E-ISSN 2667-4610

bulletin of UROONCOLOGY

galenos yayinevi

UROONCOLOGY ASSOCIATION - 1999

December
2023
Volume
22(4)

The Official Journal of Urooncology Association of Turkey

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Publisher Certificate Number: 14521

Online Publication Date: December 2023
E-ISSN: 2667-4610
International scientific journal published quarterly.

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

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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).

-Statistical Evaluation:

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.

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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.

E. Acknowledgements Form

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

2) Title Page

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)

5) Figure(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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G. Surgery Videos (Video-urooncology)

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Publisher

Galenos Publishing House

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Contents

bulletin of
UROONCOLOGY

BEST REVIEWER of ISSUE

Cemil Aydın

Review

DOI: 10.4274/uob.galenos.2023.2023.8.2

Bull Urooncol 2023;22(4):129-137

PSMA Targeted Ligands in Imaging and Theranostics for Prostate Cancer

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Abstract

Prostate cancer (PCa) is the second most common type of cancer in men. Compared with conventional imaging methods, prostate-specific membrane antigen (PSMA)-targeted positron emission tomography has higher accuracy and specificity for the detection and treatment of PCa. Through targeted imaging, ligands are labelled with ^{18}F, ^{68}Ga, or ^{64}Cu, and the disease is staged and managed more accurately. It is also desirable to use PSMA-targeted theranostics that are labelled with either imaging radioisotopes or treatment isotopes such as ^{177}Lu, ^{225}Ac, ^{131}I. Here, we summarized some of the commonly used small molecule PSMA ligands for imaging and theranostic purposes.

Keywords: PET imaging, prostate cancer, theranostics

Introduction

Prostate cancer (PCa) is the second most prevalent type of cancer and the fifth cause of cancer-related mortality in men (1). Conventional imaging (CI) methods, such as computed tomography (CT) and magnetic resonance imaging (MRI), have severe limitations, especially in detecting lymph nodes (LN), misleading the staging and management of the disease (2,3,4,5). Compared with CI, prostate-specific membrane antigen (PSMA)-positron emission tomography (PET) has a higher accuracy and plays an important role, especially for preliminary staging (6) and biochemical recurrence (BCR) of PCa (7,8).

PSMA is a type II transmembrane glutamate carboxypeptidase found in the prostate secretory-acinar epithelium (9,10,11,12). The amount of PSMA expression increases with increasing tumor dedifferentiation and in metastatic and hormone-refractory disease, and it is considerably overexpressed in PCa cells compared with its normal expression in prostate cells (13,14). This cell surface protein is highly expressed (nearly a thousand times more than in normal prostat tissues) in most PCa cells (15), and PSMA expression is a key predictor of disease prognosis (16). Because of these factors, PSMA targeting for imaging and therapy (I&T) of PCa has been considered a promising option in recent years.

PSMA inhibitors are divided into three groups: urea-based, phosphorus-based, and thiol-based. PSMA PET radiolabelled compound development focuses on small urea-based PSMA ligands that target the extracellular part of PSMA and recognize regions of high binding affinity to PCa cells, leading to rapid plasma clearance and high tumor background levels (17). In this review, we will discuss the well-known small-molecule PSMA-targeted ligands in two parts (Figure 1); diagnostics (tracers that can be labelled nuclides, such as ^{68}Ga or ^{18}F, Figure 2) and theranostics (tracers that can be labelled with both imaging and therapeutic nuclides, such as ^{177}Lu or ^{225}Ac; Figure 3). This review is not entirely comprehensive as not mentioning antibodies, conjugation therapies and immunotherapies.

PSMA Ligands for PET Imaging

Imaging has two main functions in the early determination of PCa. First, it identifies the disease in patients who are confirmed by biopsy and have a high possibility of metastasis. Second, it determines the primary tumor site in cases with a negative biopsy but a high probability of PCa. Proper staging has an important impact on guiding additional local or systemic treatment options, such as radical prostatectomy, radiation therapy, or palliative care, as well as dissection of pelvic LN during surgery or planning for radiotherapy. Before the start of

Cite this article as: Şen B, Özkan E, Küçük NÖ. PSMA Targeted Ligands in Imaging and Theranostics for Prostate Cancer. Bull Urooncol 2023;22(4):129-137.

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Received: 07.08.2023 **Accepted:** 23.09.2023

the treatment plan, PSMA imaging is also used in patients with BCR or metastatic castration-resistant PCa for the determination of disease management.

^{68}Ga-PSMA-11

^{68}Ga-HBED-CC (PSMA-HBED or HBED) was first synthesized by Eder et al. (18) in 2012. HBED-CC was added as a radiometal chelator to the PSMA inhibitor motif Glu-urea-Lys to improve the interactions of the pharmacophore with the hydrophobic pocket of the PSMA S1 binding site (the structure is shown in Figure 2). HBED-CC is a highly efficient and stable radiometal chelator that enables quick radiolabelling at room temperature and exhibits exceptionally high complex stability, much like the DOTA chelator, which is commonly used in clinical settings. Different temperature during the radiolabelling reaction can be controlled to promote the formation of a diastereomer that is more thermodynamically stable. Nonetheless, because HBED-CC is highly selective for ^{68}Ga, the radiopharmaceutical cannot be used for labeling with therapeutic radionuclides such as ^{177}Lu or ^{90}Y. This drug is also quickly eliminated from non-target tissue. Physiological absorption is strong in the salivary and lacrimal glands. There is moderate uptake in the intestine, liver, spleen, and ganglia, e.g., cervical and celiac ganglia, and negligible uptake in normal prostate cells (19). When compared with traditional imaging, PSMA PET/CT has a much reduced radiation dose (8.4 mSv vs. 19.2 mSv, respectively) (20). For all these reasons, nearly 10 years after its discovery, in 2020 ^{68}Ga-PSMA-11

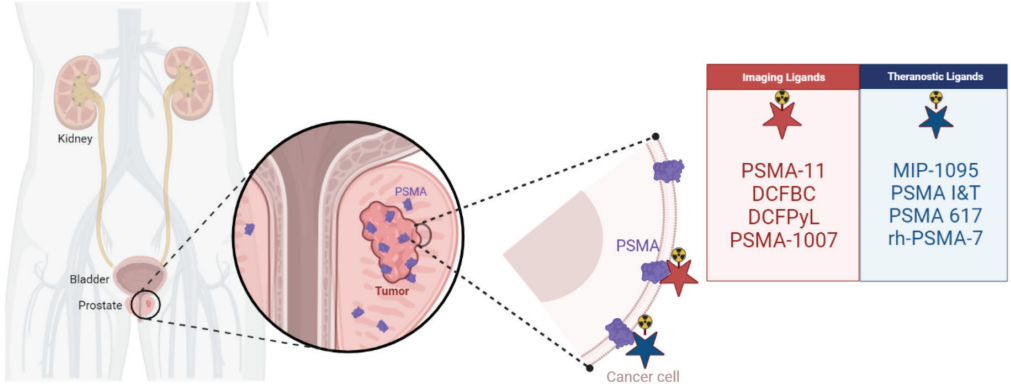

Figure 1. PSMA-targeted imaging and theranostic ligands
PSMA: Prostate-specific membrane antigen

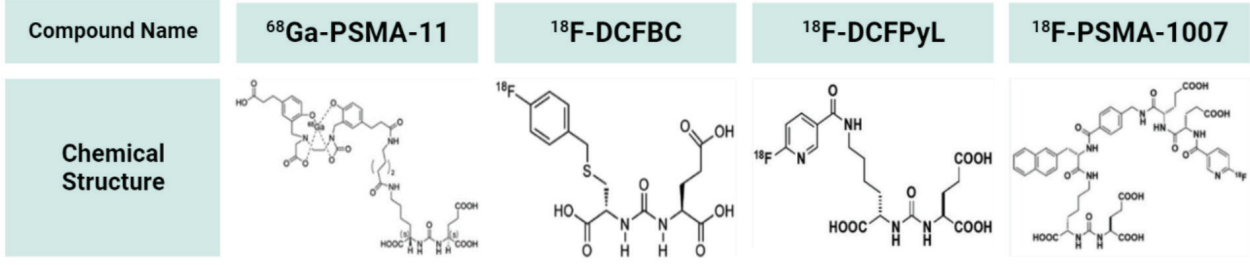

Figure 2. PSMA-targeted small-molecule PET agents and their structures
PSMA: Prostate-specific membrane antigen, PET: Positron emission tomography

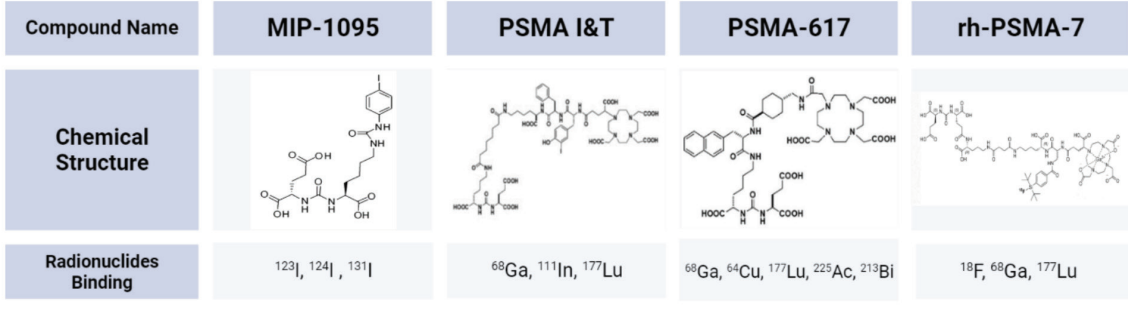

Figure 3. PSMA-targeted small molecule theranostics and their structures
PSMA: Prostate-specific membrane antigen

was approved as the first ^{68}Ga-labelled radiopharmaceutical for imaging of PCa.

In one of the earliest studies, Afshar-Oromieh et al. (20) examined ^{68}Ga-PSMA PET imaging for biodistribution and PCa lesion detection abilities in 37 patients. The highest radiotracer uptake was observed in the kidneys and salivary glands of healthy organs. As early as 1 h after injection, PCa-like lesions showed excellent contrast even at low PSA levels, with high detection rates (20). Similarly, recent studies have also shown a high detection rate, ranging from 33-56% at low PSA levels to 95-97% at PSA levels above 2.0 ng/mL (7,8,21).

According to Müller et al., (21) ^{68}Ga-PSMA-11 PET/CT has an important influence in modifying the therapeutic plans of patients with PSA rise (21), greater than 50% of patients experienced a treatment approach adjustment. It is very effective in the diagnosis of recurrent PCa (22). The ability of the ^{68}Ga-PSMA-11 probe to detect diffused PCa was also demonstrated. In two studies of PCa patients with BCR, 90% of those with elevated PSA levels had recurrent sites (23,24). Perera et al. (8) found that 76% of patients with BCR and 40% of patients with main staging were positive for ^{68}Ga-PSMA PET. The expected positive results were 48% for PSA levels of 0.2 ng/mL, 56% for PSA levels of 0.5 ng/mL, and 70% for PSA levels of 1.0 ng/mL. Shorter PSA doubling times also improved ^{68}Ga-PSMA PET positivity (8).

Because of a significant degree of binding and intracellular accumulation, ^{68}Ga-PSMA-11 can also identify highly small metastases. When compared with CT (specificity: 82% and sensitivity: 42%); and MRI (specificity: 82% and sensitivity: 39%), ^{68}Ga-PSMA-11 was reported to be able to detect metastasis in the nodal region with a specificity of 99% and sensitivity of 75% (8). According to the Pro-PSMA 2020 trial, ^{68}Ga PSMA PET/CT for nodal staging was 27% more precise than CI. They reported that CI had lower specificity (91% vs. 98%) and sensitivity (38% vs. 85%) than PSMA PET/CT (19). Over 5% of the options, treatment change was conducted in 27% of patients who had ^{68}Ga-PSMA-11 PET/CT. With combined specificity and sensitivity of 82% and 79%, respectively, bone scintigraphy (BS) is the most extensively used approach for evaluating bone metastases derived from PCa (25). Pyka et al. (24) showed that ^{68}Ga-PSMA PET was superior to BS for detecting afflicted bone areas and assessing overall bone metastases in PCa. The specificity and sensitivity for total bone activity were 99-100% and 88-100% for PET, respectively, and 87-89% and 61-96% for BS (24).

Because of its unpatented structure, ^{68}Ga-PSMA-11 has been used to gather a significant amount of PSMA PET data throughout the years. The broad accessibility of ^{68}Ga-DOTATATE shows the viability of developing a chain of ^{68}Ga generators for local distribution, even if ^{67}Ge/^{68}Ga generators are not currently the norm for every nuclear medicine clinic globally. It may be possible to provide ^{68}Ga generator more quickly with increased availability, an increase in clinically effective ^{68}Ga-using PET agents, and kit-based radioactive labeling methods that make radiotracer production easier at the spot and are currently being developed for PSMA (26,27). Since the very first human research completed in 2013 (22), ^{68}Ga-PSMA-11 has gained widespread acceptance as well as use at research centers all over the world, and data of over 15,000 patients have been published.

From an economical viewpoint, using data gathered from a clinical trial (19), de Feria Cardet et al. (28) assessed the costs and precision of diagnosis associated with applying ^{68}Ga-PSMA-11 PET/CT vs traditional imaging for staging high-risk PCa. PET/CT using ^{68}Ga-PSMA-11 cost estimate was shown to be AUD 1203, which was less expensive than the traditional imaging price of AUD 1,412. ^{68}Ga-PSMA-11 PET/CT is inexpensive and more accurate. There were also documented savings of AUD 959 for every extra accurate nodal localization and AUD 1,412 for every accurate distant metastases diagnosis.

^{18}F-DCFBC

^{68}Ga can provide less radiation exposure to patients with a quicker absorption time compared to ^{18}F, yet ^{18}F has a superior positron energy (633keV vs. 1,899keV for ^{68}Ga) and inferior positron yield (96.9% vs. 89,1% for ^{68}Ga), affecting both the qualitative and quantitative parameters of the image. Given its longer half-life (108 mins for ^{18}F vs. 68 mins for ^{68}Ga), ^{18}F can provide higher image quality because of the time prolongation between injection and imaging, resulting in an image with less interference and a preferable tumor-to-background ratio. ^{18}F also allows for centered manufacturing and delivery across longer distances. The discovery of ^{18}F-labelled PSMA drugs has resulted in an important change in the availability of PET imaging for metastatic, primary, and recurrent PCas (29,30,31). This is largely due to a larger supply of the radioisotope ^{18}F generated by cyclotrons than that of ^{68}Ga, which is eluted from generators.

The first-generation ^{18}F-PSMA agent, ^{18}F-DCFBC (N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-^{18}F-fluorobenzyl-l-cysteine), is a low-molecular-weight urea-based radiotracer that targets PSMA (Figure 2). First, it was synthesized by Mease et al. (29) in 2008 and was later developed from firstly introduced ([^{11}C]DCMC) by the same group. For ^{18}F-labelled PSMA radioinhibitors, a 2019 meta-analysis found a cumulative detection percentage of 49% on a PSA level that is 0.5 ng/mL or fewer along with 86% on a PSA value of equal or greater than 0.5 ng/mL (30). ^{18}F-DCFBC was investigated for its detection rates, and it was discovered that, although using a poor contrast resolution, they were equivalent to those of recent studies using ^{68}Ga-PSMA PET agents (7,8,21). A drawback of using this drug was its high background activity, which interfered with the identification of LN metastases (32). This led to the synthesis of second-generation ligands.

^{18}F-DCFPyL

^{18}F-DCFPyL exhibits less blood pool activity, stronger affinity, and quicker clearance, increasing the tumor-to-background ratio and potentially enabling the detection of lower-grade or smaller PCa compared with ^{18}F-DCFBC (31) The second generation ^{18}F-labelled PSMA ligand, ^{18}F-DCFPyL, was introduced in 2011 with promising findings due to improved image quality and the ability to show small prostatic lesions with high sensitivity (33). For PSMA-PET/CT imaging in recurrent PCa, ^{18}F-DCFPyL is a potential alternative to ^{68}Ga-PSMA-11 with similar biodistribution (34,35). This ligand is distinguished by its fast excretion through the urinary system (the structure is shown in Figure 2).

A phase II single-center prospective study evaluating PET/CT results using ^{18}F-DCFPyL in 25 patients demonstrated that the specificity and sensitivity for detecting nodal metastasis were 88.9% and 71.4%, respectively. Three mm nodes made up about 50% of the nodes, and 12% of the patients had unexpected distant metastases (36). Even among men with low PSA levels who had BCR in the CONDOR study, DCFPyL effectively determined disease regions. Most males with BCR presenting negative or inconclusive with CI (bone scan plus CT) were found to have localized disease by DCFPyL PET/CT, which changed the course of treatment for most patients. According to these results, ^{18}F-DCFPyL PET seems to be more advantageous than ^{68}Ga-PSMA-HBED-CC PET for the identification of recurrence in PCa patients. However, neither ^{18}F-DCFBC nor ^{18}F-DCFPyL includes radionuclide-binding chelators for targeted treatment.

^{18}F-PSMA-1007

Fluorinated tracers currently in use are frequently not suitable for theranostic applications. Although not applied for therapeutic purposes, only ^{18}F-PSMA-1007, another second-generation PSMA agent, was synthesized for developing a radiofluorine molecule similar to the structure of the PSMA-617 which is used for theranostic purposes (the structure is shown in Figure 2) (37). Because PSMA-1007 is derived from PSMA-617 ^{18}F-PSMA-1007 and ^{177}Lu-PSMA-617 can be used as theranostic pairs of the PSMA radioligand. Other tandem combinations are also possible because the diagnostic component does not have to be an accurate reproduction of the therapeutic component. ^{18}F-PSMA-1007 PET imaging at very low PSA levels provided critical information to correctly restage disease and to discuss appropriate treatment options in a case report by Giesel et al. (36).

^{18}F-PSMA-1007 shows high labelling yield, high tumor absorption and rapid non-urine background removal (38). PSMA-1007 is at least comparable to ^{68}Ga-PSMA-11, but the longer half-life, superior energy properties, and urinary excretion overcome some of the practical limitations of ^{68}Ga-PSMA target tracers. Because of the benefit of hepatobiliary excretion excretion, ^{18}F-PSMA-1007 is a very useful tool for providing more precise pelvic nodal evaluation (36). According to a meta-analysis, in patients with biochemical relapse the detection rate of ^{18}F-PSMA-1007 PET/CT is comparable to that of ^{68}Ga-PSMA-11 PET/CT (27), providing the information of its usefulness in BCR PCa patients. Despite these advantages, compared with ^{68}Ga-PSMA-11, ^{18}F-PSMA-1007 revealed a higher absorption in benign tissue, resulting in more probable false positive conclusions (39).

Apart from these agents, some relatively new agents such as ^{18}F-CTT-1057 use a phosphoramidate backbone to enable irrepleviable binding to PSMA, a lower dose of radiation to the salivary glands and kidneys compared to urea-based agents, and an elevated tumor-to-background ratio in some patients (40).

Clinical Application of PSMA Imaging

The medical community appears to agree that PSMA PET should not be used in low-risk patients; however, further studies are needed to estimate its use in patients with intermediate risk. In high-risk patients, however, PSMA PET outperforms CT and BS combined. Patients with biochemical failure, regardless of castration status, should be referred for PSMA PET. Although PSMA PET shows a more extensive disease than predicted or exonerates similar lesions, this influences therapy optimization. However, if an extensive metastatic burden has already been proven, there is no need for PSMA PET because it will not modify the treatment plan (apart from identifying the PSMA target in the case of radioligand therapy). Furthermore, there is no convincing evidence that PSMA PET may be used to stage PC with Gleason <7 (41). Long-term androgen deprivation treatment (ADT) lowers tracer uptake, possibly due to therapeutic response and associated limitation of the extent of lesions, as well as a larger chance for fractional volume effects. As a result, the European Association of Urology recommendations propose using PSMA PET/CT as a restaging method when a patient's PSA level rises beyond 0.2 ng/mL, ideally before ADT initiation. Considering the contribution of PSMA expression by short-term ADT, the sensitivity of PSMA PET/CT might be enhanced in patients with BCR with PSA levels less than 0.5 ng/mL.

PSMA Ligands for Theranostics

Despite numerous advancements in recent years, managing metastatic PCa remains a challenge. To detect PCa lesions through PET or SPECT imaging, low-molecular-weight ligands have been developed by studying PSMA inhibitors extensively. However, optimizing the endoradiotherapeutic use of these compounds requires optimum consideration of the chelating agent of the radionuclide and the linker moiety between the chelator and pharmacophore, as they affect the overall pharmacokinetic properties of the resulting radioligand. The radioactive isotopes ^{90}Y, ^{131}I, ^{177}Lu, and ^{225}Ac are suitable options for systemic radionuclide therapy. While ^{131}I and ^{177}Lu emit both β-particles and γ-radiation, ^{90}Y is solely a β-particle emitter and ^{225}Ac is an alpha emitter (42,43). Here, we summarize some theranostic agents developed for PCa.

MIP-1095

MIP-1095 [(*S*)-2-(3-((*S*)-1-carboxy-5-(3-(4 iodophenyl)ureido) pentyl)ureido)pentanedioicacid] was first synthesized by Maresca et al. (41) in 2009 (Figure 3). First-in-man evaluation in 2013 showed that ^{123}I-MIP-1095 detects soft tissue, bone, and prostate lesions in just 1-4 h and exhibits excellent pharmacokinetic and pharmacodynamic profiles (44). This makes it a promising diagnostic agent for the ability of labeling with therapeutic radionuclides. Accordingly, in 2014, Zechmann et al. (43) reported first therapy results with ^{124}I/^{131}I-labelled MIP-1095 in individuals suffering from PCa that is resistant to hormone therapy. The radioactive tracer displayed remarkable absorption in the lesions of all patients. Over 50% of treated males experienced a decline in PSA levels, whereas 84.6% of males with bone discomfort reported either complete or substantial relief from pain. However, because of the high level of gamma radiation emitted, patients were required to stay in the hospital for approximately one week, and mild hematological toxicities were observed (43).

PSMA-I&T

For the first time, in 2015, Weineisen et al. (45) synthesized PSMA-I&T ligand with DOTAGA [1,4,7,10-tetraazacyclododecane-1-(glutamic acid)-4,7,10-triacetic acid] conjugate with a peptidic linker to enable rapid and high yield labeling with ^{68}Ga and ^{177}Lu (the structure is shown in Figure 3). Compared with ^{131}I, ^{177}Lu emits a lower proportion of gamma radiation, which would reduce hospital stays and decrease the hemotoxicity observed in patients. Using ^{68}Ga-PSMA-I&T for the first time in human PET imaging provided high-contrast detection of bone lesions, LN and liver metastases. Internal radiotherapy with ^{177}Lu-PSMA-I&T was also proved to be effective and safe for both patients, with no obvious side effects, suggesting that its targeting and confinement properties are suitable for successful endoradiotherapy (46).

Due to the suitability of the chelator, the ligand is also radiolabelled with ^{111}In for SPECT imaging. Rauscher et al. (44) assessed the efficacy of ^{111}In-PSMA-I&T SPECT/CT for detecting early recurrent PCa in comparison with ^{68}Ga-PSMA-11 PET in a group of patients. Nonetheless, ^{111}In-PSMA-I&T SPECT/CT demonstrated a patient-based detection rate of 59%, indicating its potential as a useful imaging tool in situations where PET is unavailable. PSMA-I&T also appears to be diagnostically similar to PSMA-11 and PSMA-617 (47,48,49).

For theranostic purposes, ^{177}Lu-PSMA-I&T was used in a trial of 56 patients with mCRPC who received a mean dosage of 5.76 GBq in each cycle. PSA progression-free survival (PFS) was 14 months, and 59% of patients had PSA levels that were reduced by more than 50% (45). In another trial with 100 patients, within 12 weeks of therapy, PSA levels were reduced by almost 50%. PFS (4.1 months) and OS (12.9 months) in 38 patients were both longer than average (47). ECLIPSE is another clinical study in males with mCRPC to evaluate the effectiveness of ^{177}Lu-PSMA-I&T in males with metastatic castration-resistant PCa. In total, 400 males with mCRPC will be administered ^{177}Lu-PSMA-I&T, enzalutamide, or abiraterone at random (48). The completion of the study is scheduled for 2029, with rPFS as the main research outcome.

^{68}Ga-THP-PSM, a kit-based formulation with a different chelator than PSMA-I&T, offers the advantage of one-step manufacturing but poorer tumor absorption (50).

PSMA-617

Although the clinical outcomes are very promising with the abovementioned radiopharmaceuticals, further studies are needed to optimize the effectiveness of the treatment and to decrease the side effects that have been reported. To achieve both detection and optimal treatment of PCa, a tailor-made PSMA inhibitor containing naphthyl and DOTA has been developed. PSMA-617, consisting of the pharmacophore glutamate-urea-lysine, was developed and advanced through systematic chemical modification of the linker region, leading to improved tumor-targeting and pharmacokinetic properties (Figure 3) (49). It can advance the treatment of patients with recurring PCa through the use of a single radiolabelling precursor that can be radiolabelled with either ^{68}Ga or ^{64}Cu for diagnosis or ^{177}Lu, ^{225}Ac, or ^{213}Bi for therapy. The PSMA-617 compound demonstrated high PSMA-specific tumor uptake, rapid background clearance, and fast kidney excretion. This provides clear clinical advantages for high-quality imaging of recurrent PCa. In terms of therapeutic use, the extended tumor uptake and high tumor-to-background rate provide advantages for PSMA-617 over previously published DOTA-based PSMA inhibitors (51,52). Compared with PSMA-11 (53), PSMA-617 appears to be more suitable for endoradiotherapy because of its higher tumor uptake at later time points, lower spleen accumulation, and highly efficient kidney clearance.

PET/CT imaging has already been applied with successful results using ^{68}Ga-PSMA-617. However, the superior internalization rate of ^{68}Ga-PSMA-617 in the diagnosis of PCa is counterbalanced by slightly slower tracer kinetics than that of PSMA-11, which may be caused by PSMA-617's larger size (53). As a result, images taken only 3 h after injection could benefit from the improved internalization rate. Another approach for imaging, PSMA agents based on copper 64 (^{64}Cu), have been developed because the prolonged ^{64}Cu half-life (12.7 hours) allows for delayed imaging of ambiguous lesions as well as enhanced long-distance delivery logistics (54). In a 2018 study, ^{64}Cu-PSMA-617 PET/CT was reported to be superior to ^{18}F-choline PET/CT in BCR PCa (55). Although the results of the diagnostic performance of ^{64}Cu-PSMA agentare promising, it may expose patients to more radiation compared with ^{18}F inhibitors.

^{177}Lu-PSMA-617 radioligand treatment is widely used in clinical practice and has been the topic of several recent clinical investigations (50,56,57). A retrospective analysis found that 59% and 75% of patients had a PSA decrease after 1 and 2 treatments, respectively, while after 1 injection, 32% of patients and two injections after 50% of patients had a PSA decline of 50% or more. In the past, the optimal supportive therapy group had a median survival of 19.7 weeks; the predicted median lifetime was 29.4 weeks in this study; this difference was statistically significant (58). With the use of ^{177}Lu-PSMA-617, receptor binding causes endocytosis, aggregation within the cell, and intracellular free radical production, which causes cell damage and death. The use of ^{177}Lu-PSMA therapy for treating metastatic CRPC has also been shown to be a promising approach (47,56). Thirty patients were treated during the LuPSMA trial, and 57% of the patients showed PSA responses (59). With the TheraP trial, ^{177}Lu-PSMA-617 was compared to cabazitaxel, which is commonly used for mCRPC treatment. PSA responses were more prevalent among male individuals in the ^{177}Lu-PSMA-617 group than in the cabazitaxel group (60). The VISION trial enrolled 831 patients with mCRPC and revealed important progress in overall survival with a median survival of 4 months along with PFS-based imaging showing significantly greater survival spans. The FDA approved ^{177}Lu-PSMA-617 on March 23, 2022, and it is now marketed as Pluvicto (61). This is because the study's positive treatment outcome and relatively low rate of adverse events support the use of ^{177}Lu-PSMA-617 as a standard procedure in advanced PSMA-positive metastatic castration-resistant PCa. Patients with mCRPC who have earlier received treatment with taxane-based chemotherapy and androgen receptor pathway inhibitor (ARPI) and who

have PSMA imaging results that show PSMA expression in metastatic lesions are suitable for this treatment.

^{177}Lu-PSMA-617 has been shown in several trials to have a strong objective response and tolerable dosimetry, including an advancement in radiological findings and PSA levels, in the treatment of mCRPC. However, ^{177}Lu-labelled PSMA ligands were ineffective in approximately 30% of patients. ^{177}Lu-PSMA-617 therapy-resistant individuals have been observed to respond well to targeted alpha radiotherapy, which may be a better option for treating mCRPC. High ^{177}Lu radioactivity buildups in bone metastases that are in or near the red marrow, despite being well tolerated, indicate that the real dosage taken in to some parts of the active marrow could be somewhat more than anticipated due to disintegration, resulting in a related developing associated risk for hematologic toxic effects. Recent research has demonstrated that patients with mCRPC in this situation greatly benefit from targeted alpha radiation treatment (62).

Having a 20-fold greater linear energy transfer than beta emitters, alpha emitters are the focus of numerous radioligand treatments in preclinical and clinical research (63). ^{225}Ac-PSMA-617 has been shown to be a potential PSMA treatment drug in early studies (64). In a 2019 pilot study, Sathekge et al. (65) evaluated 17 patients with advanced PCa for the treatment efficacy of ^{225}Ac-PSMA-617. The findings revealed that 94.1% of patients experienced a good antitumor response, as shown by PSA levels and ^{68}Ga-PSMA-PET/CT. After therapy, 82.4% of cases experienced at least 90% PSA decrease. All patients had grade 1/2 xerostomia; however, none of them had any serious symptoms (65). Another study found a more than 50% decrease in PSA levels in 33% of such individuals, suggesting that ^{225}AcPSMA-617 may be beneficial in patients who have failed ^{177}Lu-PSMA-617 (63). The half-life of the alpha emitter ^{225}Ac is 9.9 days, which is relatively long. Targeted therapy with ^{225}Ac-PSMA-617 is currently regarded as experimental, but it appears that individuals with advanced stage PCa might benefit greatly from it.

Bismuth-213, a combination of alpha and beta emitting agents with a relatively short half-life of 45.6 min, is also labelled with PSMA-617 for use in treatment (39). Sathekge et al. (66) reported a first-treatment patient with ^{213}Bi-PSMA-617 (two cycles, 592 MBq) who showed PSMA imaging response and biochemical response with a reduced PSA from 237 g/L to 43 g/L in mCRPC patients who had advanced on standard treatment. Kratochwil et al.'s (67) earlier work revealed that the dosimetry of ^{213}Bi-PSMA-617 is suitable for clinical application. This drug is an alternate preferred radiolabel choice for the targeted alpha treatment of PCa because PSMA-617's biological half life in dose-limiting organs is longer than ^{213}Bi's physical half life. However, when compared with ^{225}Ac-PSMA-617, it suffers from higher perfusion-dependent non-target radiation. The AcTION trial is a phase I investigation of ^{225}Ac-PSMA-617 that is being studied in patients with metastatic castration-resistant PCa who have had or have not received ^{177}Lu-PSMA-I&T or ^{177}Lu-PSMA-617. The trial is only taking place in Australia and South Africa, with a projected enrollment of 60 participants (68).

Trials in Progress

PSMAfore is a phase III, randomized, open-label clinical study that evaluates the efficacy of ^{177}Lu-PSMA-617 in mCRPC cases (69). Approximately 450 people will be randomly assigned to either ^{177}Lu-PSMA-617 or an ARPI. All patients must have advanced on just one ARPI (darolutamide, abiraterone, apalutamide or enzalutamide). rPFS is the trial's principal study endpoint. PSMA addition is a phase III, randomized, open-label clinical research that will compare the effectiveness of ^{177}Lu-PSMA-617 when combined with a standard of therapy against a standard of therapy alone in patients with mCSPC. One thousand one hundred twenty-six people will be divided into two groups at random: those who receive ^{177}Lu-PSMA-617 plus ARPI plus ADT and those who receive ARPI alone. rPFS (70) is the main study endpoint. In the phase II clinical study BULLSEYE, individuals with PCa and oligometastatic hormone-sensitive illness received ^{177}Lu-PSMA-I&T as a metastasis-focused treatment. Patients in the randomized controlled study will either receive the standard of care or the interventional arm, which consists of two cycles of ^{177}Lu-PSMA-I&T. However, the manufacturing of ^{177}Lu-PSMA-I&T was stopped because of issues with coronavirus disease-2019, and a protocol adjustment was made to switch out ^{177}Lu-PSMA-I&T with ^{177}Lu-PSMA-617. Disease progression, which is characterized as a 100% increase in PSA or clinical progression, is the main outcome of the trial (71).

^{68}Ga-PSMA-617 PET imaging economic benefits were also evaluated in individuals with possible recurrent PCa, ^{68}Ga-PSMA PET/MRI was compared with standard treatment (72). It was anticipated that ^{68}Ga-PSMA would cost AUD 56,961 and result in 7.48 life years, as opposed to AUD 64,499 and 7.41 years of life with standard care. ^{68}Ga-PSMA had a potential cost savings of AUD 7592 and had an indistinct higher effectiveness of 0.07 life years. According to this preliminary economic analysis, using ^{68}Ga-PSMA PET/MRI to identify recurrent PCa is more affordable than receiving standard medical attention.

^{18}F-rhPSMA-7

Radiohybrids are radiopharmaceuticals that have two labeling positions: one stable radionuclide along with a radioactive radionuclide, depending on the type of imaging or therapy purpose (Figure 3) (73). ^{18}F-rhPSMA-7 is a radiohybrid with advantageous properties with fast labeling, minimal bladder retention, and a reported identification rate of 71% in BCR PCa at low PSA (74). The phase III studies LIGHTHOUSE and SPOTLIGHT are actively investigating this drug for preprostatectomy and BCR, respectively (75,76).

Apart from the abovementioned theranostic ligand targeting PSMA, there are also some new agents being investigated. ^{177}-Lu-DOTA-N3-CTT1403 is being examined in a phase I clinical study for males with PSMA-positive mCRPC who have had a minimum of one ARPI (77). A total of 40 patients are expected to participate. In contrast, the SECuRE trial is a phase the I/II study evaluating both the safety and efficacy of ^{67}Cu-SARbisPSMA in individuals with mCRPC (78). For this study, patients must exhibit positive PSMA expression, as shown via a positive PET/CT scan using ^{64}Cu-SAR-bisPSMA. The study will

involve 44 people, and its main findings will focus on tolerability, safety, and effectiveness.

Conclusion

The imaging and treatment of PCa has become an important issue because PCa is a prevalent disease in male individuals with a high fatal rate. PSMA has recently become an attractive target to support the idea of "precision medicine" in PCa. Compared with CI, PSMA-targeted imaging can be used for the early diagnosis of PCa even at low levels of PSA, BCR, or mCRPC to define the treatment plan. Theranostics is an important concept of "treat what you see" and this approach has gained a lot of attention in the treatment and diagnosis of PCa with PSMA-targeting. It has been shown to be promising for the treatment of PCa, and it is expected that PSMA-based theranostics will soon become the norm for treating patients with PCa.

Acknowledgements

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

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

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

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

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: B.Ş., E.Ö., N.Ö.K., Design: B.Ş., E.Ö., N.Ö.K., Data Collection or Processing: B.Ş., Literature Search: B.Ş., Writing: B.Ş.

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Short Quiz

1- What is PSMA and why is it important in prostate cancer?

2- What is the most commonly used PSMA-targeted radioligand for imaging?

3- What is the most commonly used PSMA-targeted radioligand for therapy?

Original Article

DOI: 10.4274/uob.galenos.2022.2022.7.3

Bull Urooncol 2023;22(4):138-143

Adverse Pathological Outcomes in Radical Prostatectomy Specimens in Patients with a Serum Prostate-specific Antigen Level ≤3 ng/mL

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Abstract

Objective: To evaluate clinicopathological features of patients with serum prostate-specific antigen (PSA) level of ≤3 ng/mL and diagnosed with prostate cancer (PCa).

Materials and Methods: A total of 34 male patients diagnosed with PCa by either prostate needle biopsy (PNB) or transurethral resection of the prostate (TUR-P) were included in this study between January 2010 and June 2021. Patients whose preoperative serum PSA level was >3 ng/mL and those with missing clinical data were excluded. Preoperative clinical characteristics of the patients and pathological findings of PNB, TUR-P, and radical prostatectomy (RP) specimens were evaluated.

Results: The median age of the patients was 65 (60-69) years. The median preoperative serum PSA level was 1.98 (1.45-2.64) ng/mL. PCa was detected by "systematic prostate biopsy (SBx) only", combined prostate biopsy [SBx following multiparametric magnetic resonance imaging-targeted prostate biopsy (TBx)], and "TUR-P" in 6 (17.6%), 17 (50.0%), and 11 (32.4%) patients, respectively. In combination of both biopsy, PCa was detected in "SBx specimens only", "TBx specimens only", and "both TBx and SBx specimens" in 3 (8.8%), 5 (14.7%), and 9 (26.5%) patients, respectively. Clinically significant (cs) PCa was in 52.9% of the TBx (9/17) and 60.9% of the SBx (14/23) specimen. Twenty (58.8%) patients treated with RP. csPCa in RP specimens was observed in 17/20 (85.0%) patients. Upgrading in RP specimens compared with PNB specimens was observed in 5/11 (45.5%) of the TBx and 9/17 (52.9%) of the SBx specimen. At the final RP pathology, International Society of Urologic Pathology-grade group >3 or non-organ confined disease were observed in 8 (40%) and 8 (40.0%) patients, respectively.

Conclusions: Adverse pathological outcomes in RP specimens are frequent in patients with PCa with a serum PSA level of ≤3 ng/mL at the time of diagnosis, and physicians should be aware of the limitations of pre-set PSA cut-off levels.

Keywords: Pathological outcomes, prostate needle biopsy, prostate-specific antigen, prostate neoplasms, radical prostatectomy, transurethral resection of prostate

Introduction

Prostate cancer (PCa) is the 2nd most common form of cancer in men worldwide, with an estimated 1,276,106 new cases and 358,989 deaths (1). Although several potential etiological risk factors have been reported, such as family history, exogenous/environmental factors, chronic inflammation, geographical region, and dietary habits, the most important factor increasing the incidence of PCa is aging (2,3,4). The prevalence of PCa in the young male population is very low. The estimated mean prevalence of PCa at the of age <30 years is 4%, and it is increased to 49% by age >79 years (2).

Two main indications for prostate needle biopsy (PNB) are elevated serum prostate-specific antigen (PSA) levels and suspicious findings on digital rectal examination (DRE) (3). Currently, multiparametric magnetic resonance imaging (mpMRI) is recommended before a PNB decision, even in biopsy-naïve patients. Transrectal ultrasound-guided systematic prostate biopsy (SBx) (with a minimum of 10 to 12-cores) or SBx + MRI-targeted prostate biopsy (TBx) (when MRI is positive) PNB has been accepted as the standard diagnostic approach for the evaluation of patients with a clinical suspicion for PCa (3). However, the definition of elevated PSA levels is still quite vague and a source of discussion.

Cite this article as: Karşıyakalı N, Özgen MB, Özveren B, Durak H, Dinçer A, Türkeri L. Adverse Pathological Outcomes in Radical Prostatectomy Specimens from Patients with Serum Prostate-specific Antigen Level ≤3 ng/mL. Bull Urooncol 2023;22(4):138-143.

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Received: 14.07.2022 **Accepted:** 01.11.2022

Serum PSA levels of <4 ng/mL was initially defined as "normal" and PNB was recommended for higher serum PSA levels (5,6). However, a significant rate of PCa was reported in men with serum PSA levels of 2.6 to 4.0 ng/mL, and subsequently, PSA levels of ≥2.6 ng/mL were accepted as more appropriate for a PNB indication (7). Nevertheless, the risk of PCa was found to be significantly elevated for patients with PSA levels higher than their age-specific medians (8,9,10). Detection of International Society of Urologic Pathology (ISUP)-grade group ≥2 cancers with a higher frequency is quite possible with very low levels of PSA, and an optimal threshold for PSA in detecting clinically significant (cs) PCa is yet to be established (3,11). Thus, PSA has no "normal" limits, and it would only be logical to consider serum PSA levels higher than age-specific median levels as a possible sign of PCa. In this context, we aimed to evaluate the clinicopathological features of patients who had a serum PSA level of ≤3 ng/mL and were diagnosed with PCa by either PNB or transurethral resection of the prostate (TUR-P).

Materials and Methods

Study Population and Multiparametric Prostate Magnetic Resonance Imaging and Determination of Suspicious Lesions

We retrospectively reviewed the medical records of 346 male patients who were diagnosed with PCa by transperineal PNB or TUR-P (patients with lower urinary tract symptoms unresponsive to medical therapy and diagnosed with incidental PCa at pathology) at Acibadem Mehmet Ali Aydinlar University, Altunizade and Kadıköy Hospitals, Department of Urology between January 2010 and June 2021. The Acibadem Mehmet Ali Aydinlar University Ethics Committee approved the study (decision no: 2021-23/12, date: 03.12.2021). Written informed consent was obtained from all patients.

Demographic characteristics, preoperative clinical characteristics, and pathological findings of PNB, TUR-P, and radical prostatectomy (RP) specimens were noted in detail for each patient. Patients whose preoperative PSA level was >3 ng/mL and those with missing clinical data were excluded. Finally, 34 male patients were included in this study.

Patients who planned to undergo PNB were evaluated with 3-T mpMRI (Magnetom Skyra, Siemens Healthineers, Erlangen, Germany) before PNB. All mpMRI studies were evaluated by the same dedicated radiologist (A.D.), and all prostate imaging-reporting and data system version-2 (PI-RADS) lesions ≥3 were mapped (12). The border of the prostate and lesions were outlined and saved as a biopsy plan using MIM Symphony Dx™ Software Inc. version 6.7 (Cleveland, Ohio, USA). Patients who had ≥PI-RADS-3 lesions in mpMRI underwent combined prostate biopsy (SBx following TBx), whereas patients who had no ≥PI-RADS-3 lesions but with an indication for biopsy underwent SBx only.

Transperineal TBx, SBx, and TUR-P Procedures

All transperineal TBx and SBx procedures were performed under sedoanalgesia in the dorsal lithotomy position. An 18-gauge automatic biopsy gun with a 19 mm sample notch was used in the biopsy procedures (Tru-Core™ II URO Automatic Biopsy Instrument, Argon Medical Devices, Inc. Texas, USA). A single-dose parenteral antibiotic as prophylaxis was administered to all patients during anesthesia induction. Two to four samples were taken from each of the suspicious lesions with a PI-RADS score of ≥3 using a stepper and template grid as previously reported (13). All TUR-P procedures were performed under general anesthesia. All biopsy samples, TUR-P specimens, and whole mount sections after RP were evaluated by a dedicated uropathologist (H.D.) in accordance with the 2014 ISUP criteria (14). csPCa was defined for biopsies [presence of a Gleason score (GS) above 6 or GS-6 disease present in more than 2 cores and/or > 50% of all cores] and prostatectomy specimens (presence of a GS above 6 or GS-6 disease and tumor volume greater than 0.5 cm^3) separately as previously reported (3,15).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 software (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to check the normality of data for quantitative variables. Descriptive data are expressed as median (interquartile range, minimum and maximum), and number and frequency.

Results

The median age of the patients was 65 (60-69) years. Age distributions according to decades were as follows: 3 (8.8%) patients aged 40 to 49 years, 5 (14.7%) patients aged 50 to 59 years, 18 (52.9%) aged 60 to 69 years, and 8 (23.5%) patients aged 70 to 79 years. The median preoperative serum PSA level and prostate volume were 1.98 (1.45-2.64) ng/mL and 46.8 (34.3-57.0) mL, respectively (Table 1). All patients aged 40 to 49 years and 50 to 59 years had serum PSA levels higher than 0.7 and 0.9 ng/mL, respectively. The preoperative demographic and clinical characteristics of the patients and the pathological features of the PNB specimens are summarized in Table 1.

Only 2 (5.9%) patients had suspicious findings on DRE. Five (14.7%) patients had a negative PNB history. Twenty-three (67.6%) patients were evaluated using mpMRI before PNB. The distribution of PI-RADS-3, -4, and -5 lesions on mpMRI was 4/23 (17.4%), 11/23 (47.8%), and 6/23 (26.1%), respectively (Table 1).

PCa was detected by "SBx only", "combination of both biopsy (CBx)", and "TUR-P" in 6 (17.6%), 17 (50.0%), and 11 (32.4%) patients, respectively. In CBx, PCa was detected in "SBx specimens only", "TBx specimens only", and "both TBx and SBx specimens" in 3 (8.8%), 5 (14.7%), and 9 (26.5%) patients, respectively. csPCa was in 52.9% of the TBx (9/17) and 60.9% of the SBx (14/23) specimen. The distribution of cT1a, cT1b, cT1c, and cT2 stages was 8 (23.5%), 3 (8.8%), 21 (61.8%), and 2 (5.9%), respectively.

GS of 6 (3+3), 7 (3+4), and 7 (4+3) tumors were observed in 6 (35.3%), 6 (35.3%), and 2 (11.8%) patients in TBx specimens (n=17), and their distribution was 9 (39.1%), 5 (21.7%), and 4 (17.4%) in SBx specimens (n=23), respectively.

Twenty (58.8%) patients were treated with RP, while 2 (5.9%) of them underwent radiotherapy. One patient (2.9%) who had

only one tumor foci in TBx specimens with a GS of 6 (3+3) received focal ablative interstitial laser thermotherapy. Eleven (32.4%) patients were managed with active surveillance (AS). None of the AS patients required active treatment due to any cause, with a median follow-up period of 16 (8-24) months.

pT2a, pT2c, pT3a, and pT3b diseases were observed in 5 (25.0%), 7 (35.0%), 6 (30.0%), and 2 (10.0%) patients who underwent RP (n=20), respectively (Table 2). csPCa in prostatectomy specimens was observed in 17/20 (85.0%) patients. Surgical margin positivity was observed in 2/20 (10.0%) patients. Extended pelvic lymph node dissection was performed in 4/20 (20.0%) patients, and regional lymph node metastasis was observed in 1/20 (5.0%) patients (Table 2). The pathological features of RP specimens are summarized in Table 2.

GS of 6 (3+3), 7 (3+4), 7 (4+3), and 9 (5+4) diseases were observed in 3 (15.0%), 9 (45.0%), 6 (30.0%), and 2 (10.0%) prostatectomy specimens (n=20), respectively. In patients who underwent RP, 8 (40.0%) were diagnosed by "SBx specimens only", 2 (10.0%) by "TBx specimens only", 7 (35.0%) by "both TBx and concomitant SBx specimens", and 3 (15.0%) "TUR-P", respectively. Upgrading in prostatectomy specimens compared with PNB was observed in 5/11 (45.5%) and 9/17 (52.9%) patients who underwent TBx and SBx, respectively (Table 3).

Table 1. Demographic and clinical characteristics of patients and pathological features of prostate biopsy specimens

Variables		**Median (IQR)**
Age (year)		65 (60-69)
Preoperative prostate specific antigen level (ng/mL)		1.98 (1.45-2.64)
Prostate volume (mL)		46.8 (34.3-57.0)
Digital rectal examination (n, %)	Benign	32 (94.1%)
	Suspicious	2 (5.9%)
Previous negative prostate needle biopsy history (n, %) (yes)		5 (14.7%)
PI-RADS-3 lesion in mpMRI (n=23) (n, %) (yes)		4/23 (17.4%)
PI-RADS-4 lesion in mpMRI (n=23) (n, %) (yes)		11/23 (47.8%)
PI-RADS-5 lesion in mpMRI (n=23) (n, %) (yes)		6/23 (26.1%)
Total number of suspicious lesions in mpMRI		2 (0-3)
Number of sampled cores in targeted prostate biopsy		12 (7-13)
Number of sampled cores in a systematic prostate biopsy		12 (12-13)
Total number of sampled cores in prostate biopsy		23 (12-25)
Number of tumor-positive cores in targeted prostate biopsies		1 (1-1)
Number of tumor-positive cores in systematic prostate biopsies		2 (1-4)

IQR: Interquartile range, PI-RADS: Prostat imaging-reporting and data system, mpMRI: Multiparametric magnetic resonance imaging

Table 2. Pathological features of radical prostatectomy specimens (n=20)

Variables		**n, %**
Pathological (pT) Stage	pT2a	5 (25.0%)
	pT2b	0
	pT2c	7 (35.0%)
	pT3a	6 (30.0%)
	pT3b	2 (10.0%)
ePLND (yes)		4 (20.0%)
Total number of lymph nodes excised in ePLND [median (IQR)]		30 (25-34)
Pathological regional lymph node (pN) stage	pNx	16 (80.0%)
	pN0	3 (15.0%)
	pN1	1 (5.0%)
Surgical margin (positive)		2 (10.0%)
Tumor volume in prostatectomy specimens (mL) [median (IQR)]		2.6 (0.7-7.0)
Tumor volume ratio in prostatectomy specimens (%) [median (IQR)]		5.9 (1.4-15.0)
Clinically significant prostate cancer in radical prostatectomy (yes)		17 (85.0%)
Estimated blood loss during surgery (mL) [median (IQR)]		100.0 (50.0-200.0)

ePLND: Extended pelvic lymph node dissection, IQR: Interquartile range

Table 3. Gleason score concordance between prostate biopsy techniques and radical prostatectomy specimens (n=20)		
Variables		**n, %**
Targeted prostate biopsy	Same grade	6 (54.5%)
	Up grade	5 (45.5%)
Systematic prostate biopsy	Same grade	8 (47.1%)
	Up grade	9 (52.9%)

Discussion

Patients with a low serum PSA level may harbor life-threatening cancers and should not be ruled out without proper evaluation. In 1994, Catalona et al. (6) compared the efficacy of DRE and serum PSA in the early detection of PCa. In this multicenter, prospective clinical trial, 6.630 male volunteers were assessed, and quadrant prostate biopsies were performed on patients who had a PSA level of greater than 4 ng/mL and/or suspicious DRE findings for PCa. The PCa detection rate was 3.2% for DRE, 4.6% for PSA, and 5.8% for the 2 methods combined (6). According to their findings, the authors recommended using PSA in conjunction with DRE to enhance early PCa detection. They recommended a PSA cut-off value of 4 ng/mL as a trigger for PNB (6). Subsequently, they investigated the detection rate of PCa in a screening population of men with serum PSA levels of 2.6 to 4.0 ng/mL and normal DRE findings (7). The authors reported a significant PCa prevalence (22%) in this population, and most cancers detected appear to be clinically important. Thus, they suggested that detecting PCa in men with these serum PSA levels may help reduce PCa mortality and morbidity rates (7).

PSA is a serine protease produced by the epithelial cells of normal, hyperplastic, and cancerous prostatic tissue (16) and has a high false positive rate when used as a screening tool because of its non-specific nature for possible malignancy. PSA levels may also increase with aging, mainly because of increased prostate volume due to benign prostatic hyperplasia (8,17). In this context, several studies have been conducted to determine age-specific reference ranges of PSA in different populations (8,9,18,19,20). The major concerns in all of these studies were both identifying high-risk PCa and reducing the number of unnecessary PNBs. However, the possibility of missing a csPCa was the major problem. In their pioneering work, Oesterling et al. (20) recommended different reference ranges for PSA for men based on their age (i.e, for 40 to 49 years 0-2.5 ng/mL; 50 to 59 years 0-3.5 ng/mL; 60 to 69 years 0-4.5 ng/mL; and 70 to 79 years 0-6.5 ng/mL) (8). The authors claimed that age-specific reference ranges have the potential to make PSA a more discriminating tumor marker for detecting csPCa in older men (by increasing specificity) and to find more potentially curable cancers in younger men (by increasing sensitivity) (8). A few years later, Morgan et al. (9) determined the age-specific reference ranges of PSA in black men with and without PCa. According to sensitivity analyses, they recommended that using age-specific reference ranges can improve the clinical value of screening and recommended the following reference ranges: 0 to 2.0 ng/mL for men in their 40s, 0 to 4.0 ng/mL for men in their 50s, 0 to 4.5 ng/mL for men in their 60s, and 0 to 5.5 ng/mL for men in their 70s (9). In the following years, in a PCa screening study, the median serum PSA level was reported as 0.7 ng/mL for men aged 40 to 49 years and 0.9 ng/mL for men aged 50 to 59 years (10). In this study, baseline serum PSA values between age-specific median and 2.5 ng/mL in high-risk men in their 40s were associated with a 14.6-fold increased risk of later PCa diagnosis and a 7.6-fold increased risk for men in their 50s. Because of these findings, the authors warned clinicians that they should no longer regard men younger than 60 years with a serum PSA level of less than 2.5 ng/mL as "normal" (10). Although there were only 3 and 5 patients aged 40 to 49 years and 50 to 59 years, respectively, in our study, all had higher serum PSA levels than the age-specific medians determined by Loeb et al. (10). Patients in this study who had a serum PSA level of ≤3 ng/mL at the time of diagnosis revealed csPCa in 85.0% of the RP specimens, and adverse pathological findings such as grade group 3 or higher tumors or extraprostatic disease extension were also common (40% and 40% respectively). Surgical margin positivity and regional lymph node metastasis were observed in 10.0% and 5.0% of the cases, respectively. Finally, upgrading in prostatectomy specimens ranged from 45.5% to 52.9% according to the PNB technique. All these findings suggest that a comprehensive diagnostic approach should be considered in patients with a PSA value of ≤3 ng/mL but higher than their age-specific median levels.

Nevertheless, the optimum trigger value for PSA is still unclear. Bosch et al. (17) created a model for the prediction of "normal" changes in serum PSA levels over time in individual men based on age and initial serum PSA levels in a community-based European male without PCa. The major aspect of "Krimpen study" was that longitudinal changes in PSA were evaluated (17). In a recent study, Gilbert et al. (21) developed a new age-specific PSA threshold based on "Krimpen study" for detecting PCa. In this study, the authors compared the ability of their age-specific PSA thresholds to discriminate between high- and no/low-risk PCa with 2 other existing thresholds: (i) PSA threshold of 3 ng/mL for all agesand (ii) National Institute of Clinical Excellence guidelines dependent on age-group thresholds (21). The authors found that a simple threshold of PSA 3 ng/mL for all ages identified more PCa at a high risk of progression than either of the other two methods, resulting in fewer missed PCa, and more men received unnecessary PNB. Moreover, while age-dependent thresholds were more discriminatory, too many PCa at high risk of progression were missed (21). In contrast, we demonstrated that adverse pathological outcomes in RP specimens can be observed in patients with a serum PSA level of ≤3 ng/mL. Therefore, we consider that patients with serum PSA levels higher than age-specific medians should be evaluated at least by mpMRI.

In addition to the pathological characteristics specific to PCa, the different features and inherent risks of current biopsy approaches may influence the discordant histopathological results. One of the important findings of our study was the increased frequency of csPCa and upgrading in GS in RP specimens compared with that in PNB specimens. A recent Cochrane meta-analysis comparing mpMRI with template biopsies in biopsy-naïve and repeat biopsy settings reported that mpMRI-targeted biopsies were a more favorable diagnostic test than SBx in all men with

suspected csPCa (22). However, Westhoff et al. (23) reported that TBx detected significantly less PCa without being superior to SBx in detecting csPCa, except in men with previous negative biopsies, and they concluded that a combination of TBx and SBx was the single approach for csPCa detection. Thus, even the most current approach is still far from perfect, as we demonstrated previously, where the frequency of csPCa was much lower in TBx and SBx specimens than in RP specimens (24). In this study, CBx performed better in predicting the ultimate RP pathology, missing csPCa in 4.3% of cases (24). Several studies have shown that biopsy concordance with RP samples ranges from 37% to 58% using SBx alone (25,26,27). There are also significant differences in the literature regarding the ability of TBx to better predict the GS of RP (28). The concordance ratios of the GS between biopsy and RP specimens for TBx and SBx were reported as 91.5% vs. 53.8%, respectively (29). In this study, patients with a negative SBx history underwent TBx (29). Alshak et al. (30) recently reported ISUP grade group upgrading and downgrading ratios between TBx and RP samples 25% and 22.1%, respectively. Similarly, in the present study, we observed that the frequency of upgrading in RP specimens was 45.5% in TBx specimens and reached 52.9% in SBx specimens.

Study Limitations

Our study has several limitations that need to be considered. First, the retrospective and non-randomized nature of our study introduces the possibility of selection bias. Second, the major limitation was the small sample size of our study cohort, and only 20 patients were treated with RP. On the other hand, we demonstrated that adverse pathological outcomes in RP specimens can be observed in patients with a serum PSA level of ≤3 ng/mL. Therefore, we believe that our study results may contribute to the body of knowledge on this specific patient population. Further investigations with larger cohorts that were treated with RP are needed to confirm our study results.

Conclusion

In conclusion, adverse pathological outcomes in RP specimens are frequent in patients with a serum PSA level of ≤3 ng/mL. Physicians must be aware of blanket recommendations suggesting the absence of csPCa below certain thresholds of PSA, and a comprehensive diagnostic approach for the possible presence of PCa should be considered, especially in young patients with PSA above their age-specific median level. Further prospective investigations with larger patient populations are required to confirm our study results.

Acknowledgements

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

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

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

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

Ethics

Ethics Committee Approval: The Acibadem Mehmet Ali Aydinlar University Ethics Committee approved the study (decision no: 2021-23/12, date: 03.12.2021).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Original Article

DOI: 10.4274/uob.galenos.2023.2023.2.2

Bull Urooncol 2023;22(4):144-149

Smoking Status in Relation to Clinicopathological Characteristics, Oncological Outcome, and Presence of Second Primary Lung Cancer in Patients with Bladder Cancer: A Population-based Registry Study

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Abstract

Objective: To evaluate the relationship between smoking status and clinicopathological characteristics and oncological outcome in bladder cancer (BC) patients and those with concomitant BC and lung cancer (LC) who developed BC or LC as a second primary cancer during their survivorship.
Materials and Methods: A total of 2621 BC patients registered in the Turkish Urooncology Association Bladder Cancer Database between 2001 and 2021 were retrospectively analyzed. Patients were divided into two groups: those with BC only (BC group, n=2568) and those with concomitant BC and LC (BLC group, n=53). Data on patient demographics and smoking status (active smoker, former smoker, non-smoker) were recorded, as were the clinicopathological characteristics and oncological outcomes with respect to smoking status.
Results: Active smokers comprised 50.5% and 49.1% of patients in the BC and BLC groups, respectively. The percentage of former smokers was 14.3% and 13.2% and percentage of non-smokers was 31.4% and 18.9% in the BC and BLC groups, respectively. In both BC and BLC groups, a higher percentage of males than females were active smokers (45.8% vs. 4.6% in BC and 47.2% vs. 1.9% in BLC). In the BLC group, the percentages of active smokers, former smokers and non-smokers in the BC first group were 56.0%, 24.0% and 20.0%, respectively, whereas the corresponding ratios in the LC first group were 50.0%, 8.3%, and 41.7%, respectively. The presence of smoking (active or former) vs. non-smoker status was associated with more advanced clinicopathological characteristics and poor oncological outcomes in both BC and BCL groups.
Conclusions: This population-based registry study in patients with BC revealed the presence of smoking history (active or former) in almost two-thirds of patients in both BC and BLC groups, which was associated with more advanced clinicopathological characteristics and poor oncological outcomes in both BC and BCL groups.
Keywords: Smoking status, bladder cancer, lung cancer, second primary cancer, clinicopathological features, oncological outcome

Introduction

Tobacco smoking is considered among the most important threats to public health and is one of the major preventable causes of death. It was reported that more than 1 billion people smoked tobacco regularly in 2019, and approximately 8 million deaths were related to smoking (1). In Turkey, the prevalence of tobacco smoking in adults was 31.3% in 2019, while an estimated 77000 and 11000 deaths in 2017 were attributed to tobacco smoking and secondhand smoke exposure, respectively (2,3).

Although different forms of tobacco (i.e., cigars, electronic cigarette hookah, bidis) are available in the market, none are considered safe, and each may lead to significant cardiovascular and respiratory (i.e., restrictive or obstructive lung diseases) problems (4). Furthermore, one of five cancer cases is directly caused by smoking (5). The International Agency for Research

Cite this article as: Bolat D, Tinay İ, Aslan G, Özkök S, Göker E, Akkoçlu A. Smoking Status in Relation to Clinicopathological Characteristics, Oncological Outcome, and Presence of Second Primary Lung Cancer in Patients with Bladder Cancer: A Population-based Registry Study. Bull Urooncol 2023;22(4):144-149.

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Received: 23.02.2023 **Accepted:** 06.05.2023

on Cancer (IARC) declared tobacco smoking a group 1 carcinogen in humans and associated it with cancers of the oral cavity, pharynx, larynx, lung, nasal cavity/accessory sinuses, esophagus, stomach, colorectum, liver, pancreas, kidney, ureter, urinary bladder, ovary, cervix, and myeloid leukemia (6).

Both lung cancer (LC) and bladder cancer (BC) are among the most common and mortal cancers globally (7). Tobacco smoking is the strongest modifiable risk factor for both cancer types. Approximately 85% of LCs result from smoking, and smoking accounts for nearly 50% of the BC burden (8,9).

Cigarette smoking is commonly continued after an initial diagnosis of smoking-associated cancer, despite being a strong and modifiable oncological risk factor (10,11,12,13). Smoking and/or alcohol consumption are causally linked to more than one-third of all second primary cancers (SPCs) in the United States, whereas the risk of developing a second smoking-associated cancer is also higher in survivors of smoking-associated cancers than in the general population (12).

BC and LC are the two most frequently diagnosed and mortal cancers that share tobacco smoking as a common risk factor. Therefore, this population-based registry study aimed to evaluate the relationship between smoking status and clinicopathological characteristics and oncological outcome in BC patients and in those with concomitant BC and LC who developed BC or LC as a SPC during their survivorship.

Materials and Methods

Study Population

A total of 2621 BC patients registered in the Turkish Urooncology Association Bladder Cancer Database between 2001 and 2021 were retrospectively analyzed. The database included the demographic, pathologic, and clinical parameters of patients with non-muscle-invasive and muscle-invasive BCs. Patients were divided into two groups: those with BC only (BC group, n=2568) and those with concomitant BC and LC (BLC group, n=53). The BLC group was further divided into two subgroups based on the type of SPC, including those who developed LC as an SPC during BC (BC first, n=25) and those who developed BC as an SPC during LC (LC first, n=12). Patients with missing data, those with benign lesions and/or metastatic lesions of the lung, and those with benign lesions of the bladder were excluded from the analysis.

In accordance with the registry database design of the study, ethics committee approval was not required.

Assessments

Data on patient demographics (age at diagnosis, gender) and smoking status (active smoker, former smoker, non-smoker) were recorded in each group. Clinicopathological characteristics and oncological outcomes (advanced tumor stage at diagnosis, high grade tumor at diagnosis, nodal disease, metastasis at the time of initial diagnosis, complications, postoperative recurrence, postoperative metastasis, need for additional treatment [radiotherapy (RT)/computed tomography (CT), and mortality] were evaluated with respect to smoking status in the BC and BLC groups. In the BLC group, smoking status was also evaluated with respect to primary diagnosis (LC first and BC first).

Statistical Analysis

Statistical analysis was performed using Python and Pandas (14,15), Numpy (16), Scipy (16), and JupyterLab (17) as the coding interface. The normality of distribution was evaluated using visual (Histograms, QQ Plots) and analytical methods (Kolmogorov-Smirnov, Shapiro-Wilk, and D'Agostino's κ^2 tests). Descriptive statistics were reported, and the data were expressed as mean (standard deviation), median (interquartile range), and n (%) where appropriate. This is a sectional study; therefore, no hypothesis tests or p-values were presented.

Results

Patient Demographics and Smoking Status

Of 2621 BC patients included in the registry database, 2568 (97.9%) were diagnosed with BC only (BC group), whereas 53 (2.1%) were diagnosed with concomitant BC and LC (BLC group). Males comprised 85.7% (2201/2568) and 96.2% (51/53) of patients in the BC and BLC groups, respectively (Table 1).

In the BC group, the mean age at cancer diagnosis was 68 years overall, and it was 66 years, 67 years, and 68 years in active smokers, former smokers, and non-smokers, respectively (Table 1).

In the BLC group, the mean age at cancer diagnosis was 70 years overall, and it was 68 years, 77 years, and 70 years for active smokers, former smokers, and non-smokers, respectively (Table 1).

Active smokers comprised 50.5% (1296/2568) and 49.1% (26/53) of patients in the BC and BLC groups, respectively. The percentage of former smokers was 14.3% (367/2568) and 13.2% (7/53) and the percentage of non-smokers was 31.4% (807/2568) and 18.9% (10/53) in the BC and BLC groups, respectively (Table 1, Figure 1).

Accordingly, a history of smoking (current or former) was evident in 1663 (64.8% overall, 67.3% of those with available data) patients with BC only and in 33 (62.3% overall, 76.7% of those with available data) patients with concomitant bladder and LC (Table 1).

In both BC and BLC groups, a higher percentage of males than females were active smokers (45.8% vs. 4.6% in BC and 47.2% vs. 1.9% in BLC) and former smokers (13.5% vs. 0.8% in BC and 11.3% vs. 1.9% in BLC) (Table 1, Figure 2).

Demographics and Smoking Status in the BLC Group with Respect to SPC

In the BLC group of 53 patients with concomitant BC and LC, data on the type of SPC were available in 37 patients. The first diagnosed cancer was BC, and LC appeared as an SPC in 25 (67.6%) patients, whereas LC diagnosis preceded the development of BC as an SPC in 12 (32.4%) patients (Table 2).

The mean patient age at diagnosis was 71 years and 70 years in the BC first and LC first groups, respectively. LC was detected a

mean of 3.7 years after the diagnosis of BC, and BC was detected a mean of 4.2 years after the diagnosis of LC (Table 2).

The percentages of active smokers, former smokers and non-smokers in the BC first group were 56.0%, 24.0% and 20.0%, respectively, while the corresponding ratios in the LC first group were 50.0%, 8.3%, and 41.7%, respectively (Table 2, Figure 1).

Clinicopathological Characteristics and Oncological Outcomes

Figure 3 illustrates the clinicopathological characteristics and oncological outcomes with respect to smoking status (active smokers, former smokers and non-smokers, respectively) in the BC group, including advanced tumor stage at diagnosis (57.2%, 55.2%, 49.3%), high-grade tumor at diagnosis (72.8%, 72.5%, 61.5%), nodal disease (37.0%, 36.7%, 34.6%), metastasis at the time of initial diagnosis (3.8%, 2.2%, 1.9%), complications (43.3%, 20.4%, 36.0%), postoperative recurrence (23.7%, 28.0%, 19.6%), postoperative metastasis (11.8%, 25.7%, 14.5%), need for additional treatment (RT/CT; 66.1%, 63.6%, 52.1%), and mortality (14.2%, 26.5%, 12.1%) (Figure 3).

Figure 4 illustrates clinicopathological characteristics and oncological outcomes with respect to smoking status (active smokers, former smokers and non-smokers, respectively) in the BLC group, including advanced tumor stage at diagnosis (42.4%, 28.6%, 28.6%), high-grade tumor at diagnosis (65.6%, 55.6%, 28.6%), nodal disease (15.4%, 0.0%, 0.0%), metastasis at the

Table 1. Patient demographics and smoking status in the study groups

		Cancer registry (n=2621)	
		Bladder cancer (n=2568)	**Bladder cancer + lung cancer (n=53)**
Gender, n (%)			
Male		2201 (85.7)	51 (96.2)
Female		367 (14.3)	2 (3.8)
Age at diagnosis (year), mean	Total	68	70
	Active smoker	66	68
	Former smoker	67	77
	Non-smoker	68	70
Smoking status, n (%)			
Active smoker	Total	1296 (50.5)	26 (49.1)
	Male	1177 (45.8)	25 (47.2)
	Female	119 (4.6)	1 (1.9)
Former smoker	Total	367 (14.3)	7 (13.2)
	Male	347 (13.5)	6 (11.3)
	Female	20 (0.8)	1 (1.9)
Non-smoker	Total	807 (31.4)	10 (18.9)
	Male	622 (24.2)	10 (18.9)
	Female	185 (7.2)	0 (0.0)
Missing data	Total	98	10
	Male	55	10
	Female	43	0
History of smoking (current or former)	Total	1663 (64.8)	33 (62.3)
	In those with available data (n=2470 and n=43)	1663 (67.3)	33 (76.7)

Table 2. Demographics and smoking status in patients with concomitant bladder and lung cancer with respect to the type of SPC

		Bladder cancer + lung cancer (n=53)	
		Bladder cancer first	**Lung cancer first**
Total (n=37), n (%)[a]		25 (67.6)	12 (32.4)
Age at diagnosis (year), mean		71	70
Time between two diagnoses (year), mean		3.7	4.2
Smoking status, n (%)	Active smoker	14 (56.0)	6 (50.0)
	Former smoker	6 (24.0)	1 (8.3)
	Nonsmoker	5 (20.0)	5 (41.7)

[a]Unknown in 16 patients, SPC: Second primary cancer

time of initial diagnosis (12.5%, 0.0%, 0.0%), complications (73.3%, 33.3%, 20.0%), postoperative recurrence (16.7%, 66.7%, 20.0%), postoperative metastasis (23.8%, 33.3%, 0.0%), need for additional treatment (RT/CT; 41.2%, 33.3%, 0.0%), and mortality (26.7%, 33.3%, 0.0%) (Figure 4).

Discussion

This population-based registry study in BC patients revealed the presence of smoking history (active or former) in almost two-thirds of patients in both BC and BLC groups, which was associated with an increased risk of advanced tumor stage, high-grade tumor and metastasis at the time of initial diagnosis, more invasive surgeries and related postoperative complications, recurrence and metastasis, and a higher rate of mortality compared with non-smoker status. The association of smoking with poor prognostic factors and mortality was more marked in the BLC group than in the BC group, whereas the postoperative recurrence, metastasis, and mortality rates remained high even after smoking cessation in both the BC and BLC groups. Younger age at diagnosis (2 years earlier overall and 10 years earlier for former smokers) in the BC than in the BLC groups, and for active smokers than non-smokers in both BC and BLC groups.

The current population of Turkey is 85 million, and there are approximately 65.000 LC survivors (18). Our findings revealed the presence of LC as a SPC in 2.1% of patients with BC, which seems to indicate that LC is approximately 28-fold more common in patients with BC than in the general population. This situation is related to smoking, which is a common risk factor for both cancers.

Tobacco use is considered to be the main cause of 90% and 79% of LCs in males and females, respectively, and approximately half of BC cases as well (19,20). Similarly, our findings also indicate that almost two-thirds of patients with BC or concomitant bladder and LC have smoked at some point in their lives.

Overall, 75% of new BC cases occur in men, with an M:F ratio ranging 6:1 to 2:1 in different regions worldwide (21). Similarly, LC incidence is also 2-3 times higher in men than in women in different countries of the world (22). This is related to the fact that men smoke more than women (23). In the current study, BC alone or together with LC was also more common in men than in women. Moreover, both BC and concomitant BC + LC were 2-fold more common in smoker men than in non-smoker men.

Although nicotine itself is not carcinogenic, many substances in cigarette smoke, such as polycyclic aromatic hydrocarbons and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, have been deemed carcinogenic by the IARC. The activation of these substances is considered to be responsible for the formation of DNA adducts and subsequent gene methylation, DNA sequence alterations, DNA segment amplification/deletion, or whole chromosome gains/losses (24).

Recent studies have reported the association of continued smoking with a higher risk of SPC and adverse outcomes, whereas smoking cessation lowered the incidence of SPC in survivors of LC (13,25). Barclay et al. (13) described the incidence of second- and higher-order smoking-related primary cancers in LC survivors and noted that BC is the second most common smoking-related SPC after non-small cell LC among survivors of primary LC. The standardized incidence ratios (SIRs) for second

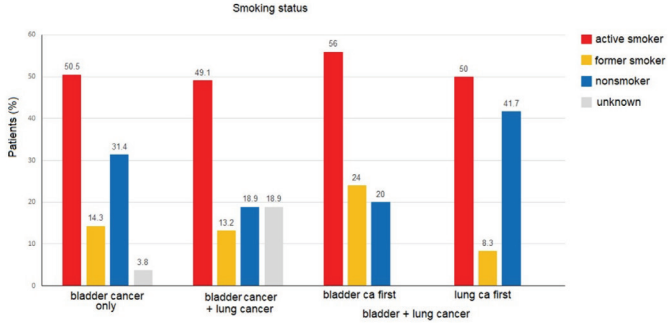

Figure 1. Smoking status in "bladder cancer only" and "bladder cancer plus lung cancer" groups

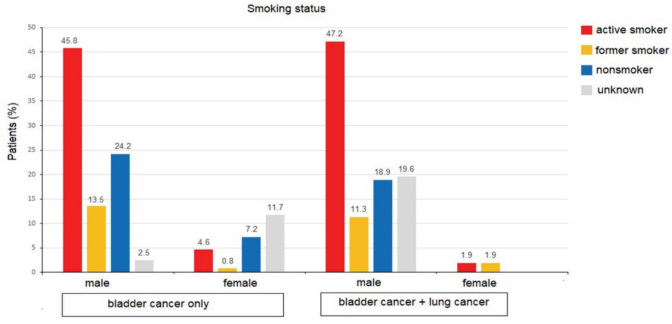

Figure 2. Smoking status with respect to gender in "bladder cancer only" and "bladder cancer plus lung cancer" groups

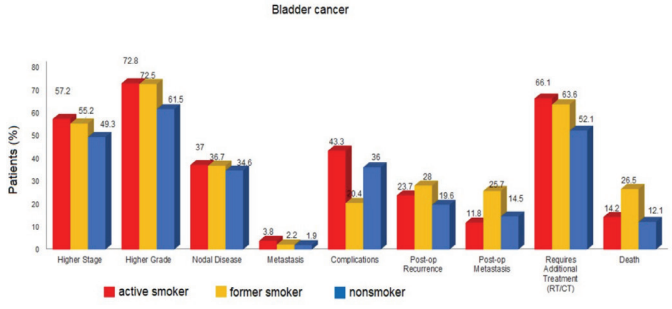

Figure 3. Clinicopathological characteristics and oncological outcomes with respect to smoking status in bladder cancer patients

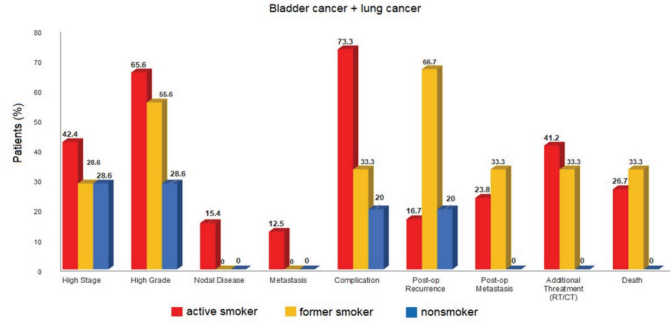

Figure 4. Clinicopathological characteristics and oncological outcomes with respect to smoking status in patients with concomitant bladder and lung cancers

primary BC were found to be similar to the general population at the beginning and end of follow-up, which appears to peak at approximately 5 years, with an SIR of 1.8 [95% confidence interval (CI) 1.5 to 2.2], from first primary LC diagnosis (13). Zheng et al. (11) investigated the sex-specific risks for any SPCs following urothelial cancers and, in reverse order, for urothelial cancers as SPCs following any cancer in 46234 BC patents. The authors noted that after BC, the SIR for LC as an SPC was 2.08 (95% CI 1.93-2.25) and 2.82 (95% CI 2.43-3.26) in males and females, respectively. However, the second BC risk after LC was 1.31 (95% CI 1.12-1.52) in males and 1.81 (95% CI 1.34-2.4) in females. The authors also emphasized that this association was most likely related to smoking (11). In a study by Shiels et al. (12) from five cohorts including stage I LC (n=2,552), BC (n=6,386), kidney cancer (n=3,179) and with head/neck cancer (n=2,967) patients, smoking before the first cancer diagnosis was found to increase the risk of SPC in cancer survivors, in relation to the increased smoking prevalence. In our study, 37 of 2568 patients with BC also had LC. Of these, 67.6% were diagnosed with LC after a mean of 3.7 years of initial BC diagnosis. In the remaining 32.4%, BC developed a mean of 4.2 years after the diagnosis of LC. Moreover, we found that secondary primary lung or BC occurred in approximately half of the patients with primary cancer who smoked over the years. According to our results, it seems that if patients survive to primary bladder or LC, they will develop the other one of these cancers in about 4 years. Thus, these patients will begin to struggle with two aggressive cancers in their early 70s.

A growing body of evidence indicates the association of smoking with adverse outcomes in BC patients treated with transurethral resection and/or radical cystectomy, although not uniformly. Rink et al. (26) suggested the potential of smoking in causing unfavorable outcomes after radical cystectomy and the likelihood of smoking cessation to attenuate these effects. Recently, in a cohort study of 1472 adult NMIBC patients (two-thirds were former or current cigarette smokers at the time of diagnosis), the recurrence risk was reported to increase with longer duration and increasing pack-years of cigarette smoking in an exposure-response manner (~ two-fold greater risk for ≥40 years of smoking and ≥40 pack-years). Pipe, cigar, marijuana, and e-cigarette usage were not associated with an increase in recurrence risk (27). Moreover, in a systematic review and meta-analysis by Cacciamani et al. (28), smoking status was found to be associated with lower neoadjuvant chemotherapy response rates, higher overall and cancer-specific mortality, and higher rate of BC recurrence after radical cystectomy. In a meta-analysis by Tellini et al. (29), it was demonstrated that smoking status at the time of radical cystectomy is related to an increased risk for major postoperative complications, infections, and mortality. Besides the increased risk of mortality and subsequent malignancies, cigarette smoking in cancer patients is also known to increase surgical complications and chemotherapy-related and radiation-related toxicities (30,31). In our study, BC was at a more advanced stage at the time of diagnosis in smokers along with a more aggressive course in these patients. Our observations regarding postoperative complications, prognosis, response to treatments, and survival outcomes were consistent with those of previous studies. Additionally, we found that even if patients with concomitant bladder and LCs quit smoking, BC relapsed and metastasized more frequently.

Study limitations

This study has certain limitations. First, we did not consider the amount and duration of smoking because it is self-reported and may cause bias. Secondly, although there are many forms of tobacco in the market, we considered all in one as tobacco smoking. Third, in our cohort, we considered cancer-specific and other causes of mortality as a single parameter. However, smoking also increases the risk of non-cancer-related deaths, primarily by affecting the cardiovascular system. Fourth, concomitant cancers have some genetic mutations that affect tumor suppressor genes. Smoking is not solely responsible for bladder and LCs. Due to the lack of genetic information in our database, we could not analyze the impact of genetic factors on this patient population. Lastly, while this is a population-based study with a high number of participating centers and patients, increasing the strength of the study, our results may not be generalizable because all participating centers were referral centers in their region and across Turkey.

Conclusion

In conclusion, this population-based registry study in patients with BC revealed the presence of smoking history (active or former) in almost two-thirds of patients in both BC and BLC groups, which was associated with more advanced clinicopathological characteristics at diagnosis and poor oncological outcomes in both BC and BCL groups. The association of smoking with poor prognostic factors and mortality was more marked in the BLC group than in the BC group, whereas the postoperative recurrence, metastasis, and mortality rates remained high even after smoking cessation in both the BC and BLC groups. Tobacco smoking is a common risk factor for both bladder and LCs. If survivors of one of these cancers continue to smoke, the risk of developing another cancer is high. Patients with BC who smoke have adverse pathological outcomes, worse treatment response, and lower survival rates. Therefore, healthcare providers should counsel cancer patients regarding the importance of smoking cessation.

Acknowledgements

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

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

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

Financial Disclosure: Astra Zeneca-Turkiye provided unconditional support for updating the Turkish Association of Urooncology Bladder Cancer Database.

Ethics

Ethics Committee Approval: In accordance with the registry database design of the study, ethics committee approval was not required.

Informed Consent: Database report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Original Article

DOI: 10.4274/uob.galenos.2022.2022.10.2

Bull Urooncol 2023;22(4):150-155

What is the Optimal Time Period for Postponing Nephrectomy in Patients with Renal Cell Carcinoma of Various Stages?

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Abstract

Objective: The coronavirus disease-2019 pandemic has shown us that postponing elective surgeries that include nephrectomy due to renal cell carcinomas (RCC) was undertaken by the physicians to use hospital facilities in a balanced way. However, both urologists and patients were concerned about postponements that may increase the risk of progression. To determine the optimal threshold of postponement time-period for surgery (PTP) and according to the clinical T stages in patients who underwent nephrectomy due to RCC, we used the Urologic Cancer Database-Kidney.

Materials and Methods: Patients who underwent detailed clinical T stage analysis with admission and surgery dates were included in the study. PTP was calculated using the dates of definitive preoperative diagnosis and surgery date. Recurrence, overall mortality (OM), recurrence-free survival, and overall survival (OS) were evaluated. The effects of PTP on oncological outcome according to tumor diameter and clinical T stages were also evaluated. We also analyzed the optimal cut-offs of PTP based on clinical T stages.

Results: Among 3.258 patients, in the evaluation of 2.946 clinically localized patients, PTP and tumor diameter were found to be important predictors of recurrence ($p=0.037$ and $p<0.001$). The optimal PTP of 30 days was found to be an important significant threshold time for the T1 stage and 20 days for T2-4 stage tumors. Patients with longer PTP according to the thresholds shown in this study had higher upstaging for clinical T1a, T2a, and T3 stages; higher recurrence rates for T1b and T2b stages; and higher OM for T2a and T3 tumors. The survival have also shown that more than 20 days of PTP affected OSs for clinical-stage T1 ($p=0.019$), T2 ($p=0.021$) and T3 ($p=0.007$) tumors.

Conclusions: All patients with tumors, including clinical T1 tumors, had worsening oncological results as the PTP increased (>20-30 days).

Keywords: Mortality, nephrectomy, overall survival, postponement time-period for surgery (PTP), recurrence free survival, renal cell carcinoma (RCC)

Cite this article as: Çelik S, Tinay İ, Sözen S, Özen H, Akdoğan B, Aslan G, Baltacı S, Süer E, Bayazıt Y, İzol V, Özkan TA, Gölkalp F, Members of Turkish Urooncology Association. What is the Optimal Time Period for Postponing Nephrectomy in Patients with Renal Cell Carcinoma of Various Stages? Bull Urooncol 2023;22(4):150-155.

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Received: 04.10.2022 **Accepted:** 11.12.2022

Introduction

The coronavirus disease-2019 (COVID-19) pandemic has shown us that postponing elective surgeries that include nephrectomy due to renal cell carcinomas (RCC) was undertaken by most of the physicians to use hospital facilities in a balanced way and to minimize the risk of contact. In this context, many recommendation guidelines on postponing elective surgeries have been published (1,2,3). Although some of these recommendations are related to the postponement of oncological surgeries such as RCC, which are tumors with a high risk of progression, it is predicted that the postponement of RCCs may lead to differences in survival over time. Therefore, determining the optimal postponement time-period for surgery (PTP) in kidney tumors is crucial in terms of putting the recommendations of treatment postponements on a scientific basis and minimizing patient victimization.

We revealed the optimal PTP and its thresholds according to the clinical T stages in patients who underwent radical nephrectomy (RN) or partial nephrectomy due to kidney tumors in the current study.

Materials and Methods

Completely anonymize kidney tumor data from the Urologic Cancer Database-Kidney (UroCaD-K), Turkish Urooncology Association (TUOA), were retrospectively reviewed in compliance with local regulations. Study data were collected and managed using research electronic data capture (REDCap) tools hosted at the TUOA (4,5).

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.

From the database, patients who were diagnosed with RCC after partial or RN between 2007 and 2019 were evaluated. Among the evaluated patients, those with complete data of radiological tumor diameter, clinical T stage, first admission (or first imaging) date, and operation date were included in the study. Clinical T stages of the patients were determined according to the maximum tumor diameter, which was measured on the images (computed tomography or magnetic resonance imaging) and noted in the database.

PTP was defined and calculated from the first clinical diagnosis of renal tumor to the operation date. From the follow-up data, the recurrence time (operation date to recurrence date), survival time (operation date to death date), and follow-up time (operation date to last follow-up date) were determined. Upstaging status (concordance between clinical and pathological stages), recurrence (detecting locally or metastatic new lesion on the images of patients in follow-up), local recurrence, metastasis, overall mortality (OM), and cancer-specific mortality (CSM) were evaluated. Survival data were also investigated as recurrence-free survival (RFS), overall survival (OS), and cancer-specific survival (CSS). The effects of PTP on oncological outcomes according to tumor diameter and clinical T stages and the cut-off values of PTP based on clinical T stages were aimed to determine.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Completely anonymized kidney tumors data of the UroCaD-K, TUOA was retrospectively reviewed in compliance with local regulations. Study data were collected and managed using REDCap tools hosted at TUOA. The project approval number of Turkish Urooncology Association: TUO-RE-20-01.

Statistical Analysis

For all statistical analyses, the Statistical Package for the Social Sciences (SPSS) version 22.0 was used. To determine the cut-off values of PTP affecting oncological outcomes such as upstaging, recurrence, and mortalities, receiver operating characteristic curve analysis was used. To detect the effects of PTP on oncological outcomes, the chi-square test was used based on detected cut-off values according to the clinical T stages. Kaplan-Meier survival analysis was used for RFS, OS, and CSS of PTP according to the clinical T stages. Statistical significance was set as a p-value less than 0.05 level.

Results

A total of 3258 patients were evaluated in this study. The clinical, pathological, and oncological data of all patients are given in Table 1. From the clinical data, 2.946 of the patients had clinically localized (clinical T1-2 stage) RCC, whereas locally invasive (clinical T3-4 stage) disease was observed in 312 of the patients.

In the evaluation of clinically localized patients, PTP and tumor diameter were found to be important predictors of recurrence. PTP was 56.1 days and 49.8 days in patients with no recurrence and recurrence, respectively ($p=0.037$). Similarly, tumor diameters were 7.3 cm and 5.1 cm, respectively ($p<0.001$).

There were 2.324 patients in the clinical T1 stage 622, 220, and 92 patients evaluated in the clinical T2, T3, and T4 stages, respectively. When we look at the oncological outcomes, upstaging was found in 10.7% (n=248) and 26.7% (n=166) of patients in clinical T1 and T2 stages ($p<0.001$). Recurrence was observed in 2.8% (n=64), 10.9% (n=68), 20% (n=44) and 23.9% (n=22) of patients with clinical T1, T2, T3, and T4 stages, respectively ($p<0.001$). Similarly, OM was observed in 2%, 5%, 6.8%, and 10.9% of T1, T2, T3 and T4 tumors, respectively ($p<0.001$).

Cut-off values of PTP according to the clinical T stages were determined based on the status of upstaging (to T3 or T4), recurrence, and OM. The cut-off values, sensitivities, and specificities of the PTP values that affect oncological outcomes according to the T stages are given in Table 2. In this context, PTP was found to be associated with upstaging (especially in T1a), recurrence (especially in T1b), and OM for the clinical T1 stage and with upstaging (especially in T2a) and OM (especially in T2a) for the T2 stage (Table 2). When we look at the cut-offs, 30 days was an important significant threshold for T1 stage

and it was detected to be as 20 days for T2-4 stage tumors. In addition, the oncological outcomes of the determined cut-offs based on T stages are given in Table 3. Upstaging was significantly higher above the PTP thresholds of T1a (8.9% vs. 5.5%, p=0.021), T2a (30% vs. 20.7%, p=0.026) and T3 (15.7% vs. 7.1%, p=0.044) than below the values. Recurrence was higher in T1b and T2b with above the PTP thresholds compared with below values (for T1b 5% vs. 2.6%, p=0.037 and for T2b 14.9% vs. 4.8%, p=0.021). OM was found to be higher in T2a and T3 tumors with above the PTP thresholds compared with below values (for T2a 7% vs. 2.3%, p=0.015 and for T3 9.7% vs. 2.4%, p=0.030) (Table 3).

When we look at the survivals, defined PTP of 20 days affected OSs for clinical stage T1 (p=0.019), T2 (p=0.021) and T3 (p=0.007) tumors (Figure 1). RFSs for clinical stage T1 (p=0.205), T2 (p=0.160) and T3 (p=0.003) tumors according to the cut-off 20 days of PTP are given in Figure 2. Among these, only the RFS of the clinical T3 stage was found to be significantly different according to the cut-off 20 days of PTP. However, in the subgroup of clinical T2a and T3a stage tumors, treatment in

Table 1. Clinical, pathological, and oncological data of the patients

		n=3258
Age (year)		57.2±12.2 (14-99)
Gender, n (%)	Female	1093 (33.5)
	Male	2148 (65.9)
BMI (kg/m^2)		27.7±4.7 (15.2-53.2)
Time to surgery (day)		49±96.7 (1-1830)
Mean radiological tumor diameter (cm)		5.5±3.3 (1-49)
Clinical T stage, n (%)	T1a	1265 (38.8)
	T1b	1059 (32.5)
	T2a	444 (13.6)
	T2b	178 (5.5)
	T3a	180 (5.5)
	T3b	39 (1.2)
	T3c	1 (0.03)
	T4	92 (2.8)
Mean pathological tumor diameter (cm)		5.9±3.5 (1-37)
Operation type, n (%)	Partial nephrectomy	1328 (40.8)
	Radical nephrectomy	1894 (58.1)
Operation method, n (%)	Open	2341 (71.9)
	Laparoscopic	840 (25.8)
Histopathology of the tumor, n (%)	Clear cell RCC	2225 (68.3)
	Papillary RCC	509 (15.6)
	Chromophobe RCC	335 (10.3)
	Unclassified RCC	80 (2.5)
	Other subtypes	109 (3.3)
Upstage to T3 or T4, n (%)		441 (13.5)
Fuhrman grade (n=2327)	1	263 (8.1)
	2	1193 (36.6)
	3	646 (19.8)
	4	225 (6.9)
Recurrence, n (%)		198 (6.1)
Local recurrence, n (%)		75 (2.3)
Metastasis, n (%)		214 (6.6)
Overall mortality, n (%)		103 (3.2)
Cancer-specific mortality, n (%)		33 (1)
Mean follow-up time (month)		25.4±31 (1-165)

BMI: Body mass index, RCC: Renal cell carcinomas

<20 days affected RFS compared to more than 20 days (for T2a tumors 49±13.5 months vs 16.2±5.1 months, p=0.042, and for T3a tumors 20.4±8.1 months vs 2±1.4, p=0.013).

Discussion

In summary we evaluated 3.258 patients and found that PTP and tumor diameter were the most important predictive factors for recurrence in 2.946 clinically localized patients. PTP was also found to be associated with pathological upstage for clinical T1a and T2a stage kidney tumors. It was also associated with recurrence for the clinical substage of T1b tumors and OM for T2a stage tumors.

These two factors (stage and PTP) that we identified in our study are also emphasized in previous studies (6,7,8,9). In some of these studies, the optimal PTP stated that surgery should be considered within 1 month for kidney tumors (6,7). In one of these cases, the necessity of performing surgery has been defined and stated within 2 and 4 weeks after the diagnosis of kidney tumors in radiological imaging (7). However, with the postponement of RCCs during the COVID-19 pandemic, PTP and its possible oncological effects have come to the fore again. In parallel to the postponements within the last year, another previous study stated that median PTPs were 84 and 386 days for early and delayed times for surgery of small renal masses (≤4 cm tumors). In that study, 401 (81%) and 94 (19%) patients

Table 2. Cut-off days of PTP affecting oncological outcomes in clinically localized kidney tumors (clinical stage T1-2 tumors)

Clinical T stage	Oncological outcomes	n (%)	Cut-off time (day)	Sensitivity	Specificity	AUC	p-value
T1 (n=2323)	Upstage to T3	248 (10.7)	30	56%	51%	0.541	0.037
	Recurrence	64 (2.8)	28	69%	53%	0.605	0.004
	Overall mortality	47 (2)	29	66%	51%	0.595	0.026
T1a (n=1264)	Upstage to T3	92 (7.3)	37	59.8%	57%	0.590	0.004
T1b (n=1059)	Recurrence	39 (3.7)	30	64%	54%	0.625	0.008
T2 (n=622)	Upstage to T3	166 (26.7)	20	57%	50%	0.560	0.022
	Overall mortality	31 (5)	20	71%	51%	0.629	0.015
T2a (n=444)	Upstage to T3	113 (25.4)	20	60.2%	52%	0.568	0.032
	Overall mortality	21 (4.7)	20	76.2%	50.1%	0.660	0.013
T2b (n=178)	Recurrence	18 (10.1)	24	77.8%	56.2%	0.688	0.009

ROC curve analysis was performed for all predictions of PTP (day) and the determination of cut-off times. PTP: Postponement time-period for surgery, ROC: Receiver operating characteristic, AUC: Area under the curve

Table 3. Oncological outcomes (upstage to T3, recurrence and overall mortality) of clinical T stages according to 30 and 20 PTP cutoff days

Clinical T stage	Cut-off time (day)	n	Upstage to T3 or T4		Recurrence		Overall mortality	
			n (%)	p-value	n (%)	p-value	n (%)	p-value
T1 (n=2323)	≤30	1193	113 (9.5)	0.054	24 (2)	0.025	22 (1.8)	0.531
	>30	1130	135 (11.9)		40 (3.5)		25 (2.2)	
T1a (n=1264)	≤30	613	34 (5.5)	0.021	9 (1.5)	0.208	9 (1.5)	0.755
	>30	651	58 (8.9)		16 (2.5)		11 (1.7)	
T1b (n=1059)	≤30	580	79 (13.6)	0.262	15 (2.6)	0.037	15 (2.2)	0.484
	>30	479	77 (16.1)		24 (5)		14 (2.9)	
T2 (n=622)	≤20	301	71 (23.6)	0.091	28 (9.3)	0.207	9 (3)	0.027
	>20	321	95 (29.6)		40 (12.5)		22 (6.9)	
T2a (n=444)	≤20	217	45 (20.7)	0.026	24 (11.1)	0.896	5 (2,3)	0.015
	>20	227	68 (30)		26 (11.5)		16 (7)	
T2b (n=178)	≤20	84	26 (31)	0.745	4 (4.8)	0.021	4 (4.8)	0.639
	>20	94	27 (28.7)		14 (14.9)		6 (6.4)	
T3 (n=220)	≤20	85	6 (7.1)	0.044	18 (21.2)	0.729	2 (2.4)	0.030
	>20	134	21 (15.7)		26 (19.4)		13 (9.7)	
T4 (n=92)	≤20	31	-	-	4 (12.9)	0.063	2 (6.5)	0.277
	>20	61	-		18 (29.5)		8 (13.1)	

The chi-square test was performed for the comparison of PTP levels according to the PTP cut-off times in all clinical T stages. PTP: Postponement time-period for surgery

underwent early and delayed surgery (p<0.001) and it was stated that delayed surgery was not associated with adverse pathology (p=0.8) (8). In a recent study, delayed (>6 months) nephrectomy was compared with the immediate (<1 month) approach for small renal masses (clinical T1a tumors) in 14.677 patients, and comparable long-term OS was detected between immediate nephrectomy and the delayed approach for clinical T1a renal cell carcinoma (9). On the other hand, in the analysis of 6.237 pathological stage T1a tumors, delayed nephrectomy (>3 months) was associated with a higher risk of CSM in univariate analysis [hazard ratio (HR): 2.07, confidence interval: 1.58-2.72; p<0.001], but it has not been detected in multivariate analysis (10). In another study, after determining the threshold of PTP as 3 months, a longer PTP was found to be associated with worse OS compared with a shorter PTP (HR:1.17, p=0.0002). Gender, tumor size, and tumor histology were also determined as factors that possibly affect disease upstaging, recurrence and CSS. The most common causes have been defined for delaying more than 3 months as treatments of comorbidities and clinical evaluation of patients (11). In a recent systematic review and meta-analysis for the COVID-19 pandemic, in the evaluation of delayed surgery for localized renal cell carcinoma, there has not been indicated any sufficient evidence to support the approach that delayed surgery is safe for localized RCCs (12).

However, these studies show that there are unclear findings between recent results and previous studies. Therefore, we investigated PTP and its possible oncological effects. It was also aimed to determine the thresholds of PTP according to the clinical T stages in the study. In this context, we detected thresholds of 20 and 30 days for clinical T1 and T2-4 tumors, respectively. When we look at the thresholds, pathological upstaging rates were detected to be associated with more than 30 days PTP for clinical T1a stage tumors (8.9% vs. 5.5%, p=0.021) and also more than 20 days PTP for clinical T2a and T3a stage tumors (30% vs. 20.7%, p=0.026 and 15.7% vs. 7.1%, p=0.044; respectively). On the other hand, disease recurrences were found to be higher in clinical T1b and T2b stage tumors with longer PTP (5% vs. 2.6%, p=0.037 and 14.9% vs. 4.8%, p=0.021; respectively). In addition, we also detected that OM was associated with longer PTP in each clinical T2a and T3 stage tumor (7% vs. 2.3%, p=0.015 and 9.7% vs. 2.4%, p=0.030; respectively).

In the evaluation of the threshold of 20 days PTP in all stages, we found that OS was affected more than 20 days PTP in all T1, T2, and T3 stage tumors. On the other hand, among the RFS findings, we found that only the clinical T3 stage was significantly higher in <20 days PTP. However, when we look at the subgroups, especially in the subgroup of the clinical T2a and

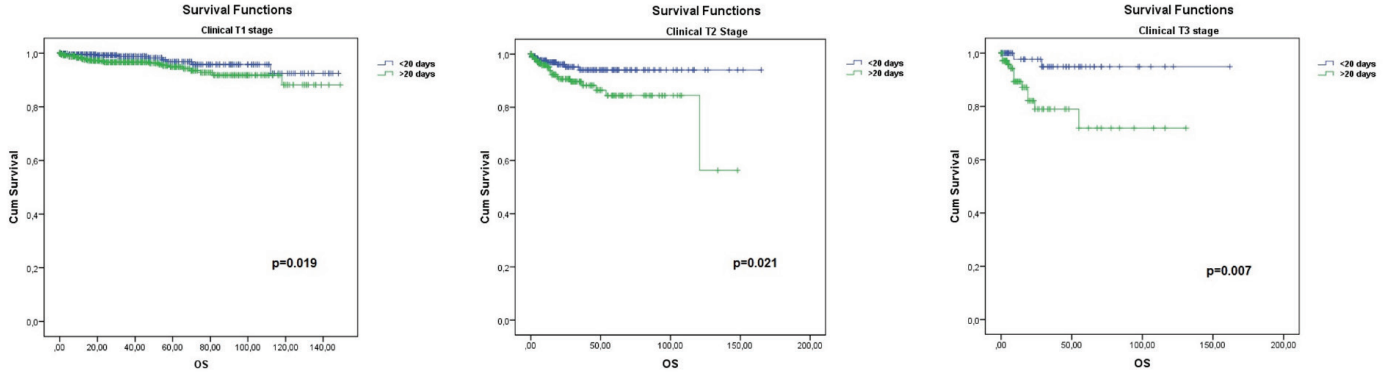

Figure 1. Overall survival plots for clinical stage T1, T2, and T3 tumors according to the cut-off 20 days of PTP

PTP: Postponement time-period for surgery

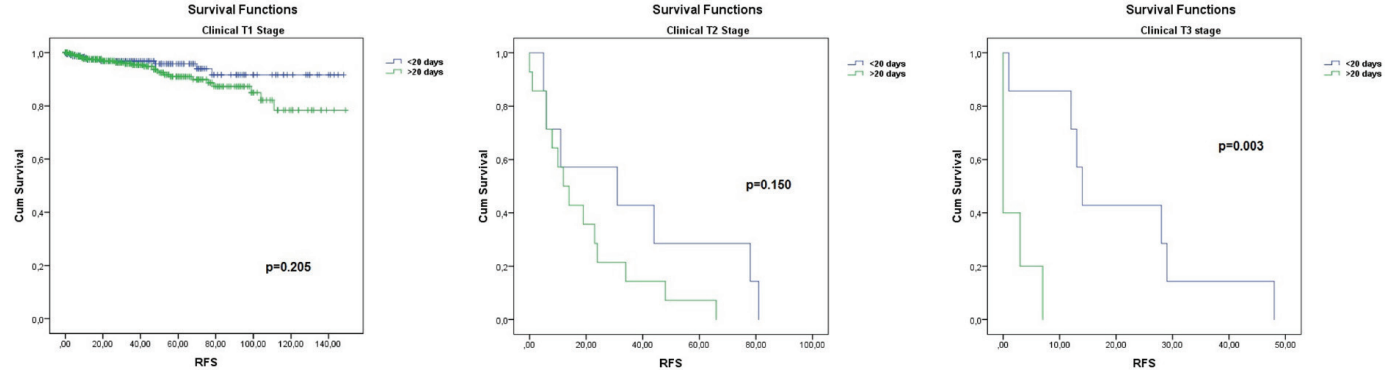

Figure 2. Recurrence-free survival plots for clinical stage T1, T2, and T3 tumors according to a cut-off 20 days of PTP

PTP: Postponement time-period for surgery

T3a stages, <20 days PTP affected RFS compared to more than 20 days PTP (49±13.5 months vs. 16.2±5.1 months, p=0.042, and 20.4±8.1 months vs 2±1.4, p=0.013; respectively).

Study Limitations

The major limitations of our study are its retrospective design and nature. Another important limitation is that it excludes any patients from the period of the COVID-19 pandemic. Although there were no centralized radiological and pathological examinations, the use of a multicentric database from the nationwide respective centers and long-term data acquisition reflect the real-life data for the current study.

Conclusion

All patients with tumors, including clinical T1 tumors, had worsening oncological results as the PTP increased (>20-30 days). These worsening were reflected as only upstaging in clinical T1a tumors, whereas, as increasing of recurrence in clinical T1b tumors, upstaging and increasing OM in clinical T2a tumors and increasing recurrence in clinical T2b tumors. For clinically local invasive tumors, the worsening has been reflected as upstaging, increasing OM, and decreasing OS and RFS, especially in clinical T3 tumors. In conclusion, postponing surgery even for a relatively short period due to the pandemic in patients with kidney tumors may cause worse oncological outcomes. Therefore, according to the results derived from our database with a substantial number of patients, we strongly recommend that these patients undergo surgery as soon as possible.

Acknowledgements

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

Contribution: We acknowledge for their contribution of data collection to Members of Turkish Urooncology Association. Talha Müezzinoğlu, Ahmet Nihat Karakoyunlu, Ozan Bozkurt, Özdal Dillioğlugil, Levent Türkeri, Hayrettin Şahin, Gökhan Toktaş, Saadettin Eskiçorapçı, Ender Özden, Barış Kuzgunbay.

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

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

Ethics

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

Informed Consent: Database report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.T., S.S., H.Ö., B.A., G.A., S.B., E.S., Y.B., V.İ., Concept: S.Ç., İ.T., Design: S.Ç., İ.T., Data Collection or Processing: S.Ç., İ.T., S.S., H.Ö., B.A., G.A., S.B., E.S., Y.B., V.İ., Analysis or Interpretation: S.Ç., İ.T., T.A.Ö., F.G., Literature Search: S.Ç., Writing: S.Ç., İ.T.

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Original Article

DOI: 10.4274/uob.galenos.2023.2022.12.2

Bull Urooncol 2023;22(4):156-160

Are the Testicular Self-examination Videos on YouTube Misleading?

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Abstract

Objective: For early diagnosis, testicular self-examination (TSE) is crucial. Videos of TSE have increased on social media platforms. In this study, we assessed the reliability of TSE videos on YouTube.

Materials and Methods: The keywords including "testicular self-examination", and "testis mass" were used for searching on YouTube (http://www.youtube.com). A total of 1311 videos were investigated, and a total of 207 videos were included in the study. Shorter videos (below 1.30 minutes) and irrelevant videos were not included in the study.

Results: The median number of views was 1846 (interquartile range: 406-30310). Most of the videos were uploaded by profit organizations (57.5%). The DISCERN score and Global Quality Score (GQS) were significantly higher in the health professional group (p=0.003, and p<0.001, respectively). In addition, the degree of information was generally low in both groups. However, misinformation was statistically lower in the health professional group.

Conclusion: YouTube is a popular platform for promoting videos about TSE. In particular, not checking health-related videos while uploading causes poor quality videos to be uploaded. Videos of TSE have a low degree of misinformation. However, the DISCERN and GQS were also low.

Keywords: Testicular cancer, diagnosis, YouTube, DISCERN, JAMA

Introduction

Testicular cancer (TC) incidence peaks on the 3rd-4th decades, and it represents 5% of the urological malignancies is 5% (1). The disease cure rates are high, and the overall survival rate is over 95% (2). In addition to the rising TC incidence, the current literature showed that higher than %85 of TC deaths occur among the patients age below 50 (1). As a result, the early diagnosis of TC, which can be acquired via testicular self-examination (TSE) and awareness, becomes vital (3,4). The data regarding the TSE and awareness of TC have increased dramatically on social media platforms in the last two decades. However, the source of information and content for various urological diseases on social media platforms are inadequate (5,6).

Social media platforms vary in many fields, and the usage of social media platforms increased dramatically, especially after pandemic restrictions (7). Additionally, through technological advantages, social media platforms and video sharing applications can be used on mobile devices, and this situation provides a limitless source of information to social media consumers (8). YouTube is one of the most popular video streaming platforms and is used as an educational source for medical information and healthcare services (8). Published papers have demonstrated that videos on YouTube contain complex information for average users or sometimes misinformation due to unsupervised uploading and streaming processes (9,10). Moreover, a novel study that assessed misinformation in TC on YouTube showed that most of the content is of low quality and there is a risk of exposure to misinformation (11).

In this study, we assessed the reliability and quality of TSE videos on YouTube.

Materials and Methods

Data Search and Inclusion Criteria

A YouTube search was conducted using the keywords "testicular self-examination" and "testis mass" (http://www.youtube.com). Irrelevant videos, shorter than 1.30 minutes, or produced

Cite this article as: Gökalp F, Akarken İ. Are the Testicular Self-examination Videos on YouTube Misleading? Bull Urooncol 2023;22(4):156-160.

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Received: 26.12.2022 **Accepted:** 20.03.2023

in a language other than English were excluded from the study. A total of 207 of the 1311 movies that were examined were included in the study (Figure 1).

Scoring Systems and Data

The videos were assessed by independent surgeons specializing in urological oncology. In the event of inconsistent evaluation between surgeons when results do not match, an additional urologist assessed the recordings. The viewer reactions were also evaluated by tracking total views, views per month, and video likes and dislikes. Based on the source of upload, the data were separated into two groups: Group 1: healthcare professionals including doctors, nurses, academic publications, and academic or nonprofit medical professionals, whereas group 2 comprised commercial companies or for-profit organizations. The degree of misinformation was determined using the most recent evidence on TC as stated by the guidelines (12). Additionally, we used a Likert scale of 1 to 5 to score (none, low, moderate, high, and excessive) the extent of disinformation in the videos (13). The verified DISCERN quality criteria were used to analyze all the videos.

Individuals without specialized knowledge can utilize DISCERN, a standardized index that evaluates the quality of consumer health information regarding treatment options. The items comprise the questionnaire (total 15), in addition to an overall quality assessment. Each item represents a distinct quality criterion, graded from 1 to 5 points (1-2 points: low, 3 points: moderate, and 4-5 points: good quality). As a result, a total score of 80 is possible, with higher scores signifying higher quality. Although not all of the videos were directly related to treatment options, they were scored using all relevant factors and given an overall quality grade for the purposes of this study. A five-point Global Quality Score (GQS) was used to assess the overall quality of the videos (1 being bad quality, and 5 being great quality). This instrument assesses a video's overall content flow and degree of accessibility (14).

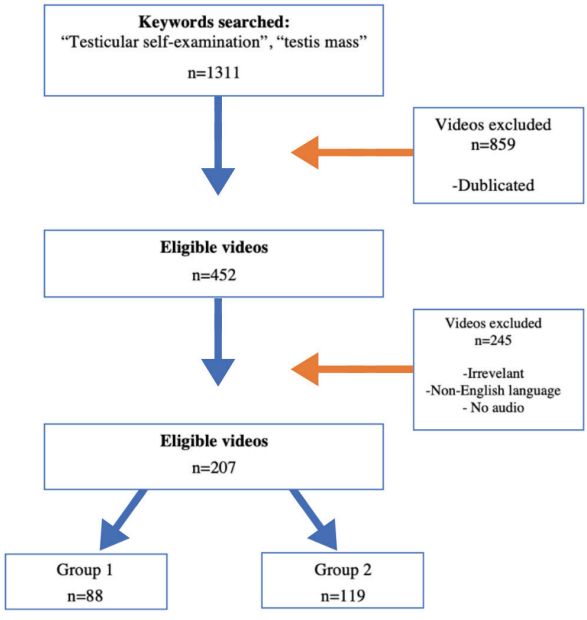

Figure 1. Selection of eligible videos from YouTube for the study

JAMA is a four-point rating system that assesses whether the video clearly identifies the authors, institutions, references, and sources; whether copyright information is present; whether there is an obvious conflict of interest; and whether the uploading and publication dates are provided (15).

Statistical Analysis

The Statistical Package for the Social Sciences version 25.0 software on MacOS (SPSS Inc.,) was used for analysis. To determine normalization, the Shapiro-Wilk test was performed. Continuous variables are given as median and interquartile range (IQR). The categorical variables are given as count and frequency. The chi-square test was used to compare the categorical variables. The Mann-Whitney U test was used for comparing the continuous variables. The Spearman test was used for correlation analysis. Inter-rater agreement was evaluated with the Kappa coefficient. The statistical significance level was set at $p<0.05$.

Results

A total of 207 videos were included in the study. The median length of videos was 222 min. (IQR: 123-374). The median number of views was 1846 (IQR: 406-30310). Most of the videos were uploaded by profit organizations (57.5%) (Table 1). Detailed information about TC was provided in only 40.6% of the total videos. The commercial bias was 29.5%,

Table 1. General characteristic of videos

		Value
Video length (min.)[a]		222 (123-374)
Number of views[a]		1846 (406-30310)
Number of comments[a]		0 (0-11)
Number of like[a]		7 (1-93)
Upload by[b]	Healthcare professional	88 (42.5%)
	Profit organization	119 (57.5%)
Detailed information[b]	Absent	123 (59.4%)
	Present	84 (40.6%)
Commercial bias[b]	Absent	146 (70.5%)
	Present	61 (29.5%)
DISCERN score[a]		35.00 (27.00-44.00)
Degree of misinformation[b]	None	26 (57.5%)
	Low	62 (30.4%)
	Moderate	82 (6.9%)
	High	15 (5.3%)
	Extreme	1 (0.0%)
GQS[b]	GQS1	52 (24.2%)
	GQS2	69 (33.33%)
	GQS3	65 (31.4%)
	GQS4	20 (9.7%)
	GQS5	1 (0.5%)

[a]Data expressed as median and range, [b]Data expressed as numbers and percentages, GQS: Global Quality Score

and the degree of misinformation was generally absent or low (57.5% and 30.4%, respectively). However, the GQS was generally lower than 3 scores. When the distribution of the videos by years was assessed in particular, the upload rate peaked in 2018, but gradually lost interest and the number of uploaded videos decreased (Figure 2).

The median video length was similar between the groups (p=0.577). The median number of views, number of comments, and the median number of likes were similar between the groups (p=0.212, p=0.119, and p=0.503, respectively) (Table 2). However, the DISCERN score was significantly higher in group 1 (p =0.003). Additionally, the degree of information was generally low in both groups. However, misinformation was statistically lower in group 1 (p<0.001) and the GQS was significantly higher in group 1 (p<0.001). The JAMA score was significantly higher in group 1 (p=0.002), but there was a statistically significant difference in the JAMA score subgroup (p=0.063).

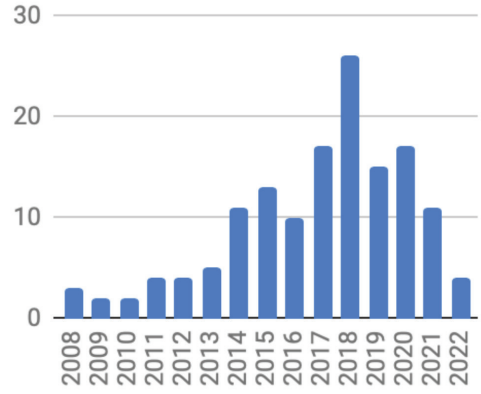

Figure 2. Video upload rate in years

Discussion

Our study showed that TSE is an attractive area for social media. Although it is crucial to protect public health, more videos prepared by health professionals are needed in this field. With technological advancements, the use of smart phones and social media platforms are spreading widely. People seeking health information on the internet have increased recently (14). However, increasing health information on the internet does not indicate that people have obtained the right information or are able to read or interpret its content (15). YouTube is a common platform for seeking or learning health information and has gained popularity on the internet (16). However, many studies have shown that YouTube contains many low-quality or misinformative videos (6,9,11,17). A novel mini-review showed that misinformation was highest in prostate cancer videos (70%), followed by kidney cancer (30%), bladder cancer, and TC (20% each) (5). The literature has shown that kidney cancer videos were generally reliable (mean DISCERN score of 3.9) or moderate quality (mean GQS score of 3.7), and prostate cancer videos (mean DISCERN score of 3.0) (18,19). In addition, Duran and Kizilkan (11) evaluated the reliability of videos about TC on YouTube and showed that most of the videos were uploaded by non-healthcare professionals, and the JAMA score, DISCERN score, and GQS were statistically significantly

Table 2. Comparison of video scores between the groups

		Group 1 (n=88)	Group 2 (n=119)	p-value
Video length (min.)[a]		232.00 (132.00-356.00)	208.00 (120.00-401.00)	0.577
Number of views[a]		1447.00 (464.00-5703.00)	2161 (401.00-57397.00)	0.212
Number of comments[a]		0.00 (0.00-5.00)	0.00 (0.00-20.00)	0.119
Like[a]		6.00 (2.00-35.00)	15.00 (1.00-182.00)	0.503
Discern total[a]		38.00 (27.00-50.00)	34.00 (25.00-40.00)	0.003*
Degree of misinformation[b]	**None**	17 (22.4%)	9 (8.2%)	<0.001#
	Low	31(40.8%)	31 (28.3%)	
	Moderate	27 (35.5%)	55 (50.0%)	
	High	1 (1.3%)	14 (12.7%)	
	Extreme	0 (0.0%)	1 (0.9%)	
JAMA score[a]		0.00 (0.00-1.00)	0.00 (0.00-0.00)	0.007*
JAMA group[b]	**JAMA <2**	82 (93.2%)	117 (98.3%)	0.063
	JAMA >2	6 (6.8%)	2 (1.7%)	
GQS[b]	**Very low**	9.0 (10.2%)	43.0 (36.1%)	<0.001#
	Low	29.0 (33.0%)	40.0 (33.6%)	
	Moderate	36.0 (40.9%)	29.0 (24.4%)	
	Good	13.0 (14.8%)	7.0 (5.9%)	
	Very good	1.0 (1.1%)	0.0 (0.0%)	

[a]Data expressed as median and range, [b]Data expressed as numbers and percentages, *The Mann-Whitney U test was used, #Chi-square test was used, GQS: Global Quality Score

higher in videos uploaded by healthcare professionals (1.59, 2.13 and 2.61; p<0.001, p<0.001 and p<0.001 respectively). Similar to these results, our study demonstrated that the degree of misinformation was generally low; however, similar to the literature, DISCERN and GQS scores were also lower than 3 points. Comparable to the literature, a study by Esen et al. (20) assessed breast self-examination videos on YouTube and showed that 33.3% of the useful videos were uploaded by healthcare professionals. The GQS, reliability, and comprehensiveness scores were significantly higher among healthcare professionals (p<0.05 for each). In another study which assessed the reliability and quality of YouTube videos related to TSE demonstrated that less than 25% of useful videos were uploaded by healthcare professionals and also pointed that GQS was significantly lower in healthcare professionals when compared to the stand-alone health information websites (p<0.001) (17). Similarly, our study showed that DISCERN, JAMA, and GQS were lower in both groups and these scores were significantly lower in videos uploaded by profit organizations.

TSE is a key point for the early diagnosis of TC and seems to be an easy method to learn and apply. There are many useful tools such as realistic models, well-edited step-by-step instructional videos, and some cards used in the videos. However, not providing sufficient information about TSE may actually cause this method to be considered less important than desired. In addition, our study showed that the video upload rate has decreased after the recent pandemic. Unfortunately, this may lead to a gradual decrease in the importance and habit of TSE. Additionally, an early review, which assessed intervention TSE studies, pointed out that a knowledge gap regarding awareness and the efficacy of preventative behavior is brought on by the general population's lack of access to information on the cancer's occurrence, prevalence, etiology, treatment, and prevention strategies. Moreover, the authors summarized that there was a significant increase in pre- and posttest reported TSE among the experimental group. However, three of 10 participants did not meet the statistically sufficient criteria (21). On the other side of the coin, all of this also shows how difficult it is for this subject to learn or acquire a habit. Again, in the first evaluation, the fact that more than half of the videos were completely irrelevant or inadequate also prevented people from reaching the truth. Furthermore, distorting the subject with prank videos, even if they are few in number, may give the audience false impressions about the disease's importance. Here again, we healthcare professionals play an important role to play, and we should promote this important issue and upload quality videos on social media platforms.

Study Limitations

Our study has some limitations. Videos from other social media platforms such as Vimeo or TikTok or websites of academic institutes were not included. However, YouTube is still one of the most popular video sharing platforms for professionals and individuals who seek health information. Another important point is that the videos were not assessed with other scoring systems such as Patient Education Materials Assessment Tool. However, there is still no consensus on scoring systems to evaluate the health information videos.

Conclusion

YouTube has become a popular platform for individuals seeking health information. It is considered to be an appropriate tool for explaining and disseminating TSE. The majority of videos were uploaded by non-healthcare professionals, and even though the misinformation rating was low, the videos also had low global quality and DISCERN scores. Health professionals should upload more videos so that people can access accurate and quality information on this important issue.

Acknowledgements

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

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

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

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

Ethics

Ethics Committee Approval: This study does not require an ethics committee.

Informed Consent: This study does not require patient consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.G., İ.A., Design: F.G., İ.A., Data Collection or Processing: F.G., Literature Search: F.G., İ.A., Writing: F.G., İ.A.

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Case Report

DOI: 10.4274/uob.galenos.2023.2023.4.2

Bull Urooncol 2023;22(4):161-165

Urachal Masses Detected in Our Clinic in the Last Year: Reports of Four Cases and Review of the Literature

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Abstract

Urachal tumors are a rare form of malignancy with poor prognostic features, accounting for only 0.5-2% of bladder-related malignancies and 0.01% of all cancers in adults. The most common presenting symptoms are hematuria and a palpable suprapubic mass. This study presents a case series of four patients with urachal masses, including a 54-year-old woman with frequent urination, a 78-year-old man with urgency, a 41-year-old woman with suprapubic pain, and a 43-year-old woman with hematuria. Over the past year, all four masses were detected and underwent cystoscopic examinations and surgical resections. Only one of the four cases was benign, whereas the others were malignant. The objective of this study was to evaluate patients with urachal masses using clinical, radiological, and histopathological approaches to raise awareness about the diagnosis, treatment, and follow-up of these rare tumors and to contribute to the current literature on this topic.

Keywords: Hematuria, partial cystectomy, suprapubic pain, urachal mass

Introduction

The urachus is an embryonic remnant that forms a fibrous band connecting the fetal bladder to the allantois, which is later defined as the umbilical cord in adulthood. Failure in the closure process can lead to cell proliferation, potentially resulting in malignancy. Urachal carcinomas, comprising only 0.01% of all malignancies but accounting for 0.17-0.34% of bladder tumors, are non-urothelial in origin and exceptionally rare (1,2). While urachal carcinomas are more commonly observed in males, they are typically diagnosed in the fifth to sixth decades of life (3). These carcinomas are generally characterized by a poor prognosis and aggressive behavior. In the largest series reported to date, a 5-year overall survival rate of approximately 50% and a 5-year cancer-specific survival rate of approximately 35% have been documented (4). Hematuria is the most frequently observed symptom; however, by the time this symptom manifest, the disease has usually progressed (5). Because of the frequent invasion of the bladder from the midline or dome, urachal carcinomas are often asymptomatic in the early stages and are commonly detected in advanced stages (6).

In this study, we present four patients with urachal masses. By examining this highly uncommon condition clinically, radiologically, and histopathologically, we aim to advance its diagnosis and treatment.

Case Reports

Case 1

A 54-year-old female patient was admitted to our clinic with complaints of frequent urination and burning during urination. No pathological findings were detected in the physical examination. The results of laboratory tests (hemogram, complete urinalysis, liver and kidney function tests) were observed within normal reference ranges. However, because of abdominopelvic ultrasonography (USG) performed on the patient, we decided to perform a cross-sectional examination of

Cite this article as: Nebioğlu A, Doruk HE, Akbay E, Aykıroğlu NG, Yuyucu Karabulut Y, Yüksek HH. Urachal Masses Detected in Our Clinic in the Last Year: Reports of Four Cases and Review of the Literature. Bull Urooncol 2023;22(4):161-165.

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Received: 20.04.2023 **Accepted:** 06.08.2023

the patient after a 30x25 mm anechoic structure was observed in the superficial neighborhood of the bladder, which may be associated with the bladder. Contrast-enhanced abdominopelvic computed tomography (CT) revealed that the nodular lesion, approximately 30x26 mm in size in the anterior part of the bladder, containing areas of calcification and having a lobulated contour in places, might be a urachal mass (Figure 1). Pelvic diffusion magnetic resonance imaging was additionally applied to the patient, and it was reported that the 30x35 mm sized nodular lesion with peripheral enhancement was consistent with the urachal mass, which was heterogeneously hyperintense on T2W examination and hypointense on T1W examination (Figure 2).

Subsequently, cystoscopy was performed on the patient, and a tumoral formation with a hyperemic, irregular border, and solid appearance was observed in an area of approximately 3 cm on the anterior wall of the bladder. Therefore, pelvic exploration was performed for the patient. Intraperitoneal pelvic exploration was performed using a subumbilical median incision. On exploration, a mass invading the anterior wall of the bladder from the umbilicus level was observed, and the patient underwent radical mass excision and partial cystectomy, considering the surgical margins of the tumor. Histopathological examination of the excised mass revealed mucinous adenocarcinoma (Figure 3). After the operation, the patient was discharged on postoperative day 5 with full recovery.

Case 2

A 78-year-old male patient was admitted to our clinic with complaints of frequent urination and urgency. Physical examination revealed a suprapubic palpable mass. Because of laboratory examinations, no abnormal pathological findings were detected except for microscopic hematuria (328 erythrocytes in each field) in the complete urinalysis. Because of non-contrast abdominopelvic CT, a mass lesion was detected in the anterior superior of the bladder, in close relationship with the right rectus abdominis muscle, measuring 7x6.5 cm in the widest part, with a multiloculated appearance and thin calcifications on the walls, and it was interpreted that it might be a urachal mass (Figure 4).

Then, cystoscopy was performed on the patient, and a tumoral formation with irregular borders was observed in the area of approximately 4 cm at the junction of the anterior wall of the bladder opposite wall, with a hyperemic and solid appearance around it, and it was decided to perform pelvic exploration for the patient. Intraperitoneal pelvic exploration was performed using a subumbilical median incision. On exploration, a giant mass invading from the umbilicus to the anterior wall of the bladder was observed, and the patient underwent radical mass excision and partial cystectomy, preserving the surgical margins

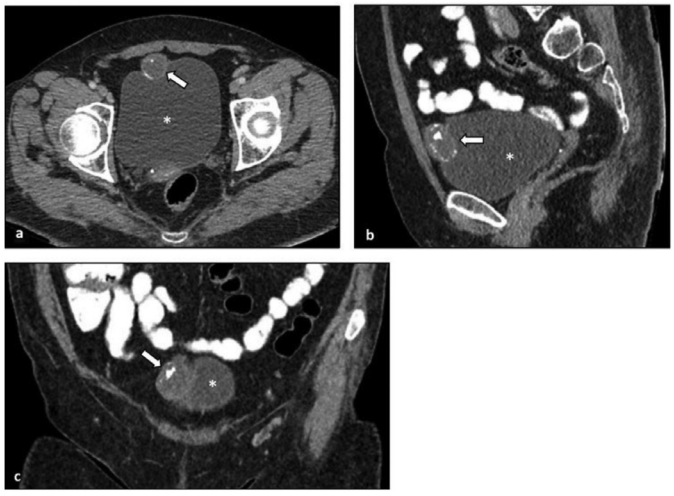

Figure 1. Axial **(a)**, sagittal **(b)**, and coronal **(c)** intravenous contrast-enhanced CT sections show a nodular lesion (arrows) with a diameter of approximately 30 mm, which extends toward the prevesical fat tissue and the anterior abdominal wall, contains coarse and curvilinear calcifications, and appears hypodense, most likely due to the presence of mucinous content. The lesion (*) is noted to be of similar density to the bladder

CT: Computed tomography

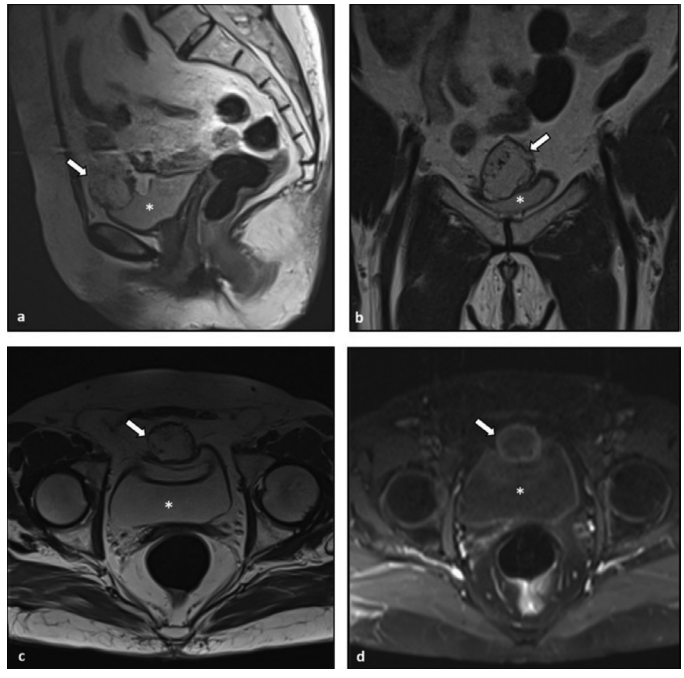

Figure 2. In the anterior segment of the bladder, a nodular lesion (arrows) with a diameter of approximately 35 mm is observed on T2-weighted sagittal **(a)**, coronal **(b)**, and axial **(c)** MRI as hyperintense and fat-suppressed. On T1-weighted intravenous contrast-enhanced axial MRI, the lesion appeared as a peripherally ring-enhancing hypointense nodule. Note that the lesion (*) has a similar signal intensity to the bladder

MRI: Magnetic resonance imaging

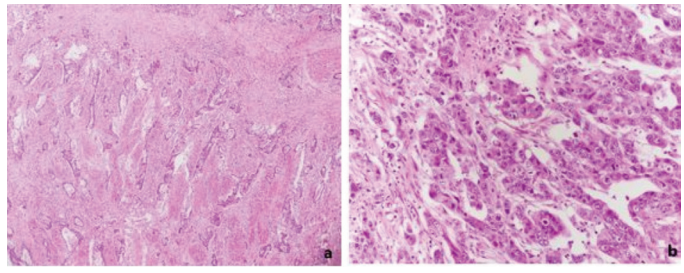

Figure 3. Tumor development composed of large hyperchromatic nuclei with prominent nucleoli and atypical epithelial cells, some of which exhibit a cribriform pattern, is observed on a fibrotic background (a; H&E; x40, b; x400)

of the tumor. Histopathological examination of the excised mass revealed mucinous adenocarcinoma (Figure 5). After the operation, the patient was discharged on postoperative day 7 with full recovery.

Case 3

A 41-year-old female patient was admitted to our clinic with complaints of suprapubic pain and burning on urination. Physical examination revealed a suprapubic palpable mass. The results of laboratory tests (hemogram, complete urinalysis, liver and kidney function tests) were observed within normal reference ranges. However, because of abdominopelvic USG performed on the patient, after a 62 mm anechoic structure was observed in the superficial neighborhood of the bladder, which may be associated with the bladder, it was decided to perform a cross-sectional examination of the patient. As a result of contrast-enhanced abdominopelvic CT, a heterogeneous contrast-enhancing soft tissue mass lesion with dimensions of 65x25 mm at its widest point, extending from the anterior wall of the bladder to the inside of the abdomen, invading the muscles of the anterior abdominal wall was detected, and it was interpreted that it might be a urachal mass (Figure 6).

Then, cystoscopy was performed on the patient, and a tumoral formation with a solid and hyperemic appearance was observed in an area of approximately 5 cm on the anterior wall of the bladder, and pelvic exploration was performed for the patient. Intraperitoneal pelvic exploration was performed using a subumbilical median incision. On exploration, a giant mass invading from the umbilicus to the anterior wall of the bladder was observed, and the patient underwent radical mass excision and partial cystectomy, preserving the surgical margins of the tumor. Histopathological examination of the excised mass revealed fibroblastic proliferation (Figure 7). After the operation, the patient was discharged on postoperative day 3 with full recovery.

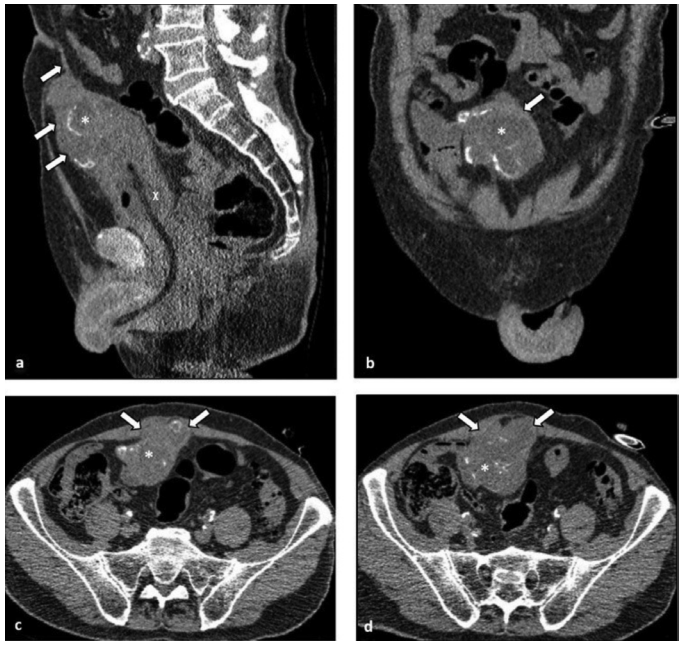

Figure 4. On sagittal **(a)**, coronal **(b)**, and axial (**c, d**) non-contrast CT images, a large solid mass (arrows) is observed extending from the anterosuperior segment of the bladder toward the anterior abdominal wall and umbilicus, containing curvilinear calcifications and hypodense areas (*) most likely corresponding to mucinous content, with indistinct borders from the bladder walls.

x: Catheter balloon, CT: Computed tomography

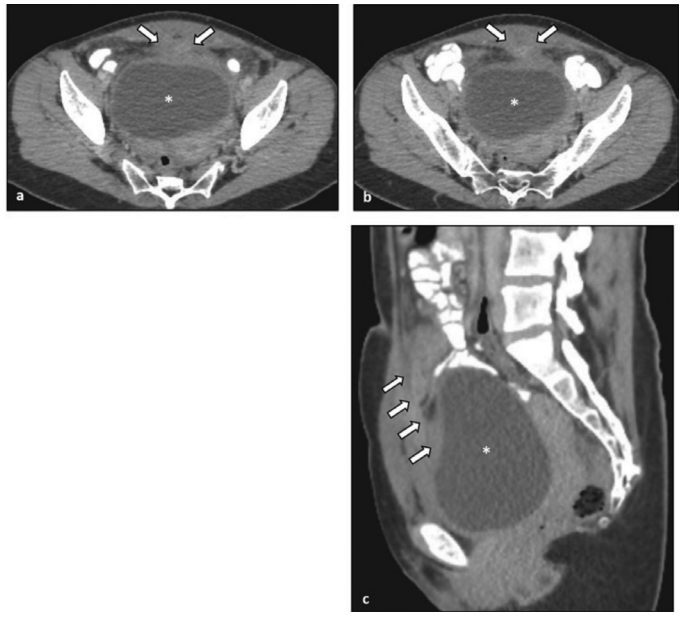

Figure 6. On axial (**a, b**) and sagittal **(c)** intravenous contrast-enhanced CT images passing through two different levels, a thick-walled appearance is seen in the anterior segment of the bladder (*), with a heterogeneous contrast-enhancing mass lesion (arrows) of approximately 60x20 mm size that cannot be clearly distinguished from the bladder wall and extends cranially toward the anterior abdominal wall, with an invasive appearance into the rectus muscle, without a distinctive shape

CT: Computed tomography

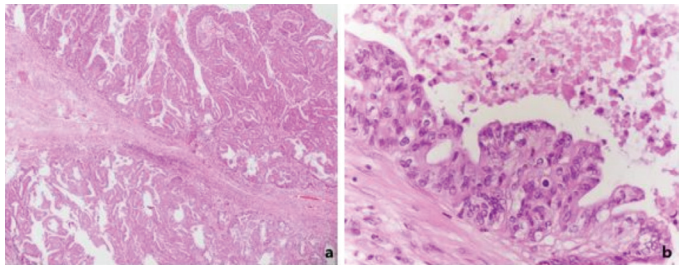

Figure 5. An adenocarcinoma exhibiting glandular architecture and frequent mitotic activity is observed (a; H&E; x40, b; x400)

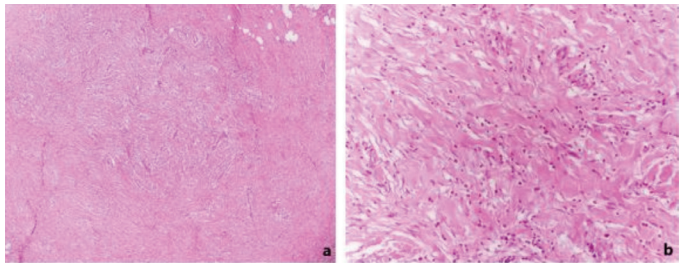

Figure 7. Fibroblastic cell proliferation is observed in a fibrocollagenous background (**a**; H&E; x40, **b**; x200)

Case 4

A 43-year-old female patient was admitted to our clinic with a complaint of bleeding in the urine. No pathological findings were detected in the physical examination. The results of laboratory tests (hemogram, complete urinalysis, liver and kidney function tests) were observed within normal reference ranges. However, because of abdominopelvic USG performed on the patient; After a 30x45 mm anechoic structure was observed in the superficial neighborhood of the bladder, which may be associated with the bladder, it was decided to perform a cross-sectional examination of the patient. As a result of contrast-enhanced abdominopelvic CT; A 25x47 mm mass protruding into the lumen was observed in the anterior wall of the bladder, in the midline, and in the locus of the urachus, and it was interpreted that it might be a malignancy of urachal origin (Figure 8).

Then, cystoscopy was performed on the patient, and a tumoral formation with a hyperemic and solid appearance, with irregular borders, was observed in an area of approximately 3 cm on the anterior wall of the bladder, and pelvic exploration was performed for the patient. Intraperitoneal pelvic exploration was performed using a subumbilical median incision. On exploration, a mass invading from the umbilicus to the anterior wall of the bladder was observed, and the patient underwent radical mass excision and partial cystectomy while preserving the surgical margins of the tumor. Histopathological examination of the excised mass revealed mucinous adenocarcinoma (Figure 9). After the operation, the patient was discharged on postoperative day 5 with full recovery.

Oral and written informed consent for the study was obtained from all patients.

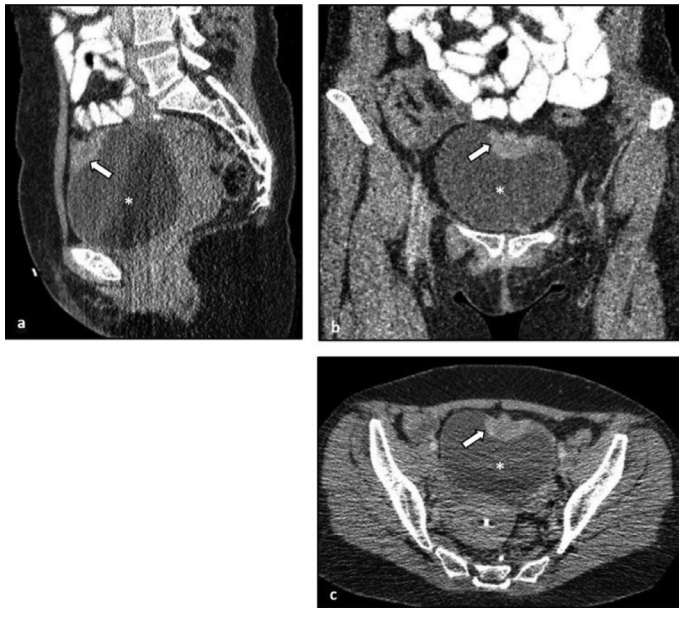

Figure 8. In sagittal **(a)**, coronal **(b)**, and axial **(c)** intravenous contrast-enhanced CT images, a soft tissue mass (arrows) measuring 20x40x40 mm with a slightly hypodense contrast-enhanced center is observed in the anterior dome of the bladder (*), located in the midline and not clearly distinguishable from the bladder walls, with a nodular extension toward the anterior perivesical fat

CT: Computed tomography

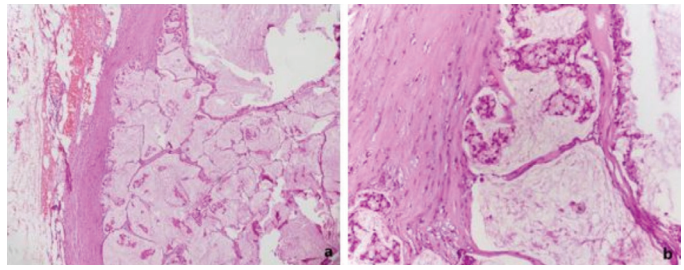

Figure 9. Adenocarcinoma composed of atypical epithelial cells with hyperchromatic nuclei and containing mucin pools in wide areas is observed (**a**; H&E; x100, **b**; x400)

Discussion

The urachus is a channel between the allantois and fetal bladder. With the development of the fetus, the lumen of the urachus becomes obliterated, but it remains as a small fibromuscular band called the median umbilical cord, which connects the dome of the bladder to the umbilicus. Epithelial cells in this band may cause the development of urachal cancer (7).

Primary urachal adenocarcinoma is a very rare tumor that was first described by Hue and Jacquin (8) in 1863. Approximately 70% of urachal adenocarcinomas are mucin-producing tumors that contain calcifications (5). Although hematuria is the most common symptom, the disease usually progresses when this symptom occurs. Commonly metastasized sites include the lymph nodes, peritoneum, and lungs. In bladder apex tumors, the urachus remnant extending toward the umbilicus may not always be discernible, but it is a very important finding in the diagnosis.

The use of abdominopelvic CT with contrast is particularly important in the diagnosis of urachal masses. A study in which urachal adenocarcinomas were evaluated radiologically; reported that calcifications observed on contrast-enhanced abdominopelvic CT are characteristic in the diagnosis of urachal adenocarcinomas, especially urachal mucinous adenocarcinomas (9). Calcifications were also observed in the contrast-enhanced abdominopelvic CT of the patients we reported.

Currently, there is no effective treatment for this rare disease, and the main treatment option is surgery. To compare the prognosis of surgical and nonsurgical treatment, Pinthus et al. (10) conducted a retrospective study involving 40 patients with urachal adenocarcinoma and found that surgical treatment was associated with higher survival rates. Currently, there are two main surgical treatment options: partial and radical cystectomy. When comparing partial and radical cystectomy, Bruins et al. (11) did not observe a significant difference in overall survival. However, recurrence rates were found to be higher after partial cystectomy than after radical cystectomy (11). However, extensive tumor resections with surgical margins can be curative in most non-metastatic urachal cancers (12). In addition, there is currently no conclusive evidence of the curative effect of chemotherapy and radiotherapy.

Conclusion

In conclusion, urachal masses are tumoral formations that are difficult to diagnose early, are quite rare, can be benign and malignant, and have a very poor prognosis. Here, we contribute to the literature by examining four cases of urachal masses, three malignant and one benign, clinically, radiologically, and histopathologically to better illuminate these diseases, reduce the rate of clinical and pathological misdiagnosis, and contribute to treatment management.

Acknowledgements

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

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

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

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

Ethics

Informed Consent: Oral and written informed consent for the study was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Case Report

DOI: 10.4274/uob.galenos.2023.2023.6.3

Bull Urooncol 2023;22(4):166-168

Rare Cause of Testicular Mass: Adenomatoid Tumor of the Testis

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Abstract

Adenomatoid tumors are rare benign neoplasms. In this case report, a 38-year-old patient was diagnosed with an intratesticular adenomatoid tumor following orchiectomy because of a suspicious mass in the testis. Adenomatoid tumors, which are most commonly observed in paratesticular tissues, can also be seen as testicular masses that cannot be distinguished from malignant solid testicular masses with clinical findings and imaging methods, causing many unnecessary orchiectomies. When evaluated together with previous cases, adenomatoid tumors do not show clinically aggressive behavior.
Keywords: Adenomatoid tumor, testicular mass, benign tumor

Introduction

Adenomatoid tumors are rare benign tumors of the male and female genital system that are commonly located in paratesticular tissues in men. Adenomatoid tumors, which constitute approximately 32% of paratesticular masses, rarely present with intratesticular localization (1). To date, 15 cases of intratesticular adenomatoid tumor have been described. Typically, they appear between the third and fifth decades of life. These benign tumors are most commonly observed in Caucasians, followed by African Americans (2,3). In this case report, the management of a patient diagnosed with testicular adenomatoid tumor, which could not be distinguished from a malignant tumor preoperatively, is presented.

Case Report

A 38-year-old male patient presented with a complaint of right scrotal pain that had been ongoing for 2 weeks. No history of trauma. Physical examination revealed palpable firmness in the lower pole of the right testicle. Scrotal Doppler ultrasonography revealed a well-defined isoechoic solid lesion with a hypoechoic halo measuring 9x8 mm in size, located in the lower pole of the right testicle. Testicular tumor markers (alphafetoprotein, beta human corionicgonadotropin, lactate dehydrogenase) were within normal limits. Magnetic resonance imaging (MRI) of the scrotum performed at an external center showed a well-defined lesion measuring 14x13 mm with a central cystic - necrotic appearance and a periphery showing intense contrast enhancement, which extended caudally to the testis in the lower pole of the right testicle (Figure 1). Thoracoabdominopelvic computed tomography performed for staging did not reveal any evidence of metastasis. After the patient was informed about the testicular tumors, he underwent right radical inguinal orchiectomy. Histopathological examination revealed a relatively well-defined 1.5 cm lesion with a central hemorrhagic area and a cream-white periphery located 0.5 cm away from the capsule in the lower pole of the testicle. In the serial section examination of the lesion, irregularly defined cell infiltration was observed between the seminiferous tubules and rete testis (Figure 2A). Large cytoplasmic, spindle-polymorphic nuclei with distinct nucleoli were observed in the stroma, and the cells had slightly atypical features. Some cells had a wide eosinophilic cytoplasm, whereas others had a wide vacuolar cytoplasm (Figure 2B). There was no mitosis, lymphovascular invasion, or perineural invasion. No tumor was observed at the surgical margins. Immunohistochemical examination showed positive staining for calretinin (Figure 2C), vimentin, PanCK (Figure 2D), BRAP1, and S100, whereas it was negative for inhibin, CD34, and HBME-1.

Cite this article as: Coşer Ş, İvelik Hİ, Akkaş Akgün G, Er MM, Kartal İG. Rare Cause of Testicular Mass: Adenomatoid Tumor of the Testis. Bull Urooncol 2023;22(4):166-168.

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Received: 14.06.2023 **Accepted:** 14.08.2023

After the pathological diagnosis, the patient was recommended for follow-up. No problems were detected in the patient's outpatient clinic controls at 3 and 6 months. Patient consent was obtained for the case reports to be published for academic purposes.

Discussion

Adenomatoid tumors were first described as a group of benign tumors with a glandular pattern localized in the urogenital system in 1945 (4). Adenomatoid tumors are quite rare in the testis and are most commonly presented in the epididymis (77%). In men, other urogenital localizations where they are observed include the spermatic cord, tunica albuginea, and ejaculatory ducts, whereas in women, typical sites of occurrence are the uterus and fallopian tubes. In addition to these sites, they can also appear in extragenital regions such as the pleura, heart, omentum, mesentery, and mediastinal lymph nodes (3,4). They usually appear as painless hard nodules measuring less than 2 cm, detected incidentally on physical examination. However, sometimes mild pain or accompanying conditions such as hydrocele or periorchitis may also be present. Tumor markers for testicular tumors were negative in all cases. The radiographic appearance of adenomatoid tumors is non-specific, and they appear as hypoechoic, isoechoic, and hyperechoic lesions on testicular ultrasonography. In scrotal MRI, no distinguishing appearance from malignant neoplasms of the testis, as seen in ultrasonography, is observed. In conclusion, adenomatoid tumors of the testis have clinical and radiological characteristics similar to those of malignant testicular neoplasms. Although the origin of adenomatoid tumors is controversial, studies using electron microscopy and immunohistochemical staining suggest that they are of mesothelial origin. Macroscopic evaluation of the specimen shows adenomatoid tumors as small, solid, hard, gray-white, well-defined nodules. On microscopic evaluation, the tumor consists of cuboidal, vacuolated, eosinophilic cells that form dilated tubules, cords, and cell clusters within the fibrous stroma. The vacuolization observed in the cytoplasm is specific to adenomatoid tumors. Mitoses are not observed. In the differential diagnosis of adenomatoid tumors of the testis, metastatic tumors, sex cord-stromal tumors, malignant mesothelioma, and vascular lesions should be considered (5). Although clinical and morphological features are decisive in making a differential diagnosis, specialized immunohistochemical markers are also used. In adenomatoid tumors, positivity for calretinin, vimentin, cytokeratin, WT1, and EMA is observed (5). Unlike sex cord stromal tumors, inhibin negativity is observed in adenomatoid tumors. Negativity for CD31, CD34, and FLI-1 can also be used to distinguish them from vascular neoplasms. Unlike malignant mesotheliomas, adenomatoid tumors do not exhibit mitoses or necrosis, and they have a more destructive growth pattern. Because of the similarity of their appearance to malignant testicular tumors based on clinical and radiological imaging, radical inguinal orchiectomy is widely performed for treating adenomatoid tumors. However, testis-sparing surgery may also be considered among the treatment options in selected cases suspected of having a benign tumor, with intraoperative frozen biopsy taking priority (6,7). There is currently limited data on the recurrence and malignant degeneration of adenomatoid tumors in the literature (8,9). These views are not recommended to be followed by serial imaging methods and keys of tumor markers (10). In this case, similar to our cells, the main problem is that the clinical and radiological features of adenomatoid tumors can hardly be distinguished from malignant neoplasms. For this reason, the possibility of a good tumor should always be kept in mind in testicular masses, thus preventing the appearance of unnecessary orchiectomies.

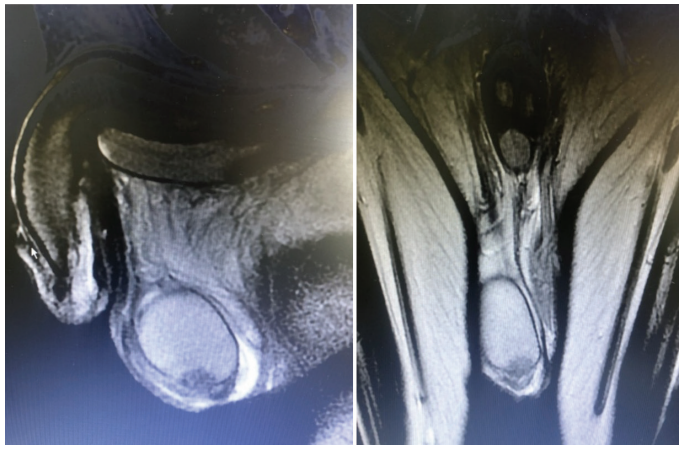

Figure 1. Scrotal magnetic resonance imaging of the tumor: Well-defined lesion located in the lower pole of the right testis

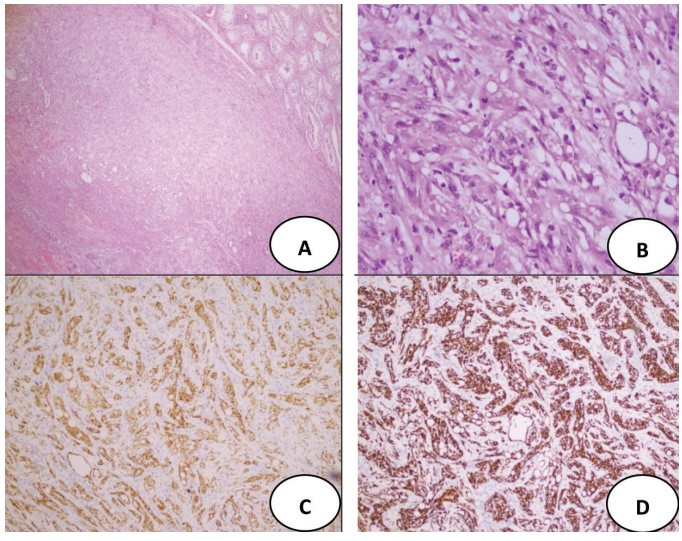

Figure 2. A) Nodular tumoral lesion with a smooth boundary separated from the surrounding testicular tissue (HEx40). **B)** Cells with eosinophilic, spiky cytoplasm, vesicular structure, thin chromatin condensation, punctate nucleoli, and minimal atypia (HEx100). **C)** Calretinin (x100). **D)** Pankeratin (x100)

Acknowledgements

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

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

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

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

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Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.C., İ.G.K., Concept: Ş.C., M.M.E., Design: H.İ.İ., İ.G.K., Data Collection or Processing: H.İ.İ., M.M.E., Analysis or Interpretation: İ.G.K., G.A.A.,, Literature Search: Ş.C., İ.G.K., Writing: Ş.C., H.İ.İ.

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