and routes (15), research on the effect of anesthesia type on csPC detection rates is limited. Previous research has focused on the effect of anesthesia type on patient comfort and procedure-related complications. In our literature search, we found no studies that investigated the effect of anesthesia type (local vs. sedoanalgesia) on the csPC detection rate of targeted biopsies.

Biopsies taken under general anesthesia are more comfortable for both the patient and the physician (16). However, because of the significant time and cost associated with biopsies under general anesthesia, we only perform transrectal prostate biopsies under local anesthesia on patients with PZ lesions in our clinic. Local anesthesia causes fewer cardiac and pulmonary complications; however, it is unclear whether patients are under higher stress levels during the procedure than if they were under general anesthesia. General anesthesia can increase cardiopulmonary complications but may be less stressful for the patient (16). In our clinic, if there is a PIRADS ≥3 lesion with an anterior location, we perform targeted biopsy under sedoanalgesia. In targeted prostate biopsies performed transrectally on an anterior lesion, the biopsy needle must travel a longer distance in the prostate, causing more pain. Thus, real-time ultrasound and MRI matching may be disrupted because of patient movement, resulting in decreased biopsy quality.

We conducted a retrospective analysis of MR-TRUS-targeted prostate biopsy data and found no statistically significant difference in csPC detection rates between the local anesthesia and pseudoanalgesia groups for biopsies taken from PZ lesions. Similarly, Hogan et al. (17) compared prostate cancer detection rates in transperineal prostate biopsies based on anesthesia type and found no statistically significant difference between the general and local anesthesia groups. In a recent study by Kim et al. (18), sedation anesthesia was found to have a cancer detection rate statistically significantly higher than IRLI in 12-core systematic biopsies (34% vs. 29.2%, p=0.024). In the

same study, logistic regression analysis showed that sedation anesthesia was an independent predictor of cancer detection in patients with PSA levels <10 ng/mL (18). However, no data on the csPC detection rates were presented in the study. In the present study, we only compared csPC detection rates, and unlike the work of Kim et al. (18), we compared pseudoanalgesia and local anesthesia groups of patients who underwent targeted biopsy. We attribute the differing results of this study and those of Kim et al. (18) to these two factors. In a study by Temiz et al. (19), the authors compared the cancer detection rates of PPB and IRLI in 10-core systematic biopsy procedures and found a statistically significant difference in favor of PPB (25.4% vs. 19.8%, p=0.001). In the same study, patients in the IRLI group had significantly higher pain scores, as measured by the visual analog score (VAS). The authors explained the lower cancer detection rate in the IRLI group by theorizing that clinicians may not adequately sample the apex and far lateral parts of the prostate because of the relatively high pain experienced by patients in this group (19).

Prostate biopsies performed under local anesthesia are often well tolerated by patients. In their daily practice, clinicians tend to prefer local anesthesia for prostate biopsy because general anesthesia is associated with a risk of cardiopulmonary depression and increased cost (16). A meta-analysis of 47 randomized controlled studies found that a combination of PPB and intravenous sedation is the most effective method for reducing biopsy-related pain, followed by spinal anesthesia (20). In a study by Irani et al. (21) in which sextant TRUS biopsies were performed without anesthesia in 81 patients, an average patient pain value of 3 [on a scale of 0 (no pain)-10 (unbearable pain)] was measured using VAS, and the procedure was described as moderately uncomfortable. In the same study, 6% of patients stated that the procedure should be performed under general anesthesia, and 15% stated that they would prefer to undergo the procedure under any type of anesthesia if they needed to undergo a biopsy again (21). Pasali et al. (22) compared the types of local and regional anesthesia applied during transrectal prostate biopsy. The pain scores of the IRLI group were significantly higher than those of the PPB and caudal regional anesthesia groups (22). A meta-analysis of 25 randomized controlled studies found that PPB is an effective and safe method to reduce biopsy-related pain, whereas IRLI is less effective than PPB and not significantly different from a placebo method (23). In our routine practice, we do not use PPB for patients undergoing targeted prostate biopsy because we are concerned about possible mismatches in the registration of MRI and real-time ultrasound images due to the anatomical changes that occur after injection of local anesthetic into the periprostatic area. Therefore, we use IRLI for patients undergoing targeted biopsy.

Study Limitations

The most important limitation of our study is its retrospective design. Another limitation is that the biopsies were not performed by a single clinician.

Conclusion

While performing transrectal targeted prostate biopsy for lesions located in the PZ, csPC detection rates for local and sedoanalgesia are similar. Both types of anesthesia can be effectively used according to patient and physician preference.

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Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of Gazi University Faculty of Medicine (decision no: 104 , date: 07.02.2022).

Informed Consent: Retrospective study.

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Authorship Contributions

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Case Report

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Urachal Adenocarcinoma: A Case Report with 4-Year Follow-up

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Abstract

The urachus is an embryological remnant that lies between the bladder and umbilicus as a fibrous band that attaches the cloaca to the allantois in the intrauterine period. Urachal adenocarcinoma is a rare tumor and more aggressive in behavior than primary bladder tumors. In this case report, we present a 37 years old female patient with urachal adenocarcinoma in whom transurethral resection of the bladder revealed a signet ring adenocarcinoma of the bladder with invasion of the muscularis propria. The patient had left manubrium sterni and bone marrow infiltration. Partial cystectomy and sternal resection were performed, followed by radiotherapy and chemotherapy. There was no recurrence or new metastasis at the 4-year follow-up. In conclusion, a combination of surgery, chemotherapy, and radiotherapy is a suitable approach for the treatment of oligo-metastatic urachal carcinoma.
Keywords: Urachal carcinoma, adenocarcinoma, bladder tumor

Introduction

The urachus is an embryological remnant that lies between the bladder and umbilicus as a fibrous band, which attaches the cloaca to the allantois in the intrauterine period (1). Urachal adenocarcinoma is a rare tumor that accounts for 0.07-0.34% of all bladder tumors and has mucinous, enteric, signet ring cell, mixed, and unclassifiable histopathological types (2). The most common presenting symptom of urachal carcinoma is hematuria, and it rarely presents with irritative voiding symptoms, suprapubic mass, or pain. These tumors are mostly located within the muscular layer of the bladder dome but can lead to ulceration when reaching the mucosal layer and can invade through the Retzius space or anterior abdominal wall. On average, 11-13% of patients are reported as metastatic at disease presentation (3). Urachal adenocarcinomas are more aggressive in behavior compared with primary bladder adenocarcinomas, and the 5-year survival rate is 11-55% (4). Urachal carcinomas are rare but aggressive tumors with an incidence of approximately 1 case per million per year (3). Because of its rarity, treatment modalities and prognosis of urachal neoplasm are not well known, and prospective trials limited to this disease are lacking. Treatment is different for localized or metastatic disease. In this case report, we discuss the diagnosis, treatment, and follow-up of a patient with metastatic urachal adenocarcinoma in light of the current literature.

Case Report

Informed consent was obtained from the patient for the publication of the case presentation. In 2017, a 37-year-old female patient presented with irritative voiding symptoms, hematuria, and white particles in urine. The patient did not have any systemic disorders or a history of smoking or surgery other than cesarean section. Hemogram, routine blood biochemistry, and urinalysis were within normal limits. Ultrasonography revealed a 5 cm solid, vascular mass protruding into the bladder lumen from the bladder dome. Cystoscopy revealed an atypical mass lesion located at the bladder dome, back wall, and the base of the bladder, which had leukoplakia and edematous appearance. Transurethral resection of the bladder was performed concomitantly and macroscopically, and it appeared that the muscular layer was involved. Histopathological examination revealed a signet ring adenocarcinoma of the bladder with the invasion of the muscularis propria. The primary bladder, colon, or urachus origin could not be

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determined. CK20, CK7, CDX2, CD15, and beta-catenin were positive and carcinoembryonic antigen (CEA) was negative in immunohistochemistry. Thoracic computed tomography (CT) was normal. Abdominal CT revealed thickening and irregularity of the bladder fundus where the peritoneum was attached and mild wall thickening and omental contamination on the antrum of the stomach, which was suspicious for a primary stomach tumor. There was a residual mass in the bladder and lytic lesion in the left manubrium sterni on positron emission tomography (PET), but no uptake in the lymph nodes. An exophytic tumoral mass on the anterosuperior portion of the bladder, which was 5 cm in diameter and had a cystic component in its anterior part, was observed by magnetic resonance imaging (MRI) (Figure 1). Thoracic MRI revealed bone marrow infiltration suspicious for metastasis on the left manubrium sterni. Upper gastrointestinal endoscopy and colonoscopy were normal. A biopsy of the sternal lesion showed adenocarcinoma metastasis. A partial cystectomy was performed on July 2017. The mass extending from the urachal region to the bladder dome was resected with a 5 mm safety margin. Frozen biopsies were performed from all suspicious regions. Final pathology revealed signet ring mucinous adenocarcinoma of urachal origin with intact surgical margins (Figure 2). Stereotactic external beam radiotherapy was administered in 2 fractions 10 Gy on August 2017. FOLFOX (folinic acid + 5-fluorouracil + oxaliplatin) chemotherapy was administered for 9 cycles. After the completion of these therapies, sternal resection and thoracic reconstruction were performed. Sternal pathology revealed acellular mucinous islands. The patient was followed up with thoracic and abdominal MRI every 3 months without decreasing frequency. There was no recurrence or new metastasis at the 4-year follow-up (Figure 3).

Discussion

Urachus is an embryological remnant that lies between the fetal urinary bladder and allantois, and urachal tumors mostly spread to the bladder dome, umbilicus, and Retzius space (5). Urachal tumors are rare and mostly seen in the 5th and 6th decades showing male predominance (1). Most urachal tumors are adenocarcinomas. Rarely, sarcomas, squamous cell cancer, and urothelial carcinomas can be observed (6).

The diagnosis of urachal carcinoma is made by cystoscopic observation of the tumoral lesion located in the bladder dome and a resection revealing adenocarcinoma. CT and MRI are important for supporting the diagnosis and local staging of the tumor (1). A solid or cystic mass lesion that shows small calcifications and is located in the bladder midline is pathognomonic for urachal tumors (6). PET-CT can be used to detect distant metastases (7). Most commonly, regional lymph nodes, omentum, liver, lung, and bone metastases are observed (8). In line with the literature, we managed to diagnose the midline solid lesion in the bladder both radiographically and cystoscopically and confirmed the diagnosis by histopathological examination. The distant metastasis evaluation was performed by PET-CT and verified by MRI. Most urachal adenocarcinomas are positive for CDX2, CK20, and to a lesser extent CK7 and beta-catenin (9). CEA, CA-125, and CA-19.9 are used for the diagnosis and follow-up

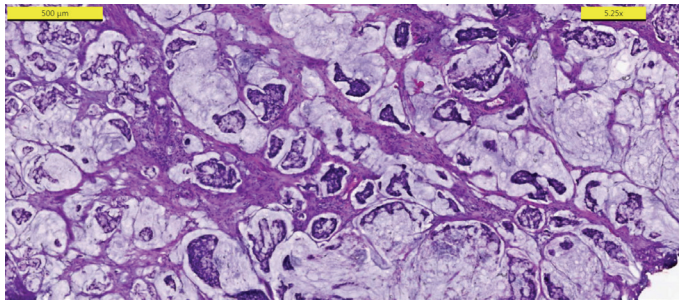

Figure 2. Microscopic appearance of urachal adenocarcinoma from a partial cystectomy specimen

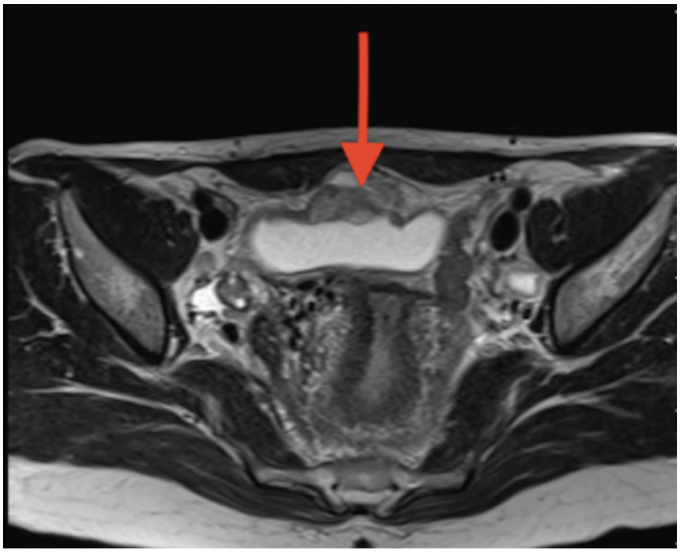

Figure 1. MRI showing a 5x6 cm diameter mass, which originates from the anterosuperior part of the bladder

MRI: Magnetic resonance imaging

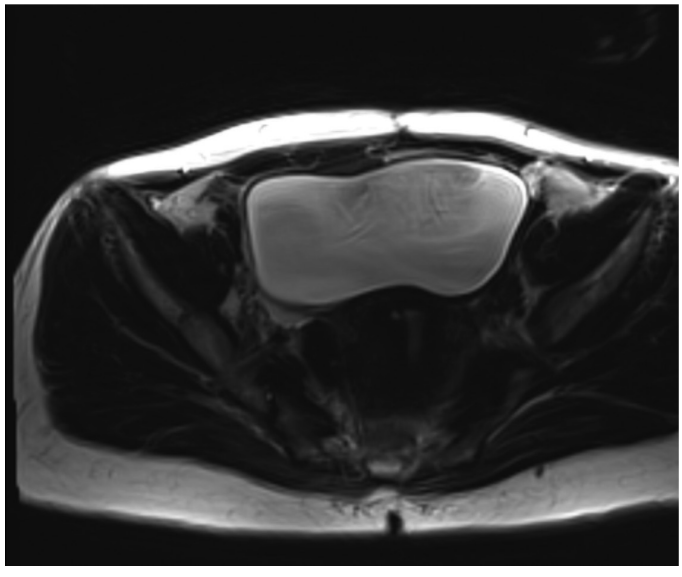

Figure 3. MRI shows that the bladder is intact after 4 year follow-up after combination treatment

MRI: Magnetic resonance imaging

of peritoneal carcinomatosis (10). CK20, CK7, CDX2, CD15, and beta-catenin were positive and CEA was negative in our patient. If necessary, colonoscopy, upper gastrointestinal tract endoscopy, mammography, or coloposcopy are recommended for primary tumor investigation (1,6). In our patient, upper gastrointestinal tract endoscopy and colonoscopy was negative for a tumoral lesion.

Stage is the most important indicator of prognosis in urachal carcinomas (11). Tumor-node-metastasis staging criteria for urothelial carcinoma of the bladder are irrelevant for urachal carcinoma because urachal carcinoma may primarily arise from outside of the bladder, secondarily grow into the bladder, and in some cases invade through the bladder (1). The Sheldon staging system is used for staging urachal carcinoma (Table 1) (6).

A suspicious lesion for metastasis was detected by PET-CT in our patient, and MRI and sternal biopsy verified the metastasis. Because of the presence of distant metastasis, our patient was classified as stage IVB according to the Sheldon staging system.

Treatment of localized urachal adenocarcinoma includes partial or radical cystectomy with urachal and umbilical resection and bilateral pelvic lymphadenectomy (12). In lymph-node-positive patients, lymphadenectomy is recommended after chemotherapy and lymph node regression (1). For stages III and IV, chemotherapy is the standard recommendation; however, for oligo-metastatic disease, local resection and metastasectomy can be performed (10). Treatment outcomes differ between different chemotherapy protocols, and there is no standard chemotherapy protocol for urachal carcinoma (1). It has been shown that the FOLFOX protocol, which shows a partial and complete response in metastatic disease, is suitable for urachal adenocarcinoma (13). Metastasectomy is recommended after chemotherapy with regression of metastatic lesions (1). Literature on the efficiency of radiotherapy in urachal carcinoma is limited, and its effects on the disease are not yet well known (10). Radiotherapy for metastatic lesions may prolong survival (14). In our patient, frozen section examination showed intact surgical margins during partial cystectomy; therefore, umbilicus resection was omitted. After radiotherapy to the sternal metastasis, FOLFOX was administered and metastasectomy was performed.

Urachal carcinoma is a rare and aggressive malignancy, and there is limited evidence for its diagnosis and treatment protocols. Stage and surgical margin status are important for local recurrence and survival after partial cystectomy (14). For metastatic urachan carcinoma, the 5-year survival rate is less than 50% (6). Chemotherapy and surgical interventions treat the disease with variable success rates, and with chemotherapy 1-year-survival is increased statistically significantly (15). After treatment, we followed up our patient with a 3-month interval thoracic and abdominal MRI, and with a 4-year follow-up, there was no local or distant recurrence. In conclusion, a combination of surgery, chemotherapy, and radiotherapy is a suitable approach for the treatment of oligo-metastatic urachal carcinoma.

Table 1. Sheldon staging system for urachal carcinoma

Stage I: Limited to urachal mucosa
Stage II: Limited to urachus
Stage III: Local dissemination
IIIA: To bladder
IIIB: To anterior abdominal wall
IIIC: To peritoneum
IIID: To viscera other than bladder
Stage IV: Metastatic disease
IVA: Regional lymph node
IVB: Distant metastasis

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Ethics

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Authorship Contributions

Surgical and Medical Practices: M.T.E., Concept: O.K., Design: M.T.E., Data Collection or Processing: B.H., Analysis or Interpretation: B.H., Literature Search: M.V.K., Writing: M.V.K.

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Case Report

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Laparoscopic Partial Nephrectomy for Multiple Masses in Situs Inversus Totalis

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Abstract

We report the case of a patient who was admitted to the emergency department of our hospital with acute left upper quadrant abdominal pain. Computed tomography revealed perforated cholecystitis and two synchronous incidental solid mass lesions in the right kidney. The patient had situs inversus totalis anomaly. The patient was evaluated by a multidisciplinary board, and simultaneous laparoscopic cholecystectomy and laparoscopic partial nephrectomy (LPN) were planned 3 months after cholecystostomy and antibiotic therapy. After uneventful laparoscopic cholecystectomy, synchronous renal masses were successfully treated with LPN. To the best of our knowledge, this is the first case report in the literature concomitant two synchronous renal masses with situs inversus totalis, which were treated with LPN.

Keywords: Laparoscopy, partial nephrectomy, situs inversus totalis

Introduction

Situs inversus totalis (SIT) is a rare anomaly in which intra-abdominal organs are transposed. Although there is no evidence of an increased risk of malignancy in patients with SIT, renal anomalies, including agenesis, dysplasia, hypoplasia, ectopia, polycystic kidney, and horseshoe kidney, have been reported (1).

Recent European Urology Association guidelines recommend partial nephrectomy as a standard of care for cT1 kidney tumors if it is technically feasible (2). In this case, we shared our experience with laparoscopic partial nephrectomy (LPN) in a patient with SIT and cT1 kidney tumors. To the best of our knowledge, this is the first case report in the literature concomitant two synchronous renal masses with SIT, which were treated with LPN.

Case Report

A 62-year-old male was admitted to the emergency department of Ondokuz Mayıs University Hospital with acute left upper quadrant abdominal pain. Computed tomography revealed perforated cholecystitis and two synchronous incidental solid mass lesions in the right kidney, 19x16 mm in the middle zone lateral (RENAL score: 5) and 16x15 mm in the lower middle zone junction anteromedially (RENAL score: 8), and the heart and all intra-abdominal organs in the image area were displaced right-left (Figure 1).

The patient was evaluated by a multidisciplinary board, and simultaneous laparoscopic cholecystectomy and LPN were planned 3 months after the cholecystostomy. An informed consent form for the planned treatment was obtained from the patient. Laparoscopic cholecystectomy performed in the right 30-degree lateral and reverse trendelenburg position. After uneventful laparoscopic cholecystectomy, the patient was placed in a left 60 degree lateral position. Pneumoperitoneum was created using a Veress needle from Palmer's point, and after a 12 mm optical port, two 5 mm and one 12 mm working ports were placed. After medialization of the descending colon, the ureter was isolated and reached the hilum under the guidance of the ureter. There was one renal artery and vein. The masses were found under the guidance of laparoscopic ultrasonography, and the margins were marked with monopolar hook cautery. The localized mass in the hilar was excised off-clamp with cold scissors, and the defect was repaired with 3/0 poliglecaprone and 37 mm 2/0 braided polyglactin sutures. Then, the mass in

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the upper-middle pole lateral was removed off-clamp; however, because of the bleeding, the renal artery and vein were clamped with the help of bulldog clamps (Figure 2). Partial nephrectomy was performed by removing the mass using cold scissors. The defect was repaired with 3/0 poliglecaprone and 37 mm 2/0 braided polyglactin sutures (Figure 3). Bulldog clamps were removed. The warm ischemia time for the second mass was 7 min. Pathological examination revealed papillary and clear cell renal cell carcinoma for middle zone lateral and hilar masses, respectively. Both tumors were pT1a, WHO/ISUP grade 2, with negative surgical margins. The follow-up creatinine level was 0.88 mg/dL in the postoperative first month.

Discussion

In this case, a 62-year-old patient with SIT and synchronous renal masses was successfully treated with LPN. In the literature, only 13 case reports of concomitant SIT with renal mass have been reported, except our case. For the first time, Bertini and Boileau (3) reported open radical nephrectomy in a 54-year-old female patient in 1987. Open radical nephrectomy was performed in seven patients; laparoscopic radical nephrectomy in two patients; open partial nephrectomy in two patients; and robot-assisted LPN in one patient (4,5).

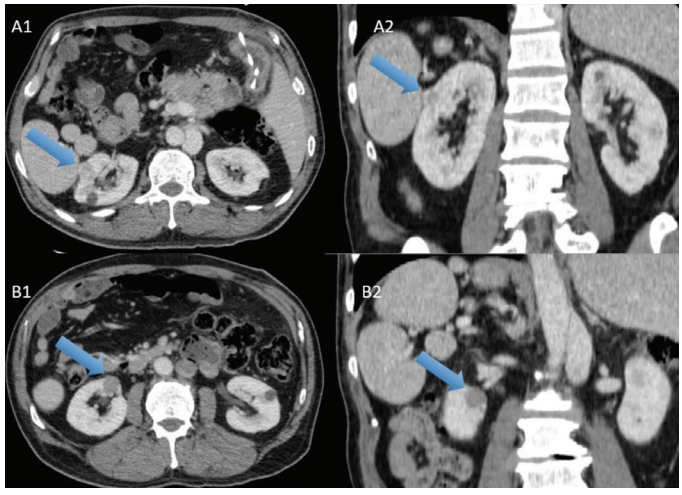

Figure 1. Patients computed tomography images. The masses are indicated by arrows

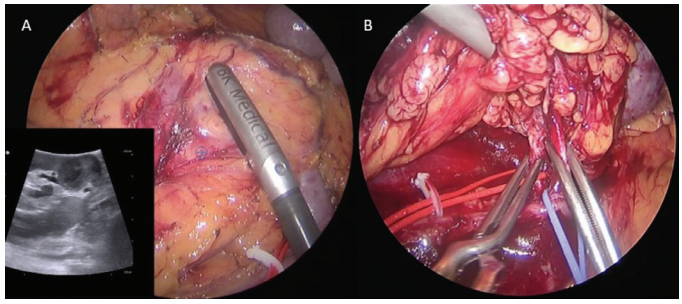

Figure 2. A) Intraoperative and laparoscopic ultrasound [4-Way Laparoscopic 8666-RF, BK Medical (Massachusetts)] image of the mass. **B)** Clamping of the renal artery and vein with the help of bulldog clamps (The mass in the hilar localized was excised off-clamp)

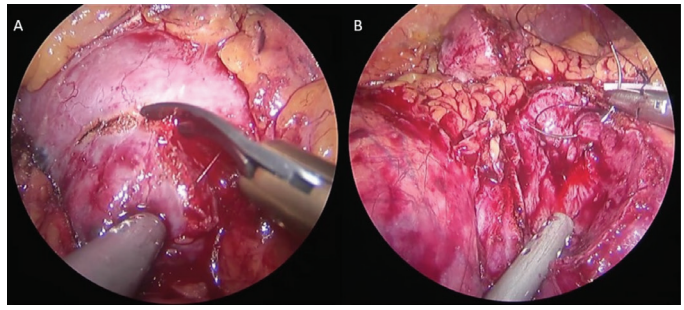

Figure 3. A) Resection of the mass with cold scissors, **B)** Reapering of the defect with 3/0 poliglecaprone and 37 mm 2/0 braided polyglactin sutures

Although LPN in patients with SIT proceeds with the same steps as in patients with normal anatomy, it may cause difficulty in orientation for the surgeon due to the transposition of the intra-abdominal organs. Technical difficulties and longer operative times have been reported in most cases of laparoscopic surgeries in patients with SIT because of disorientation caused by the reversed abdominal organs and the need to modify the surgeon's movements and techniques. Makiyama et al. (6) described the first case of laparoscopic nephroureterectomy in a patient with SIT, developed a laparoscopic simulator suitable for anatomy for preoperative training, and reported that preoperative training was useful.

Careful planning and execution of surgery are essential to minimize the risk of complications and ensure the best possible outcome for the patient. Computed tomography angiography is an imaging technique that allows for a detailed examination of blood vessels and their relationships to surrounding structures. With this information, the surgical team can identify the optimal approach to the affected kidney and plan the precise location and extent of the surgery. In cases where serious anatomical variations, such as SIT, may be present, computed tomography angiography imaging is a reliable method for anatomical detail and planning before partial nephrectomy in terms of oncological and functional outcomes.

With the increasing popularity of minimally invasive surgical procedures among surgeons, laparoscopic approaches for the treatment of renal mass are becoming more common. In patients with SIT, LPN follows the same procedures as normal anatomy and can be safely performed in experienced centers in terms of functional and oncological outcomes.

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Case Report

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Rare Case; Primary Epididymal Adenocarcinoma

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Abstract

Paratesticular masses constitute 2-3% of the scrotal masses. Epididymal masses constitute only 5% of prescrotal masses, and the most common type of tumor is adenotoid tumor, which is benign. Malignancies of the epididymis are rare. Epididymal adenocarcinoma is much less common. It can be primer and metastatic, and there are fewer than 40 cases in the literature in both groups. Primary epididymal adenocarcinoma is extremely rare, with only 23 cases reported. The disease diagnostic process, findings, and treatment are still unknown. In this article, we aimed to present a case of epidimal adenocarcinoma with primary origin from the epididymis.

Keywords: Epididymal adenocarcinoma, paratesticular masses, epididymal cancer

Introduction

As the paratesticular region contains various structures, including the epididymis, spermatic cord, tunica vaginalis, and strong fat-ligament-muscle supporting tissues, it may give rise to a number of tumor types with various behaviors. Paratesticular masses constitute 2-3% of the scrotal masses (1). 30% of paratesticular neoplasms are malignant. Sarcomas are the most common type of tumor and generally originate from the spermatic cord (2). Epididymal masses constitute only 5% of prescrotal masses, and the most common type of tumor is adenotoid tumor, which is benign. Malignancies of the epididymis are rare. Epididymal adenocarcinoma is much less common. It can be primer and metastatic, and there are fewer than 40 cases in the literature in both groups. Primary epididymal adenocarcinoma is extremely rare, with only 23 cases reported (2,3). In this article, we presented a case of epidimal adenocarcinoma with primary origin from the epididymis.

Case Report

Consent has been obtained from the patient that the disease and treatments related to the disease will be shared as scientific publications. A 63 year-old farmer presented with a 1 year history of right inguinal area and scrotal pain. It was found that he had no comorbidities, and he underwent surgery for right inguinal hernia. The physical examination revealed a right scrotal mass that made it impossible to differentiate between the epididymis and testicle. Scrotal Doppler ultrasonography showed a hypervascular right scrotal mass that filled the entire testicle and right hydrocele. Also, a 13 mm inguinal lymph node was observed. The patient's beta-HCG, alpha-fetoprotein (AFP), and lactate dehydrogenase levels were found to be 0.33 mL/U, 5.09 ng/mL, 189 U/L respectively at normal intervals. There was no evidence to suggest infection at laboratory values and physical examination. Thoracic computed tomography (CT) and abdominal CT imaging with testicular tumor preliminary diagnosis did not reveal any lesion that could be considered as metastasis. Right radical orchiectomy was performed in the patient with a preliminary diagnosis of testicular cancer. Pathology specimens evaluated from 2 different centers. The pathology result was spotted epidiymal adenocarcinoma. Immunohistochemically, EMA + CKPAN +, CK7 +, Pax8 +, CD10 +, WT1 +, ER+, calretinin +, p53 +, Ki67+ and CEA - prostate specific antigen (PSA) -, PLAP -, AFP -, bHCG -, inhibin -, CD30 - was spotted (Figure 1). The tumor consisted of solid and papillary areas. It was found to be low grade in the papillary and adenoid areas and high grade in the solid areas (Figure 2). The tumor was limited to the testis and epididymis. The spermatic cord was reported to be not invaded. The lymph node removed from the inguinal region was detected as reactive. The patient's preoperative thorax and abdominal CT images showed no

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evidence of any other adenocancer focus or metastasis that could be the primary source. It was found to be PSA - tapped and excluded the possibility of epidimal metastases of prostate adenocarcinoma. The patient was then referred to clinical oncology. In the 6th postoperative month, positron emission tomography-CT images showed metastases in the retroperitoneal lymph nodes and lung. Six cycles of carboplatin and paclitaxel chemotherapy were administered to the patient. With this treatment, disease remission was achieved.

Discussion

Epididymal adenocarcinoma is a rare condition. It can be primer and metastatic, and there are fewer than 40 cases in the literature in both groups. Primary epididymal adenocarcinoma is extremely rare, with only 23 cases reported (2,3,4). In these cases, patient ages ranged from 27 to 81 years (4). In a review 12 of the 21 reported cases of epididymal adenocarcinoma, the patient's age was greater than 50 (3). In this case, our patient was 63 years old.

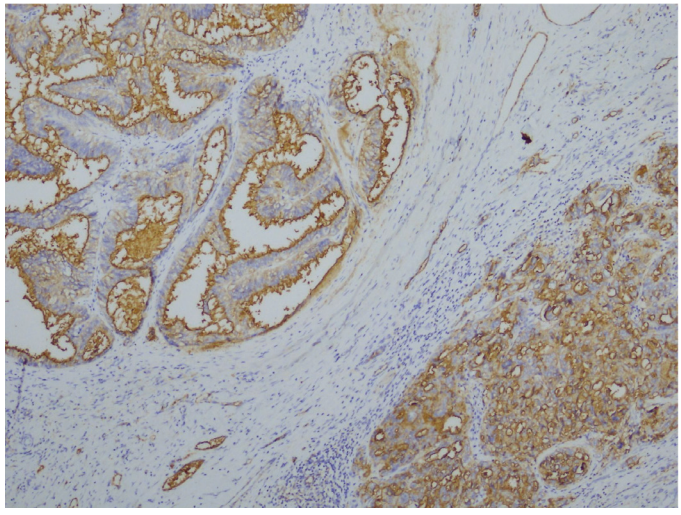

Figure 1. Immunohistochemically EMA + stained epidymal adenocarcinoma cells

EMA: Epithelial membrane antigen

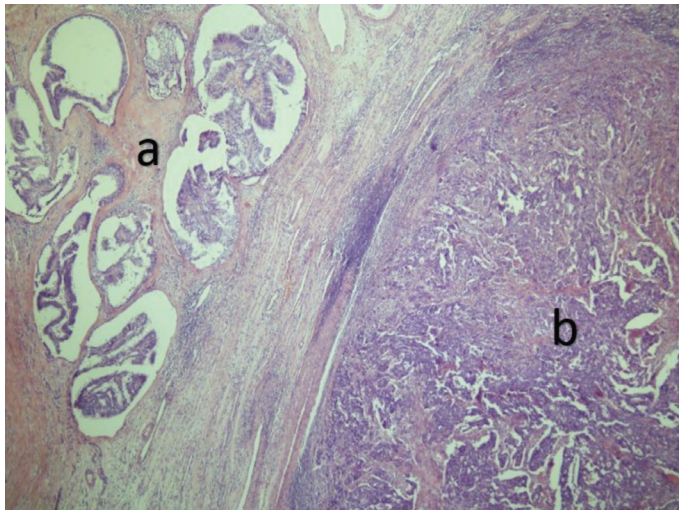

Figure 2. Epididymal adenocarcinoma cells consisting of papillary (a) and solid (b) areas

According to a review, scrotal swelling and palpable mass are the most common findings. Almost one-third of patients complain of scrotal pain (4). In some cases, the disease is accompanied by hydrocele (5). In the latest review 38.5% of patients have hydrocele (4).

Histologically, the tumor can contain papillary, tubular and solid areas. Immunohistochemically, epithelial tumor markers, such as cytokeratin and epithelial membrane antigen (EMA), are positive (3,4,5). Epididymal adenocarcinoma can be metastatic from other organ adenocarcinomas such as prostate, gastrointestinal system, and renal cell carcinoma. To differentiate the lesions from other organ adenocarcinomas, immunohistochemical markers must be used. To exclude prostate adenocarcinoma PSA staining and exclude renal cell cystadenocarcinoma metastasis CD10, CK7 staining must be performed. If epididymal adenocarcinoma PSA staining is found to be negative and CK7 and CD10 must be found positive. Also, PLAP, AFP, and bHCG must be found negative (4,6).

In this case, histologically, the tumor consisted of solid and papillary areas. It was found to be low grade in the papillary and adenoid areas and high grade in the solid areas. Immunohistochemically, EMA (+), CD10 (+), CK7 (+), PSA (-), PLAP (-), AFP (-) and bHCG were also found to be negative. In the literature, most of the cases were calretinin negative (4). However, in this case, calretinin was found positive.

Epididymal lymph node drainage occurs in the pelvic and retroperitoneal lymph nodes. Therefore, the inguinal lymph node dissection is unnecessary. In this case, inguinal lymph node dissection pathology was found benign (4).

Adjuvant treatment is uncertain because of the lack of literature. The prognostic factors of the disease are also uncertain. However, metastasis is the most common cause of death after surgery. It has been reported in bone, liver, spleen, lung, pelvic, and retroperitoneal lymph node metastases. The effects of radiotherapy and chemotherapy are unclear. Platinum-based chemotherapy was the first choice treatment of reported cases with advanced disease, and a positive effect on disease progression was observed (4). In this case, after lung and bone metastasis, 6 cycles of carboplatin and paclitaxel chemotherapy were administered to the patient. With this treatment, disease remission was achieved. The patient is followed up every 3 months. Oncological outcomes are not yet predictable.

Conclusion

Epididymal adenocarcinoma is a very rare malignancy. There are not enough data of diagnosis, differential diagnosis, pathological findings, treatment, and prognosis of the disease. the disease progresses aggressively and becomes metastatic in the early period, but there are not enough data in the literature related to its treatment. The effects of chemotherapy and radiotherapy are uncertain. In some cases, chemotherapy and radiotherapy are not responding, but in this case, the patient was fully cured with chemotherapy. As the number of reported cases increases, our knowledge of the disease will increase.

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Authorship Contributions

Surgical and Medical Practices: A.E., E.Ş., Concept: M.M., Design: E.Ş., F.T., Data Collection or Processing: A.E., Literature Search: A.E., F.T., Writing: M.M., E.Ş.

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Case Report

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Painful Testicular Metastasis of Prostate Cancer; A Case Report

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Abstract

Prostate cancer (PC) ranks as the most prevalent cancer among males and is the second primary contributor to mortality within this demographics. Diagnosed patients can undergo various treatments, from radiation to chemotherapy and surgery. While bone typically serves as the initial site for metastasis, it is crucial to consider uncommon metastatic locations, such as the testicles. In this article, we present the case of a 73-year-old male patient with multiple bone metastases who presented with left testicular pain and swelling and was eventually diagnosed with PC with testicular metastases.
Keywords: Testis, metastasis, orchiectomy, prostate cancer

Introduction

Hormone resistant prostate cancer (PC) has a high incidence of metastases, especially to solid organs such as the lungs, bones, and liver. Other organ metastases are less common. The testicles are important in the development and treatment of PCa. Metastatic disease of the testicles is rare in PCa, with an incidence rate of 0.3% to 3.6% (1). Therefore, it is often not considered a possible clinical metastasis localization.

The aim of this case report was to describe the testis as a rare metastasis localization in castration-resistant prostate cancer (CRPC) with bone metastases and to emphasize that bilateral orchiectomy is the basic step in hormonal therapy management from a different perspective.

Case Report

A 73-year-old male patient was admitted to the emergency medicine unit with complaints of lower urinary tract symptoms and colic-like pain in the left testicular region. The patient consulted the urology clinic. His past medical history was significant for hypertension, hyperlipidemia, coronary heart disease and insulin-dependent mellitus. In his social history, there was no smoking history, alcohol use, and there was no relevant family history of PCa. In the patient's history, it was determined that he had previously received radiation therapy and androgen deprivation therapy in the medical oncology clinic with the diagnosis of Gleason score 4+5 (International Society of Urological Pathology grade 5) prostate adenocarcinoma, and it was determined that the patient used abiraterone acetate, prednisolone, and luteinizing hormone-releasing hormone (LHRH) analog because of the detection of hormonal resistance in the subsequent treatment. He received weekly docetaxel systemic therapy because of the progression of radiological findings and prostate specific antigen (PSA) values under this treatment. The patient's tumor markers (alpha fetoprotein, beta human chorionic gonadotropin), urinalysis, white blood cell count, and C-reactive protein levels were within normal limits, and the PSA level was 134 ng/mL. Before orchiectomy, testosterone levels was 16 ng/mL castrated. A giant solid lesion completely filling the left testicular parenchyma was observed in scrotal Doppler ultrasonography. We performed bilateral orchiectomy, explaining that LHRH could not be continued when bilateral orchiectomy

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was performed. The situation was discussed with the patient, and the patient's decision was to discontinue LHRH therapy and perform bilateral orchiectomy. The operation time was 55 min. There were no complications during the intraoperative and postoperative periods. The hospitalization period was a day. Blood values measured in the postoperative period were within normal limits. The pathological examination under a microscope with hematoxylin/eosin and immunohistochemical staining was consistent with metastatic adenocarcinoma of prostate origin (Figure 1). Normal pathological findings were observed in the right testis. Microsatellite instability (MSI) was positive, and the patient's treatment was continued with pembrolizumab. Written valid informed consent has been obtained from the patient for the publication of this manuscript.

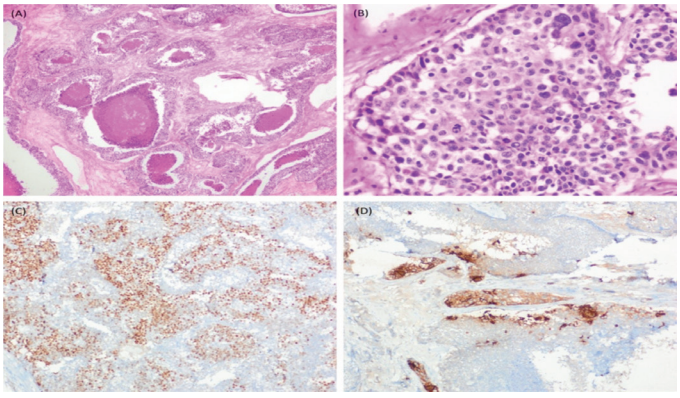

Figure 1. Prostatic adenocarcinoma metastasis in testicular parenchyma, A) Tumor metastasis in the form of solid tumor islands with necrosis in a comedo pattern, which almost completely removes the testicular parenchyma, H&EX40. B) Frequent mitosis and cytological similarity in neoplastic cells, H&EX400. C) Diffuse nuclear NKX3.1 positivity observed in neoplastic cells in immunohistochemical staining, X100. D) Immunohistochemical staining, cytoplasmic chromogranin positivity (brown staining) observed in some of the neoplastic cells, X100

Discussion

Although the testicles have an important place during the clinical course of PCa, especially due to hormone production, they are rarely seen in the areas of metastasis development. In a retrospective evaluation of 1693 orchiectomy cases, 0.18% testicular metastasis was detected (2). Testicular metastasis of PCa is mostly seen in the literature as case reports (3,4,5,6).

The precise consequences of testicular metastases remain uncertain and established recommendations for treatment are lacking. Based on influential research, therapeutic approaches for advanced prostate cancer that has spread to visceral sites (excluding the testicles) involve options such as docetaxel chemotherapy (contingent upon a favorable performance status) or hormonal interventions such as abiraterone or enzalutamide (7). In our patient, prostate cancer had already disseminated extensively at the time of diagnosis, characterized by a Gleason score of 9 and a PSA level of 134 ng/mL. The patient was treated with pembrolizumab after being diagnosed with testicular metastasis.

In terms of morphology, testicular metastases typically resemble primary prostate tumors. Consequently, they can manifest in glandular, cribriform, and cemedo patterns or as individual cells that infiltrate the interstitial space while safeguarding the seminiferous tubules, as observed in our specific case (8).

The US Food and Drug Administration has approved the use of pembrolizumab in addressing metastatic or unresectable solid tumors exhibiting MSI-high or mismatch repair deficiency (9). Manogue et al. (10) documented a solitary instance of complete remission through pembrolizumab treatment in a patient with metastatic CRPC (mCRPC) carrying an *MSH2* alteration identified via tissue sampling. This case also highlighted the potential usefulness of circulating tumor DNA in gaging mutational burden. Among patients undergoing successive tumor evaluations to assess MSI, three out of five individuals displayed MSI acquisition in a second or subsequent sample (10). Pembrolizumab monotherapy has exhibited anticancer activity with a tolerable safety profile among a subgroup of patients whose mCRPC is predominantly situated in bone and who had previously undergone treatment with docetaxel and targeted endocrine therapy (11).

Conclusion

For treating PCa, rare metastatic sites such as testis and epididymis should be appropriately evaluated for accurate staging and early detection of possible metastases. In cases with suspected testicular metastasis, physical examination or imaging, even orchiectomy in newly diagnosed or castration-resistant patients, should be the basic strategy in terms of both treatment and diagnosis regardless of the hormone level.

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