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About Us

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

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

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

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

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

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

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

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1. General Information

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

The Bulletin publishes basic and clinical research original articles, reviews, editorials, case reports, surgery videos (Video-urooncology) and letters to the editor relevant to urooncology (prostate cancer, urothelial cancers, testis and kidney cancer, benign prostatic hyperplasia, and any aspect of urologic oncology).

The Bulletin of Urooncology is indexed by several well-known international databases including Emerging Sources Citation Index (ESCI), TUBITAK/ULAKBIM Turkish Medical Database, Directory of Open Access Journals (DOAJ), EBSCO, CINAHL Complete Database, Gale/Cengage Learning, ProQuest, Index Copernicus, and British Library.

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.

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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).

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

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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.

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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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(2) drafting the article or revising it critically for intellectual content,

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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.

- First page: Title - Abstract (limited to 150 words, unstructured - Keywords (List 3-5 key words using Medical Subjects Headings [MeSH])

-Introduction

-Case Presentation

-Discussion

-References

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

-Tables and figures should be uploaded separately.

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

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

C. Review Article

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

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

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

-Introduction

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

-Conclusions

-References

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

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

-Tables and figures should be uploaded separately.

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

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

D. Literature Review

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

E. Editorial Commentary

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

F. Letters to the Editor

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

G. Surgery Videos on Urooncology (Video-urooncology)

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

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

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

Video-urooncology submission should include:

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

2) Title Page

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

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

6) "Acknowledgements From" should be uploaded separately.

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

6. Manuscript Preparation

Manuscripts should be prepared following sequence according to article type:

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

B. Title Page

The title page should include the following:

-Full title

-Running title

-Authors' names and institutions

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

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

C. Main Text (without authors' credentials)

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

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

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

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

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

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

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

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

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

Examples for writing references:

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

Example:

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

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

Example:

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

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

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

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

D. Tables and Figures

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

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

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

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

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

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

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7. Manuscript Submission

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

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

Manuscripts should be prepared as a word document (*.doc) or rich text format (*.rtf). Text should be double-spaced with 2.5 cm margins on both sides using 12-point type double spaced in Times Roman.

Submissions must include according to the following sequence:

A-Original Article

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

4) Table(s)

5) Figure(s)

6) Acknowledgements Form

B. Case Reports

1) Copyright Transfer and Author Declaration Statement Form

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

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

4) Table(s)

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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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6) Acknowledgements Form

D. Literature Review

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

4) Table(s)

5) Figure(s)

6) Acknowledgements Form

E. Editorial Commentary

1) Copyright Transfer and Author Declaration Statement Form

2) Title Page

3) Main text (Text, References)

4) Acknowledgements Form

F. Letters to the Editor

1) Copyright Transfer and Author Declaration Statement Form

2) Title Page (The title is "Letter to Editor about.....")
3) Main text (Text, References)
4) Acknowledgements Form

G. Surgery Videos (Video-urooncology)

1) Copyright Transfer and Author Declaration Statement Form
2) Title Page
3) Summary (without authors' credentials)
4) Video
5) Acknowledgements Form

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BEST REVIEWER of ISSUE
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Review

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Targeted Therapies: A Molecular Overview

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Abstract

Cancer remains a major health issue and our understanding of its etiopathogenesis needs to be improved. Cancer cells have specific abilities such as uncontrolled proliferation, differentiation, progression, and metastasis. Improved interpretation of intracellular molecular pathways and the development of new genetic or immunological diagnostic techniques have facilitated novel treatment modalities for cancer. These therapeutic agents generally have antiproliferative properties and regulate molecular mechanisms on the intracellular pathways. Small molecule inhibitors, monoclonal antibodies, and some gene-editing treatments have been suggested due to the discovery of new molecular mechanisms. However, limited and transient efficacy, and drug resistance generated by mutations are among the disadvantages of these treatments. Multi-functional inhibitors have highly side effects, but benefit from greater efficacy and evading resistance while the recent specific inhibitors possess increased potency and less toxicity. Furthermore, the combination of therapeutic modalities may potentiate the outcome.
Considering the actual literature, this review summarized targeted therapies for treating cancer patients in urology as an overview.
Keywords: Cancer, small molecules, urology, monoclonal antibodies

Introduction

Targeted therapies identify specific targets at the cancer cells and attack them. Tamoxifen is the oldest targeted therapeutic agent acting as a selective estrogen receptor modulator to treat hormone receptor-positive patients. Presently, numerous targeted therapy agents have been in us for cancer treatment owing to the evolution of molecular medicine and advances in drug technologies. The size of the global drug market for cancer patients has reached almost 200 million dollars. Nowadays, hundreds of targeted therapy agents are undergoing clinical trials and some of them are approved for cancer treatment. Mainly, these drugs either block the molecules involved in oncogenesis, such as enzymes and proteins, or help the immune system to kill the cancer cells. These agents can be classified as small molecule drugs, monoclonal antibodies, or gene editing agents. Inhibitory small molecule drugs have "-ib" and monoclonal antibodies have "-mab" as a suffix.

Targeted therapies generally have fewer side effects than other types of cancer treatment and are less harmful to a normal cell. These drugs act on molecular targets in the cancer cells and inhibit tumor cell proliferation (cytostatic). In contrast, other chemotherapeutic agents act on all cells with have high proliferation capability and kill the tumor cells (cytotoxic). Normally, the receptor is activated after binding to its ligand, and the signal is transmitted down for cell response. Some compounds are agonists that can bind to the receptor and activate it. In contrast, an antagonist blocks the agonistic effect on the receptor (1).

There are still some challenges, such as drug resistance based on gene mutations and low efficiency. Hence, the development of advanced drug design techniques is essential along with the identification of distinct targets such as epigenetic regulatory proteins, microRNA (miRNAs), and cancer stem cells (CSCs). For instance, successful outcomes are expected with antibody-drug conjugate (ADC) drugs and proteolysis targeting chimera (PROTAC) techniques in the future. The evolution of novel agents that act on intracellular mechanisms or genes can entail personalized medicine, using individual information on genes and proteins for treating cancer. Considering the current literature, this review aims to outline targeted cancer therapies for urologists.

Small Molecule Therapies

Small molecule therapies can affect many intracellular pathways during oncogenesis by changing enzymatic reactions due to receptor agonism or antagonism. Several molecules have been described in the literature and some of them have been approved for antineoplastic effect. Moreover, various combined

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therapies have been assessed to improve the treatment outcome in clinical studies.

Targeted therapies can be classified according to the mechanism of action. Enzyme inhibitors reduce catalytic activity of these enzymes. The kind of the enzyme-linked antagonist complexes are used in their classification.

Kinase Inhibitors

The protein kinase enzyme catalyzes the transfer of the γ-phosphate group from ATP to protein residues containing hydroxyl groups. They have a major effect on cell growth, proliferation, and differentiation. Kinase inhibitors can be classified into six types based on their acting mechanisms according to Roskoski's classification system (2). Instead of this pharmacological classification, protein kinases were classified such as receptor or non-receptor tyrosine kinases, serine/ threonine kinases, and tyrosine kinase-like enzymes in our review.

Receptor Tyrosine Kinase Inhibitors (TKIs)

ALK Inhibitors

Anaplastic lymphoma kinase (ALK) gene is a transmembrane tyrosine kinase of the insulin receptor family (3). ALK can stimulate several downstream signaling pathways in the cell (4). Activation of the ALK gene by mutations has been identified in different cancers. ALK inhibitors are effective against multiple tyrosine kinases, including ALK, cellular mesenchymal-epithelial transition factor (c-Met), and proto-oncogene tyrosine-protein kinase reactive oxygen species (ROS), and IGF1R/epidermal growth factor receptor (EGFR)/ FMS-like tyrosine kinase 3 (FLT3) pathway. ALK inhibitors such crizotinib, ceritinib, alectinib, brigatinib, and Lorlatinib.

c-Met Inhibitors [Hepatocyte Growth Factor Receptor (HGFR)]

The c-Met, is encoded by the MET proto-oncogene located on chromosome 7q21-31.41,42. It has a crucial role in different cellular pathways and activates HGF/c-Met, PI3K/AKT, MAPK, signal transducer and activator of transcription (STAT), and NF-κB signaling pathways. Therefore, it regulates angiogenesis, proliferation, survival, invasion, motility, and epidermal mesenchymal transition (5). c-Met overexpression has been reported to be related to poor prognosis and resistance to targeted therapies (6). These mutations are common in advanced cancers with metastases such as renal cell carcinoma (RCC) (7). c-Met inhibitors have been classified as multi-kinase inhibitors (crizotinib, cabozantinib) and selective inhibitors (capmatinib, tepotinib). As a member of this family, Cabozantinib-S-Malate inhibits vascular endothelial growth factor receptor (VEGFR) 1/2/3/ TROY3/ ROS/ TIE2/ c-MET/HGFR c-KIT/TRK2/c-RET pathways and has been approved for treating advanced RCC.

EGFR Inhibitors

EGFR is a transmembrane protein that affects some intracellular pathways. ERBB2/3/4 [human epidermal growth factor receptor (HER2/3/4)] are members of this family (8,9). EGFR TKIs clinically available such as gefitinib, erlotinib, icotinib, lapatinib, afatinib, osimertinib, neratinib, dacomitinib, almonertinib, tucatinib.

FLT3 Inhibitors

FLT3 is a transmembrane protein encoded by the proto-oncogene FLT3. It is a member of the type III receptor tyrosine kinase (RTKs) family, which also includes platelet-derived growth factor receptor (PDGFR), FMS, and KIT. After the autophosphorylation of FLT3, it activates cellular signaling pathways such as PI3K/AKT/ mammalian target of rapamycin (mTOR), RAS/RAF/MAPK, and JAK/STAT pathways (10). These pathways are related to several cellular functions such as proliferation, differentiation, survival, and apoptosis. FLT3 inhibitors have been classified as multi-kinase inhibitors (sorafenib, sunitinib, midostaurin, tandutinib, lestaurtinib) or specific inhibitors (gilteritinib, quizartinib, pexidartinib) (11). Multi-kinase inhibitors are not specific for FLT3 receptor and can inhibit various receptor tyrosine kinases such as PDGFR, KIT, VEGFR, RAF, or JAK2.

VEGFR/FGFR/PDGFR Inhibitors

Angiogenesis is a complex function and is regulated by various endogenous proangiogenic and antiangiogenic factors. By secreting pro-angiogenic factors, tumors trigger the generation of new blood vessels from the preexisting vessels in the tumor microenvironment (12). Antiangiogenic therapy inhibits this process, which is crucial to the development, growth, and metastases of cancer leading to the death of cancer cells due to starvation (13).

Angiogenesis-related genes, transcription factors, and signaling pathways are effective in this process. VEGF, basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF), insulin-like growth factor, epidermal growth factor (EGF), and angiopoietin are members of the angiogenic family. Bevacizumab is the oldest biological inhibitor for angiogenesis due to its anti-VEGF effect and has been licensed for treating advanced RCC. In the context of these growth factors, antiangiogenic treatments have inhibited the activities of their receptors such as VEGF receptors (VEGFR-1-3), FGF receptors (FGFR1-4), PDGF receptors (PDGFR α/β), and TGF-β receptors (TGF-βR I/II/III). Many anti-angiogenic TKIs have been licensed by the authorities such as sorafenib, sunitinib, pazopanib, vandetanib, axitinib, cabozantinib, regorafenib, afatinib, lenvatinib, tivozanib, fruquintinib, nintedanib, anlotinib, erdafitinib, pemigatinib, avapritinib, and ripretinib. Most of them are members of the multi-kinase inhibitors family.

A member of this family, Sorafenib can inhibit several receptor tyrosine kinases (RTKs) including VEGFR-1/2/3, c-Kit, FLT3, RET, PDGFRβ, RAF1, BRA, especially on the RAS (RAF/MEK/ ERK) signaling pathway. It has been approved as the first anti-angiogenic inhibitor (anti-VEGFR 2/3) for treating advanced RCC (14). Other approved anti-angiogenic inhibitors for the first- or second-line treatment of advanced RCC are sunitinib, pazopanib, axitinib, cabozantinib, and tivozanib. The adverse reactions to sorafenib include hand-foot syndrome, diarrhea, hypertension, decreased appetite, and fatigue. Another anti-angiogenesis-related common side effect is hypothyroidism.

Axitinib acts on the receptors as VEGFR 1/2/3, PDGFRβ, and c-KIT (15). Tivozanib hydrochloride inhibits PDGFRα, VEGFR 1/2/3, FGFR 1/2/3/4, c-KIT/RET (16). Similarly, pazopanib inhibits PDGFRβ, VEGFR 1/2/3, FGFR 1/3/ c-KIT/ Itk/Lck/ c-GSK.

Sunitinib is a member of the multi-kinase RTK inhibitor and acts on the receptors as VEGFR-1/2/3, PDGFRα/β, c-Kit, CSF1R, RET, and FLT3 (17). Sunitinib is the second approved antiangiogenic TKI for treating advanced RCC. Adverse reactions to sunitinib include nausea, vomiting, weakness, and fatigue.

Selpercatinib and pralsetinib have been certified as specific RET inhibitors. Several selective FGFR (erdafitinib, pemigatinib) or PDGFR (avapritinib, ripretinib) inhibitors have also been accepted for therapeutic use.

Erdafitinib is the initial FGFR-selective inhibitor (FGFR 1/2/3/4) that has been used for the second-line treatment of locally advanced or metastatic urothelial carcinoma (18).

Lenvatinib mesylate inhibits VEGFR1/2/3, FGFR 1/2/3/4, PDGFRα, c-KIT/ RET and has been approved for advanced RCC (19). Adverse reactions to lenvatinib include hypertension, diarrhea, loss of appetite, and weight loss.

Additionally, targeting TGF-β signaling by galunisertib, vactosertib is also an alternative for anti-angiogenic therapy.

Antiangiogenic therapy not only inhibits neovascularity but also regulates the immune microenvironment, allowing the combination of antiangiogenic agents with immunotherapy. The combination of axitinib with the PD1 antibody pembrolizumab has been used for treating advanced RCC (20).

TRK Inhibitors

The tropomyosin receptor kinase (TRK) family includes three members, TRKA, TRKB, and TRKC, which are encoded by the neurotrophic tyrosine receptor kinase (NTRK) genes (21). After binding to TRK receptors, neurotrophins (TRK ligands) stimulate autophosphorylation of TRK proteins, thereby activating downstream signaling pathways such as RAS/MAPK/ERK, PI3K/AKT, and PLCγ. Aberrant activation of TRKs and generated fusion proteins have been identified as oncogenic factors in various cancers. Therefore, TRKs are important targets for the treatment of cancer patient. Currently, TRK inhibitors have been approved for the treatment of cancer patients such larotrectinib and entrectinib. Cabozantinib has been licensed as an antiangiogenic inhibitor for treating advanced RCC and has efficacy against NTRK fusions.

Non-receptor TKIs

Breakpoint Cluster Region (BCR)-ABL-1 Inhibitors

c-Abl [Abelson murine leukemia 1 (ABL1)] gene is located on chromosome (9). The ABL family is a member of the non-receptor tyrosine kinase group. It is effective in the modulation of cell differentiation, cell cycle, and survival. The BCR-ABL fusion gene is on chromosome 22 (Philadelphia). After autophosphorylation, it activates the downstream pathway (22). Imatinib is the first approved BCR-ABL1 inhibitor and the first licensed TKI. Second-generation BCR-ABL1 inhibitors include dasatinib, nilotinib, bosutinib, and radotinib. The other is ponatinib, a third-generation BCR-ABL1 inhibitor.

Bruton's Agammaglobulinemia Tyrosine Kinase (BTK) Inhibitors

BTK is a crucial component in the BCR pathway and belongs to the non-receptor tyrosine kinase of the *TEC* gene family. *TEC* kinase is expressed in hematopoietic, liver, and kidney cells and plays a major role in T-helper cell function. The B-cell receptor (BCR) function plays a key role in the progression of B-cell malignancies (23). Ibrutinib, Acalabrutinib, and Zanubrutinib are members of this family.

Janus Kinases (JAK) Inhibitors

JAKs are members of non-receptor tyrosine kinases and are classified as JAK1, JAK2, JAK3, and TYK2 (24). JAKs regulates to the DNA transcription and protein expression. The JAK system is activated when inflammatory cytokines such as interleukin (IL) and interferon bind to their receptors. Then JAKs catalyze the phosphorylation of receptor tyrosine and phosphorylate the downstream STAT proteins. The activation of the STAT protein promotes their translocation to the nucleus and regulation of target-gene transcription and expression. The JAK/STAT cascade activates more than 50 cytokines and growth factors and is the central communication point for the immune system. For this reason, JAKs are potential targets for the treatment of cancer patients, and their inhibitors include ruxolitinib, lestaurtinib, fedratinib, and tofacitinib.

Serine/Threonine Kinase Inhibitors

BRAF/MEK/ERK Inhibitors

RAS-RAF-MAPK-ERK signaling pathway includes the small GTPase Ras, the serine/threonine kinase RAF, and the protein kinases MEK1/2 and ERK1/2. RAF system contains ARAF, *BRAF*, and CRAF and is effective on the downstream of RAS, which serves as a transducer of receptor stimuli (25). Moreover, *Src* is a human proto-oncogene and belongs to the non-receptor tyrosine kinases family. *Src* plays a major role in the field of molecular genetics of cancer and is involved in many signal transduction pathways such as the RAS/MEK/ERK pathway, STAT/c-myc pathway, and PI3K/AKT pathway. Sorafenib is a pan-RAF inhibitor and has multi-kinase inhibitor properties. Another novel MEK1/2 inhibitor is selumetinib. Currently, no ERK inhibitor has been approved for clinical use. New combinations of this targeted therapy drugs with ERK inhibitors, CDK4/6 inhibitors, or inhibitors of the PI3K/AKT/mTOR pathway have been under evaluation for more efficacy and low resistance rates. Vemurafenib, dabrafenib, encorafenib, trametinib, cobimetinib, binimetinib, selumetinib are members of this family.

Cyclin-dependent Kinase (CDK) Inhibitors

Uncontrolled proliferation due to cell cycle defects is one of the member pivotal factors in the development of cancer. CDKs regulates to the cell cycle progression and many CDKs/cyclin proteins activate to downstream phosphorylation in humans (26). Among them, CDK4 and CDK6 play a key role in regulating growth signaling and driving the transition of the cell cycle from G1 to the S phase. Non-selective pan-CDK inhibitors (flavopiridol, seliciclib, UCN-01) have been discontinued due

to their low efficacy and serious side effects. Today, clinically available three CDK inhibitors are palbociclib, ribociclib, and abemaciclib. They are orally selective reversible inhibitors that specifically target CDK4/6. Hematological toxicities such as neutropenia and gastrointestinal toxicities, particularly diarrhea, are side effects of CDK inhibitors.

PI3K/AKT/mTOR Inhibitors

The phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/V-AKT murine thymoma viral oncogene homolog (AKT)/mTOR signaling pathway has a major role in cell growth, proliferation, survival, apoptosis, and motility (27). This pathway is activated by phosphatase and tensin homolog (PTEN) loss due to be deleted from chromosome 10 for oncogenesis and progression. Moreover, inhibition of the tumor suppressor PTEN gene negatively regulates the PI3K pathway by dephosphorylating PIP3 to PIP2. *PIK3CA* gene is frequently overexpressed in many cancers by mutation and amplification. Activation of the PI3K/AKT/mTOR pathway is common in metastatic castration-resistance prostate cancer (mCRPC) and is associated with a poor prognosis. PI3K/AKT/mTOR pathways reciprocally crosstalk with the androgen receptor (AR) signaling so that inhibition of one leads to the upregulation of the other. However, activated PI3K/AKT/mTOR signaling is related to cancer cell growth and drug resistances. The PI3K/AKT/mTOR cascade interacts with many other signaling pathways such as Wnt and MAPK signaling. Therefore, this pathway has become an attractive target for developing antineoplastic drugs. AKT inhibitors bind to all three isoforms of AKT, which is a key component of the PI3K/AKT/mTOR pathway. Several small-molecule inhibitors of PI3K, AKT, and mTOR have been under evaluation. Ipatasertib is an oral, specific AKT inhibitor that shows a clinically significant activity when combined with abiraterone acetate and prednisone/prednisolone for (mCRPC) in patients with loss of the tumor suppressor protein PTEN (on immunohistochemistry) within the tumor (28,29). The adverse events are rash and diarrhea.

mTOR inhibitors have been divided into the two categories as rapamycin analogs (rapalogs) and ATP-competitive inhibitors. Sirolimus (rapamycin), temsirolimus, and everolimus have been licensed for treating various cancers such as advanced RCC. Moreover, these agents have serious immune-suppressive properties.

Another, perifosine is a member of PI3K inhibitors. Other inhibitors belonging to this pathway are idelalisib, copanlisib, duvelisib, and alpelisib.

Small molecule agents are summarized in Table 1 and Figure 1.

Epigenetic Inhibitors

Epigenetics is an important part of genetics that studies the changes in gene expression without changing the nucleotide sequence of genes. A better understanding of the mechanisms and differences of epigenetic alterations in different cancers may contribute to further development of new therapies. When we explain epigenome better, we can more sensitize chemotherapy, targeted therapy, and immunotherapy.

Epigenomic factors act on the genetic code with DNA Methylation, Histone Methylation, and Histone Acetylation. It is regulated by modifying enzymes and recognition proteins, which are named writers, erasers, and readers (30). The writers are some types of enzymes that transfer chemical groups to DNA or histones, which include DNA (DNA methyltransferases),

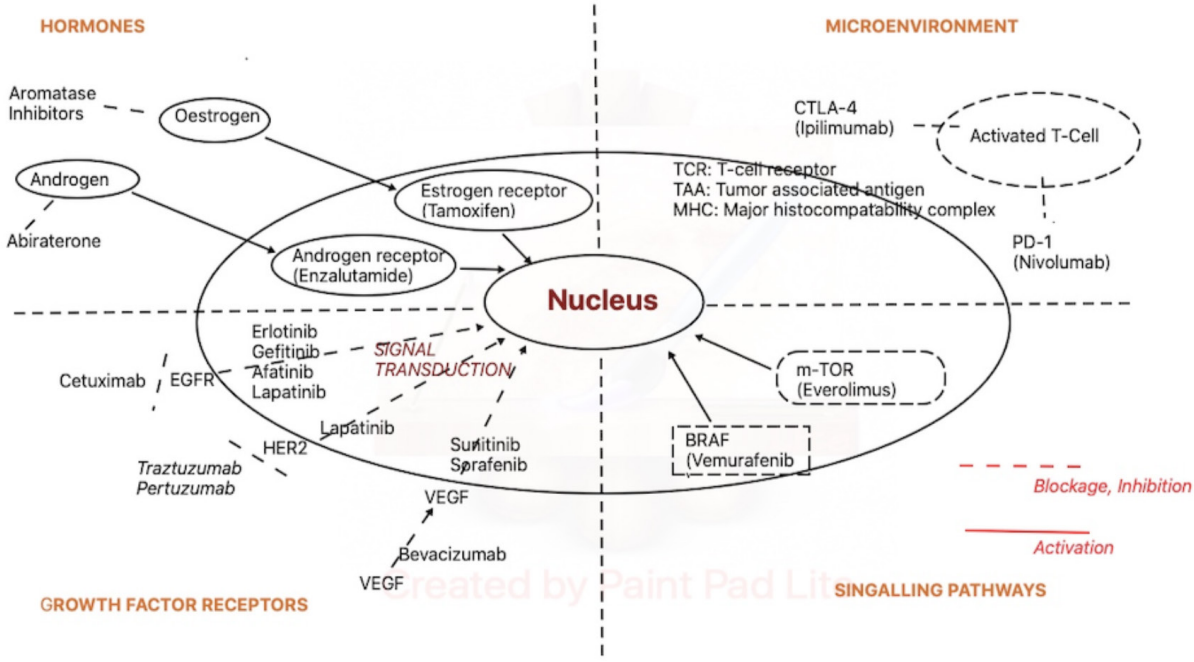

Figure 1. Illustration of the targeted therapies for cancer treatment

CTLA-4: Cytotoxic T lymphocytes-4, EGFR: Epidermal growth factor receptor, HER2: Human epidermal growth factor receptor 2, VEGF: Vascular endothelial growth factor, mTOR: Mammalian target of rapamycin

histone acetyltransferases, and histone lysine methyltransferases. The erasers remove post-translational modifications and include histone deacetylases (HDACs) and histone lysine demethylases (KDMs). The readers can recognize the modified histones or DNA, such as methyl-binding domain proteins and bromodomain and extra-terminal family proteins. The abnormal epigenetic regulation is related to various diseases, including tumors, immune diseases. Many epigenetic regulatory proteins have been identified as potential disease targets, but few epigenetic drugs are approved for clinical usage such as azacitidine, decitabine, vorinostat, and romidepsin, belinostat, panobinostat, chidamide.

Table 1. Small molecules and target pathways (2)

Small molecules	Target pathways
Afatinib	EGFR, ErBb 2/4
Axitinib	VEGFR 1/2/3, PDGFRβ, Kit
Bosunitib	BCR-Abl, Src, Lyn, Hck
Caozantinib	RET, c-Met, VEGFR1/2/3, Kit, Trkβ, Flt3, Axl, Tie2
Ceritinib	ALK, IGF-1R, InsR, ROS1
Crizotinib	ALK, c-MET (HGFR), ROS1, MST1R
Dafrafenib	B-Raf
Dasatinib	BCR-Abl, Src, Lck, Lyn, Yes, Fyn, Kit, EphA2, PDGFRβ
Erlotinib	EGFR
Everolimus	FKBP12/mTOR
Gefitinib	EGFR, PDGFR
Ibrutinib	BTK
Imatinib	BCR-Abl, Kit, PGFR
Lapatinib	EGFR, Erb2
Lenvatinib	VEGFR1/2/3, FGFR1/2/3/4, PDGFRα, Kit, RET
Nilotinib	BCR-Abl, PDGFR, DDR1
Nintedanib	FGFR1/2/3, Flt3, Lck, PDGFRα/β, VEGFR1/2/3
Palbociclib	CDK4/6
Pazopanib	VEGFR1/2/3, PDGFRα/β, FGFR1/3, Kit, Lck, Fms, ltk
Ponatinib	BCR-Abl, BCR-Abl T3151, VEGFR, PDGFR, FGFR, EphR, Src, Kit, RET, Tie2, Flt3
Regorafenib	VEGFR1/2/3, BCR-Abl, B-Raf, B-Raf (V600E), Kit, PDGFRα/β, RET, FGFR1/2, Tie2, Eph2A
Ruxolitinib	JAK1/2
Sirolimus	FKBP12/mTOR
Sorafenib	B-Raf, CDK8, Kit, Flt3, RET, VEGFR1/2/3, PDGFR
Sunitinib	PDGFRα/β, VEGFR1/2/3, Kit, Flt3, CSF-1R, RET
Temsirolimus	FKBP12/mTOR
Tofacitinib	JAK3
Trametinib	MEK1/2
Vandetanib	EGFR, VEGFR, RET, Tie2, Brk, EphR
Vemurafenib	A/B/C-Raf, B-Raf (V600E)

EGFR: Epidermal growth factor receptor, VEGFR: Vascular endothelial growth factor receptor, BCR: Breakpoint cluster region, PDGFR: Platelet-derived growth factor receptor, mTOR: Mammalian target of rapamycin

EZH2 Inhibitors

Enhancer of zeste homolog 2 (EZH2) is a member of histone methyltransferase and acts on DNA with methylation. EZH2 is frequently mutated and overexpressed in various cancers such as prostate cancer (31). This enzymatic change can be crucial for oncogenesis so the inhibition of EZH2 has been thought of as an alternative for the treatment of cancer patients. DZNep is a non-specific EZH2 inhibitor. Although treatment with DZNep showed significant antitumor activity in various preclinical studies, drug resistance is a major problem often due to EZH2. Tazemetostat and lirametostat are members of this family.

HDAC Inhibitors

HDACs are major epigenetic regulators that remove the acetyl groups from the N-acetylated lysine residues of histones. These alterations can act to the transcription of oncogenes and tumor suppressor genes, which are associated with proliferation, apoptosis, differentiation, migration, and cancer angiogenesis (32). HDAC inhibitors have been suggested to be effective for the treatment of cancer patients. Recently, a few HDAC inhibitors have been approved or are undergoing clinical trials. Vorinostat, romidepsin, belinostat, tucidinostat, and panobinostat are members of this family.

IDH1/2 Inhibitors

Isocitrate dehydrogenases (IDH1, IDH2, and IDH3) are important enzymes that catalyze the conversion of isocitrate to α-ketoglutarate using nicotinamide adenine dinucleotide phosphate ($NADP^+$) or NAD^+ as a cofactor in the tricarboxylic acid cycle (33). Enasidenib and ivosidenib are the members of this group.

BCL-2 Inhibitors

The B-cell lymphoma 2 (BCL-2) family of proteins consists of more than 20 members and includes three subfamilies (antiapoptotic proteins, proapoptotic proteins, and cell death mediators) (34). BCL-2 family proteins regulate the apoptosis and survival. Abnormality of the apoptosis is common in cancer. BCL-2 was first discovered as an inhibitor of apoptosis, after that BCL-2 inhibitors were tried for cancer treatment (35). These agents inhibit the anti-apoptotic effect of BCL-2 and promote apoptosis. Drug resistance is the main problem with this treatment. Mutations of the BCL-2 family members or pro-apoptotic proteins BAX and BAK can be effective in resistance development (36). Today, combination therapy with conventional chemotherapy is the main strategy to overcome resistance. Venetoclax, obatoclax, navitoclax, and gossypol are members of this family.

Hedgehog (Hh) Pathway Inhibitors

The Hh signaling pathway plays a key role in embryonic development and tissue regeneration. The Hh pathway contains both canonical and non-canonical parts (37). Hh ligand upregulation and transmembrane receptor Patched-1 or transmembrane transducer protein smoothened (SMO) mutations can activate the Hh signaling pathway. Abnormal activation of the Hh pathway is related to the oncogenesis

and progression due to activation of the glioma-associated oncogene transcription factors. SMO inhibitors have shown significant antineoplastic activity. This pathway may be a more attractive target for cancer therapy. Nowadays, three Hh pathway inhibitors have been approved for clinical usage such as glasdegib, vismodegib and sonidegib. High-dose itraconazole was effective in the treatment of prostate cancer due to Hh signaling inhibition rather than an anti-androgen effect (38).

Proteasome Inhibitors

Proteasomes are multi-catalytic enzymes that are expressed in the cells and are responsible for protein degradation (39). The ubiquitin-proteasome system (UPS) plays a major role in cellular protein homeostasis and regulates cell survival, signal transduction, DNA repair, and antigen presentation (40). Toxic proteins are tagged by ubiquitin and destructed to peptides by the proteasome complex. Abnormality of the UPS are related to many cancers (41). For this reason, targeting UPS can be as a potential treatment strategy. Bortezomib and carfilzomib (epoxomicin) are approved proteasome inhibitors for treating cancer patient. In contrary to bortezomib, carfilzomib is an irreversible inhibitor. Proteasome inhibitors are preferable for combination therapy with other group inhibitors for drug resistance (42). Ixazomib is the other member of this group.

PARP Inhibitors

Genomic instability is one of the main features of tumor cells. Genomic integrity can be achieved with DNA repair systems that include repair of double-strand breaks (DSBs), repair of single-strand breaks (SSBs), homologous recombination and non-homologous end-joining repair, base excision repair, nucleotide excision repair, mismatch repair (MMR). Poly (ADP-ribose) polymerases (PARPs) are a group of multifunctional post-translational modification enzymes that affect DNA repair, transcription, mitosis, and cell cycle regulation (43). Inhibition of the DNA repair pathway in cancer cells may have a lethal effect. The PARP enzyme family contains different proteins such as PARP1. It has an important role in the repair of DNA SSBs. *BRCA1* and *BRCA2* are the main tumor suppressors that repair DNA double (DSBs). Therefore, PARP inhibition in *BRCA*-mutant cancers can induce synthetic mortality of cancer cells due to the blockade of both DSB and SSB repair pathways. Poly (ADP-ribose) polymerase inhibitor (PARPi) targets *BRCA* mutant cancer cells. The interaction between *BRCA* and PARP is a form of synthetic mortal effect, which means the simultaneously functional loss of two genes leads to cell death (44). Currently, four PARP inhibitors (olaparib, rucaparib, niraparib, and talazoparib) have been licensed by the authorities. The efficacy of PARP inhibitors in cancer treatment is not only used for *BRCA1/2* mutant patients. Platinum sensitivity has also been reported as a prospective indicator for predicting the response to these inhibitors (45). Olaparib and rucaparib camsylates inhibit PARP 1/2/3 and have been approved for treating prostate cancer. Adverse events in this group included anemia, nausea, decreased appetite, and fatigue. FDA approved olaparib for patients with germline or somatic homologous recombination repair gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone. The EMA approved olaparib for patients with *BRCA1/2* alterations.

Rucaparib has been approved for patients with *BRCA1/2* mutations (germline and/or somatic) who have been treated with alternative AR-targeted agents and taxane-based chemotherapy (46).

Other Inhibitors in Targeted Therapy

HSP90 Inhibitors

HSP90 heat shock protein stabilizes various proteins required for the survival of cancer cells. HSP90 is a molecular chaperone and affects to several sets of signaling proteins critical for cell growth and survival (47). Several HSP90-inhibitor clinical trials are ongoing for treating many cancers. HSP 90 inhibitors are geldanamycin, radicicol, 17AAG, and luminespib.

Metalloproteinase Inhibitors

Matrix metalloproteinases (MMPs) belong to a family of zinc-dependent neutral endopeptidases (48). These enzymes can break down connective tissue. The expression of MMPs is increased in various pathological conditions such as cancer invasion, metastasis, and angiogenesis. In the context of this effect, many MMPs inhibitors are undergoing research for cancer treatment.

Neovastat inhibits MMPs 2/9/12, VEGFR2, and has been approved for advanced RCC treatment (49). Another a mmp, prinomastat, inhibits MMPs 2/3/9/13/14 and can be used for treating advanced RCC. Rebimastat, cipemastat, ilomastat, batimastat, periostat, tanomastat are other members of this family.

AR Pathway Targetting Agents

As we well know, we have had many drugs for treating prostate cancer since the discovery of the androgen signaling axis by Huggins. The overexpression of androgens and AR is related to prostate carcinoma. In castrate-resistance prostate cancer (CRPC), the intracellular androgen level is increased compared to androgen-sensitive cells and an over-expression of the AR has been observed, suggesting an adaptive mechanism (50). This founding has led to the development of several new compounds targeting the androgen axis. In addition to GnRH agonists (leuprolide acetate, goserelin, buserelin, nafarelin, triptoferin) or antagonists (ganirelix, degarelix, relugolix, cetrorelix), many drugs act on AR such as *bicalutamide, darolutamide, apalutamide, enzalutamide, flutamide, nilutamide* for treating prostate cancer. mCRPC, abiraterone acetate plus prednisolone and enzalutamide have been approved. In addition to androgen depletion therapy with castration, abiraterone acetate plus prednisolone, apalutamide and enzalutamide have been approved for treating metastatic hormone-sensitive PCa (mHSPC). *The abiraterone acetate* inhibits the cytochrome p450 17A1 (CYP17A1) enzyme that is hydroxylase (a combination of 17α-hydrolase and 17,20-lyase inhibition) and thereby is a key enzyme in the steroidogenic pathway that produces progestins, mineralocorticoids, glucocorticoids, androgens, and estrogens. The abiraterone acetate decreases the intracellular testosterone level by suppressing its synthesis at the adrenal level and inside

the cancer cells (intracrine mechanism). The abiraterone acetate must be used together with prednisone/prednisolone to prevent drug-induced hyperaldosteronism (51). Adverse events of this therapy are fluid retention, edema, and hypokalemia due to mineralocorticoids. Apalutamide, darolutamide, enzalutamide are novel non-steroidal anti-androgens with a higher affinity for the AR receptor than bicalutamide. These AR antagonists have been licensed for non-metastatic CRPC (nmCRPC) at a high risk of metastasis (52,53,54).

While previous non-steroidal anti-androgens still allow the transfer of ARs to the nucleus and would act as partial agonists, all three agents also block AR transfer and therefore suppress any possible agonist-like activity. In particular, in preclinical studies, darolutamide showed not to cross the blood-brain barrier (55,56).

However, clinical trials of new agents are ongoing on this pathway such as zopratelin doxorubicin. Zoptarelin doxorubicin is a cytotoxic hybrid molecule linking doxorubicin to an LHRH analog that selectively targets doxorubicin to cancer cells expressing LHRH-R.

Mitoxantrone is an inhibitor of topoisomerase II and a combination of mitoxantrone and prednisone has been approved as a second-line treatment for metastatic hormone-refractory prostate cancer. It inhibits protein kinase C activity. The first-line treatment for this disease is a combination of docetaxel and prednisone.

PSMA-based Therapy

PSMA PET can be used as a diagnostic tracer of metastases or for therapeutic purposes (theranostics) (57). 68gallium-labeled PSMA is a diagnostic isotope. Moreover, therapeutic radiopharmaceuticals labeled with beta (lutetium-177 or yttrium-90) or an (actinium-225) emitting isotopes could be used to treat metastatic PCa. Clinical trials with these agents are ongoing.

RANK Ligand Inhibitors

Denosumab is a human monoclonal antibody against RANKL (receptor activator of nuclear factor kappa-B ligand). RANKL is a mediator of osteoclast formation, function, and survival. In M_0 CRPC, denosumab has been associated with increased bone-metastasis-free survival (58).

Monoclonal Antibody Therapies

The immune response contains different cytokines such as ILs, interferons, and chemokines. As is well known, high-dose IL-2 treatment in metastatic RCC has modest successes and serious adverse events. Currently, IL-2 treatment is not first preferable in metastatic RCC due to adverse effects. Cancer immune editing is the process is regulated by immune checkpoints and immune checkpoint inhibitors (ICIs) are now indicated in some types of cancer types. Immune checkpoints are key regulators of the immune system. Checkpoint proteins, such as B7-1/B7-2 on antigen-presenting cells and cytotoxic T lymphocytes-4 (CTLA-4) on T-cells, help keep the immune responses homeostasis. The binding of B7-1/B7-2 to CTLA-4 keeps the T-cells in an inactive state while blocking the binding of B7-1/B7-2 to CTLA-4 whilst an ICI (anti-CTLA-4 antibody) allows the T-cells to be active and to kill tumor cells. Nowadays, T-cell immune checkpoint (CTLA4, PD-1) inhibitors are used to induce an immune response against cancer cells. T-cells are currently widely recognized as the key mediators of antitumor efficacy with ICI treatment. Normally, PD-L1 binds to PD-1 and inhibits the T-cell killing of tumor cells in addition to the T-cell receptor-antigen complex, contrary to that blocking PD-L1 or PD-1 allows the T-cell killing of tumor cells.

Today, approved checkpoint inhibitors affect targets that CTLA4, programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1). PD-1 is the transmembrane protein that interacts with PD-L1. Cancer-related upregulation of PD-L1 on the cell surface may inhibit T-cells. Antibodies that bind to either PD-1 or PD-L1 and therefore block the interaction, allow the T-cells to induce cell killing.

Cancer immunotherapy improves the survival and quality of life of patients. However, these therapies have some problems, such as adverse events and low efficacy. Immunotherapies are often limited by their immune-related adverse events such as autoimmunity, cytokine syndrome immune activation, and inflammatory responses against the healthy tissues. Therefore, finding the right combination of treatments to induce the optimal amount of immune activation and the tumor microenvironment remains an active area of clinical research. Tumor microenvironments have significant prognostic and predictive significance. The tumor microenvironment can affect the T-cell function and result in attenuated antitumor immune responses (59).

Targeting both cancer and T-cell metabolism can beneficially enhance immunity through metabolic checkpoints. In oncogenesis, over-dividing cancer cells require high glycolytic activity (Warburg effect) (60). This process generates high levels of lactate and metabolic wastes. The efficacy of ICIs can be affected by the metabolic pathways. Ligation of PD-L1 directly upregulates glycolysis in cancer cells by promoting glucose uptake and production of lactate, thus promoting growth and metastasis (61). However, the PI3K/AKT/mTOR pathway plays a critical role in integrating the metabolism signals of cancer and immune cells. Inhibition of this pathway with rapamycin, along with ICIs, enhances the cytotoxic effect and memory T-cell function (62). Other new targets such as amino acids (l-arginine, tryptophan, glutamine) and their metabolic pathways have become a promising strategy in cancer therapy (63). For example, indoleamine 2,3-dioxygenase-1 (IDO1)-selective enzyme inhibitor epacadostat along with pembrolizumab is under clinical trials due of its effect on tryptophan-kynurenine-aryl hydrocarbon receptor pathway (64).

Pembrolizumab and nivolumab belong to the PD-1 inhibitor family. Atezolizumab, avelumab, and durvalumab are examples of PD-L1 inhibitors, lastly, ipilimumab is a CTLA4 inhibitor (65).

PD-1 and PDL-1 Inhibitors

Pembrolizumab is an inhibitor of PD-1 proteins on the T-cells and helps the immune system kill cancer cells. It has been approved for the first-line treatment of advanced RCC in adults along with axitinib. Furthermore, it has been approved for treating locally advanced/metastatic urothelial carcinoma in adults

who have received prior platinum-containing chemotherapy as monotherapy. Another indication of pembrolizumab is the treatment of locally advanced/metastatic urothelial carcinoma in adults who are ineligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 with a combined positive score (CPS) ≥10 as monotherapy. The ICI pembrolizumab has been approved for all MMR-deficient cancers or in those with unstable microsatellite status (MSI-high) (66,67).

Nivolumab is another inhibitor of the PD-1 protein. It has been approved for first-line therapy for advanced RCC and second-line therapy for urothelial carcinoma (68). It is also used as a second-line treatment for RCC after anti-angiogenic treatment has failed. Nivolumab can be prescribed for locally advanced/metastatic forms of the conditions that experience disease progression during or following platinum-based chemotherapy or have progression within twelve months of neoadjuvant/adjuvant treatment with platinum-containing chemotherapy.

Atezolizumab is a PD-L1 inhibitor, a fully humanized engineered IgG1 monoclonal antibody. It can be prescribed for treating people with locally advanced/metastatic urothelial carcinoma who have disease progression during/following platinum-containing chemotherapy or have disease progression within twelve months of neoadjuvant/adjuvant treatment with platinum-containing chemotherapy. After atezolizumab failed a phase III trial for second-line bladder cancer, FDA altered the use of atezolizumab as a first-line treatment for metastatic bladder cancer in people who cannot receive cisplatin-based chemotherapy and have high levels of PD-L1 (69).

Durvalumab is a known as a checkpoint inhibitor drug. It is the human IgG1 kappa monoclonal antibody (IgG1k) that blocks the interaction of programmed cell death ligand 1 (PD-L1) with the PD-1. It has been approved for adults with locally advanced or metastatic urothelial carcinoma who either have disease progression during/following platinum-containing chemotherapy or have disease progression within twelve months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (70).

Avelumab is another PD-L1 inhibitor. It is used to treat locally advanced/metastatic urothelial carcinoma whose disease progresses during/following first-line platinum-containing chemotherapy or within twelve months of neoadjuvant/adjuvant platinum-containing chemotherapy and maintenance treatment of patients with locally advanced cancer (71). Furthermore, avelumab along with axitinib has been approved for the first-line treatment of RCC.

Another monoclonal antibody, Indium (^{111}In) Capromab pendetide is a mouse monoclonal antibody that recognizes a protein found in prostate cancer. It is a diagnostic murine IgG1 and is used to imagine the extent of prostate cancer (72).

The other monoclonal antibodies are: *Rituximab* targets CD20 found on B cells and activates cell death. Trastuzumab binds to the HER2/neu (ErbB2) receptor. Alemtuzumab binds to CD52, which is a protein present on the surface of mature lymphocytes. Cetuximab and panitumumab target the EGFR and bevacizumab targets the circulating VEGF ligand.

Anti-CTLA-4 Antibodies

Ipilimumab is a monoclonal anti-CTL4 antibody that works to activate the immune system by targeting CTLA-4. CTLs can recognize and destroy cancer cells. However, there is also an inhibitory mechanism (CTL4 antibody) that interrupts this destruction and anti-CTL4 antibody drugs turn off this inhibitory mechanism and allow CTLs to continue to destroy the cancer cells. Ipilimumab is undergoing clinical trials for treating advanced bladder cancer and metastatic hormone-refractory prostate cancer (73). Nivolumab along with ipilimumab is indicated for treating intermediate or poor risk, previously untreated advanced RCC (68).

Tremelimumab is a humanized monoclonal anti-CTLA-4 antibody (74). It is undergoing clinical trials for treating advanced bladder cancer with a durvalumab combination.

Treatment protocols for renal cancer, bladder cancer, prostate cancer, and testis cancer are summarized in Table 2-5.

Combination Therapies

Combination therapies are new therapy modalities for increasing the efficacy of cancer treatment with used chemotherapy, and ICIs in different regimes. Combining therapy can obtain costimulatory (agonist antibodies) and coinhibitory (antagonist antibodies) effects. Moreover, in some studies, high response rates to chemotherapy have been documented after ICIs failure (75). This additive effect can be expanded with checkpoint inhibitors, personalized cancer vaccines and novel-targeted therapies directed at the tumor microenvironment, tumor metabolism, and the host microbiome.

The first combination therapy model was used to CTLA-4 and PD-1 inhibition together. The combination use of ipilimumab and nivolumab has been approved for first-line therapy for advanced RCC. The other, durvalumab and avelumab, are anti-PD-1/PD-L1 checkpoint inhibitors that can be used in combination to treat advanced bladder cancer.

The second model is the combination of small-molecule targeted drugs with immunotherapy such as PD-1 antibody. Lenvatinib/pembrolizumab combination therapy has been approved for treating advanced or metastatic RCC. The combination of pembrolizumab with another small molecule anti-angiogenesis agent, axitinib, has been approved for the first-line treatment of advanced RCC (76,77).

The third model is the combination of ADC. Until then today, several ADC molecules have been developed. With the improvement of antibody-conjugated technology, ADC drugs such as polatuzumab vedotin-piiq, enfortumab vedotin-ejfv, fam-trastuzumab deruxtecan-nxki, sacituzumab govitecan-hziy, and belantamab mafodotin-blmf have been developed (78,79,80). Enfortumab vedotin is a new ADC agent used for locally advanced or metastatic urothelial cancer that has received a PD-1 or PD-L1 inhibitor and a platinum-containing therapy.

The other technology is PROTAC, includes uses the small molecules that recruit target proteins for ubiquitination and removal by the proteasome (81). These agents reduce the activity of target proteins by catalytic degradation. Currently, two

drugs (ARV-110 and ARV-471) designed by PROTAC technology have entered clinical trials (81). ARV-110 mediates specifically AR degradation and has been used for treating patients with metastatic CRPC (82). The other, ARV-471, is an endoplasmic reticulum protein degrading agent.

Lastly, synthetic lethality means that the inactivation of both genes simultaneously by gene mutation/deletion or pharmacological inhibition leads to cell death (83). This technology is aimed at rearranging genes by gene-editing tools. Oncogenes or tumor suppressor genes can be targeted with gains or losses. Therefore, synthetic lethality has promising potential to drive the discovery of new anti-cancer targets and subsequently the development of effective drugs or combination strategies that are still needed for treating cancers. There are the synthetic lethal interaction of combined BCL-XL and MEK inhibition in KRAS-mutant cancer models and the successful clinical application of PARP inhibitors in BRCA mutant cancer (44,84).

Tumor-Specific Vaccines

Recent studies have shown that personalized neoantigen-based tumor-specific vaccines hold considerable promise in the context of targeted therapy. Most cancer vaccines have failed for many potential reasons, including an improper selection of a target antigen. The most widely known are Oncophage and Sipuleucel-T vaccines. Oncophage is an autologous personalized cancer vaccine heat shock protein-peptide complex-9 (HSPPC-96). It has been derived from a patient's tumor by extracting heat shock protein 96. It boosts the anticancer immune response against RCC (85). The other one, Sipuleucel-T is a therapeutic vaccine as autologous cellular immunotherapy. It boosts anti-prostate cancer adaptive immune response of (86).

Toll-like Receptors (TLRs)

TLRs are receptors that recognize various pathogen-associated molecular patterns. They are key components of innate immunity which are activated in response to pathogens and non-pathogenic components of damaged tissues. TLR agonists have been developed to treat cancers by upregulating the innate immune system. In contrast, TLR antagonists may be used to treat several inflammatory conditions. TLR agonists used as single agents, especially when applied locally, can effectively eradicate tumors due to their potent stimulation of innate and adaptive immunity and their effects on the tumor microenvironment. Two TLR agonists, Bacillus Calmette-Guerin and imiquimod, have been approved for clinical use as monotherapy for cancer (87).

However, new target agents are undergoing clinical trials such as dianhydrogalacticol (VAL-083) or vintafolide. VAL-083 is a bifunctional alkylating agent that induces interstrand DNA cross-links targeting the DNA. Vintafolide is drug conjugate consisting of a small molecule targeting the folate receptor (88).

Nowadays, to deal with the major challenges of targeted anti-cancer drugs, many strategies have been applied, such as new generation anti-cancer drugs against drug resistance mutations, multitarget drugs, combination therapy, and drugs targeting CSCs (89,90). CSCs are new targets for treating cancer such as salinomycin. Moreover, some small-molecule inhibitors against miRNAs have been suggested in many types of research for cancer treatment. Furthermore, some proteins may be attractive anti-cancer targets. For example, KRAS is the most frequently mutated isoform of the RAS proto-oncogene, which has a predominant role in driving the initiation and progression of cancers (91). In addition to KRAS, novel targets can be described for anticancer therapy as myc proto-oncogene, phosphatases, and protein-protein interactions (92,93,94).

Conclusion

In summary, small-molecule targeted drugs and monoclonal antibodies will continue to be the alternative options in cancer treatment because of their advantages. With a better understanding of oncogenesis and the evolution of new drug R&D technologies (ADC, PROTAC) new targeted therapy drugs targeting new genes or mechanisms of action will be developed in the near future.

Table 2. Targeted therapies for treating RCC (95)			
First-line therapy for clear cell histology			
Risk	**Preferred regimens**	**Other regimens**	**Useful in certain circumstances**
Favorable	Axitinib + Pembrolizumab Cabozantinib + Nivolumab Lenvatinib + Pembrolizumab	Axitinib + Avelumab Cabozantinib Ipilimumab + Nivolumab Pazopanib Sunitinib	Axitinib High dose IL-2
Poor/intermediate	Axitinib + Pembrolizumab Cabozantinib + Nivolumab Lenvatinib + Pembrolizumab Cabozantinib	Axitinib + Avelumab Pazopanib Sunitinib	Axitinib High dose IL-2 Temsirolimus
Subsequent therapy for clear cell histology			
	Cabozantinib Lenvatinib + Everolimus Nivolumab	Axitinib Axitinib + Pembrolizumab Cabozantinib + Nivolumab Ipilimumab + Nivolumab Lenvatinib + Pembrolizumab Pazopanib Sunitinib Tivozanib Axitinib + Avelumab	Everolimus Bevacizumab High dose IL-2 Sorafenib Temsirolimus
Therapy for non-clear cell histology			
	Cabozantinib Sunitinib	Lenvatinib + Everolimus Nivolumab Pembrolizumab	Axitinib Bevacizumab Bevacizumab + Erlotinib Bevacizumab + Everolimus Erlotinib Everolimus Pazopanib Temsirolimus
RCC: Renal cell carcinoma			

Table 3. Targeted therapies for treating urothelial carcinoma (96)	
Adjuvant therapy	
No previous platinum-based neoadjuvant therapy (pT3, pT4a, pN+)	Other recommended regimes: After the chemotherapy regimes nivolumab
Previous platinum-based neoadjuvant therapy (ypT2-ypT4a or ypN+)	Nivolumab
First-line systemic therapy for locally advanced/metastatic disease (Stage IV)	
Cisplatin eligible	Chemotherapy followed by avelumab maintenance therapy
Cisplatin ineligible	Chemotherapy followed by avelumab maintenance therapy Atezolizumab (only for tumors express PD-L1 or who are ineligible for any platinum-containing chemotherapy regardless of PD-L1 expression) Pembrolizumab (for locally advanced or metastatic urothelial carcinoma who are ineligible for any platinum-containing chemotherapy)
Second-line systemic therapy for locally advanced/metastatic disease (Post platinum stage IV)	
Preferred regimen	Pembrolizumab
Alternative regimens	Nivolumab Avelumab Erdafitinib (or post checkpoint inhibitors) Enfortumab vedotin ejfv (or post checkpoint inhibitors)
Subsequent-line systemic therapy for locally advanced/metastatic disease (Stage IV)	
	Enfortumab vedotin ejfv Erdafitinib

Table 4. Targeted therapies for treating prostate cancer (97)	
Systemic therapy for castration naive prostate cancer	
Abiraterone Apatulamide Enzalutamide	
Systemic therapy for M0 castration resistance prostate cancer (CRPC)	
Apatulamide Enzalutamide Darolutamide	
Systemic therapy for M1 castration resistance prostate cancer (CRPC)	
No prior docetaxel/no prior novel hormone therapy	Abiraterone Enzalutamide Sipuleucel T
Prior novel hormone therapy/no prior docetaxel	Sipuleucel T Olaparib (for HRRm) Pembrolizumab (for MSI-H, dMMR, or TMB 10 mut/Mb) Rucaparib (BRCAm) Abirateron+dexamethasone Enzalutamid
Prior docetaxel/no prior novel hormone therapy	Abirateron Enzalutamide Mitoxantrone Pembrolizumab (for MSI-H, dMMR, or TMB 10 mut/Mb) Sipuleucel T
Prior docetaxel and prior novel hormone therapy	Olaparib (for HRRm) Pembrolizumab (for MSI-H, dMMR, or TMB 10 mut/Mb) Mitoxantrone Rucaparib (BRCAm) Abirateron Enzalutamide

Table 5. Targeted therapies for treating testis cancer (98)	
Third-line therapy for metastatic germ cell tumors	
Post first and second-line chemotherapy regimes	Pembrolizumab (for microsatellite instability-high (MSI-H)/double mismatch repair (dMMR) or Tumor mutational burden high (TMB-H) tumors

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Short Quiz

1- Which one is not PD-1 and PDL-1 inhibitor?

A) Pembrolizumab
B) Nivolumab
C) Bevacizumab
D) Atezolizumab
E) Avelumab

Answer: C

2- Which one is not receptor tyrosine kinase inhibitors (TKIs)?

A) c-Met inhibitors
B) BCL-2 inhibitors
C) FLT3 inhibitors
D) EGFR inhibitors
E) ALK inhibitors

Answer: B

3- Which one does not act on androgen receptors?

A) Darolutamide
B) Apalutamide
C) Enzalutamide
D) Abiraterone Acetate
E) Flutamide

Answer: D

Original Article

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Preoperative De Ritis Ratio for the Evaluation of Recurrence and Progression in Non-muscle Invasive Bladder Cancer

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Abstract

Objective: This study aimed to investigate the potential predictive value of the preoperative De Ritis ratio in patients with primary non-muscle invasive bladder cancer (NMIBC).

Materials and Methods: Of 212 patients who underwent transurethral resection of bladder tumour surgery for primary bladder cancer at a single academic centre between 2010 and 2016, we retrospectively analysed the clinical and pathological data. Blood samples were collected 1-7 days before surgery. The De Ritis ratio's potential prognostic value of was evaluated using receiver operating characteristic (ROC) curve analysis.

Results: One hundred twenty-five patients (or 59%) were found to have high-risk diseases, 17 patients (or 8%) had intermediate-risk diseases, and 70 patients (or 33%) had low-risk diseases. We investigated which cut-off value for De Ritis ratio could predict NMIBC risk groups in the preoperative period. The ROC analysis showed that there was no significant cut-off value in either low-risk [area under the curve (AUC)=0.457] or high-risk (AUC=0.551) patients. According to the European Organization for Research and Treatment of Cancer risk groups, when the quantitative values were compared, it was seen that low-risk patients were younger (p=0.005) and this group's alanine aminotransaminase (p<0.001) values were higher. De Ritis ratio was statistically similar in all patient groups.

Conclusion: According to our present results, the De Ritis ratio does not add any additional value to existing prognostic models. Investigating De Ritis ratio simultaneously with markers such as albumin, C-reactive protein, neutrophil-lymphocyte ratio, which are used successfully in many cancer types, may yield successful results in prospective, more comprehensive studies.

Keywords: Primary bladder cancer, De Ritis ratio, biological markers, prognosis

Introduction

The seventh most prevalent cancer in men and the eleventh most common cancer overall for both sexes is bladder cancer (1). 75% of bladder cancers are non-muscle invasive bladder cancers (NMIBC) at the time of diagnosis (2). Patients with NMIBC are followed up in accordance with the disease-specific risks of recurrence and progression after transurethral resection of bladder tumour (TUR-B). NMIBC development, recurrence, and disease-related death rates vary (3). As a result, the therapy of NMIBC patients is dictated by the condition's hazards and personal preferences. To predict oncological outcomes and pick the optimal course of treatment for each group of patients, it is critical to identify individuals with equivalent risks of recurrence and progression.

The World Health Organization (WHO) histological grade, the number of tumours, their size, the T-stage, and the presence of carcinoma *in situ* (CIS) are all factors that the European Organization for Research and Treatment of Cancer (EORTC) risk table uses to predict recurrence and progression (3). Numerous markers have been researched to predict the risks of progression and recurrence in routine clinical practice; however, none of them are routinely used due to their low sensitivity and specificity levels (4).

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The enzymes aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT), which are released from the liver cells into the bloodstream following hepatocellular injury, are frequently used to assess liver function (5). Fernando De Ritis originally studied the AST/ALT ratio in 1957; this ratio is now known as the De Ritis ratio (6). De Ritis ratio is changed in many conditions, including cirrhosis, viral hepatitis, and alcoholic hepatitis. The De Ritis ratio has a standard value of about 1.5 (7). Recent oncological studies have reported that AST and ALT act as catalysts in the synthesis of nucleotides and non-essential amino acids in tumour cells (8). AST and ALT levels become elevated with increases in anaerobic glycolysis and glucose and glutamine metabolism during adenosine triphosphate synthesis; this is called the Warburg effect (9,10). The De Ritis ratio is a helpful predictive indicator for individuals with malignant tumours of the lung, colon, pancreas, and upper urinary system, according to several recent studies (11,12,13,14).

In this context, we retrospectively analyzed data from NMIBC patients who underwent TUR-B to investigate whether the preoperative De Ritis ratio may predicts the risks of cancer recurrence and progression.

Materials and Methods

Ethical approval was obtained from our local ethics committee. The Medical Specialization Education Board of Samsun Training and Research Hospital granted clearance for this retrospective study with the number 203 dated 26.12.2017. The Dean of the Faculty of Medicine of the University of Health Sciences authorized this clearance with decision number 2018/4 dated 22.01.2018.

The medical records of patients with primary bladder cancer who had TUR-B at the Samsun Training and Research Hospital in Turkey between 2010 and 2016 were retrospectively reviewed. 212 NMIBC patients' individual medical records, test findings, and pathology reports were examined. Patients were excluded if they had transitional cell non-epithelial bladder cancer, concomitant tumours, chronic use of medications that elevated liver enzymes, hepatic disease, or incomplete TUR-B.

The tumour tissues had been graded using the 1973 WHO classification system (15) and staged using the 2009 tumor-node-metastasis classification system by the Union for International Cancer Control (16). The EORTC recommended using tumour size and number, recurrence rate, T-stage, concurrent CIS, and histological grade to assess the risks of progression and recurrence (3). Patients with tumours that are primary, solitary, TaG1 (low-grade, papillary urothelial neoplasm with low malignant potential), tiny (diameter 3 cm), and the absence of concomitant CIS are at low risk, according to the European Association of Urology guidelines. High-risk patients had numerous recurring TaG1/G2 tumours with diameters 3 cm, HG/G3 tumours, or CIS. Patients with tumoral characteristics, on the other hand, who range into the low- and high-risk diseases groups, are at an intermediate risk (17).

Up to one week before surgery, routine preoperative biochemical tests were conducted to evaluate the levels of AST and ALT. Automatic analyzers were used to measure the AST and ALT levels by colorimetric technique. In our biochemistry lab, the maximum standard values for AST and ALT were 40 U/L and 35 U/L, respectively. Divide AST by ALT to obtain the De Ritis ratio.

Statistical Analysis

The software program SPSS Statistics were used to examine the data (version 23; IBM Corp., Armonk, NY, USA). Using the Shapiro-Wilk test, the normality of the data distribution was evaluated. Data that weren't normally distributed were compared using the Kruskal-Wallis and Mann-Whitney U tests. To compare qualitative data, the chi-square test was employed. The De Ritis ratio was used to classify the patients, and binary logistic regression was applied to compare the independent risk factors within and between the groups. Frequencies (percentages) are used to portray qualitative data, while medians are used to present quantitative data that did not follow a normal distribution (ranges). The p-value cut-off for statistical significance was 0.05.

Results

The demographic, clinical, and histological characteristics of 212 NMIBC patients who underwent TUR-B are described in Table 1. Patients were divided into three risk groups: high (n=125; 59%), intermediate (n=17; 8%), and low (n=70; 33%).

Table 1. Demographic and clinical data of the patients

	Total (n=212)
Age	68 (23-89)
Gender	
Male	193 (91.0)
Female	19 (9.0)
The T category	
Ta	95 (44.8)
T1	117 (55.2)
WHO grade 1973	
Grade 1	95 (44.8)
Grade 2	24 (11.3)
Grade 3	93 (43.9)
Associated CIS	
No (-)	208 (98.1)
Yes (+)	4 (1.9)
Number of tumours	
Single	171 (80.7)
Multiple	41 (19.3)
Tumour diameter	
<3 cm	151 (71.2)
≥3 cm	61 (28.8)
EAU NMIBC risk group	
Low risk	70 (33.0)
Intermediate risk	17 (8.0)
High risk	125 (59.0)

WHO: World Health Organization, CIS: Carcinoma *in situ*, EAU: European Association of Urology, NMIBC: Non-muscle invasive bladder cancers

We investigated the cut-off level for the pre-treatment De Ritis ratio that could predict risk in NMIBC patients. In receiver operating characteristic curve analysis, no significant differences were identified in cut-off values between low-risk [area under the curve (AUC)=0.457] and high-risk (AUC=0.551) patients (Figure 1A-B).

Quantitative differences between risk groups showed that low-risk patients were younger (p=0.005) and had higher ALT levels (p=0.001) than high-risk patients (Table 2). The De Ritis ratio, even so, was comparable across all groups.

The De Ritis ratio was unaffected by tumour features in the univariate and multivariate studies (Table 3). Additionally, no correlation between the De Ritis ratio and the EORTC recurrence and progression scores was found to be statistically significant (Table 4).

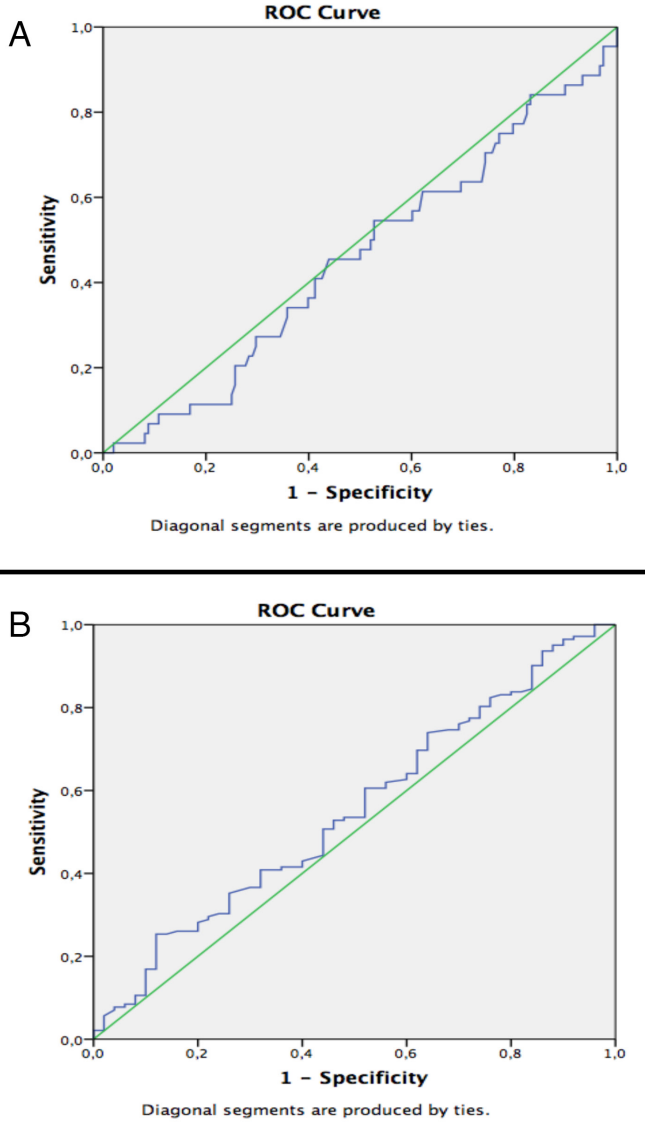

Figure 1. A- ROC curve analysis for low risk patients (AUC=0.457), B- ROC curve analysis for high risk patients (AUC=0.551)

ROC: Receiver operating characteristic, AUC: Area under the curve

Discussion

A comparison of quantitative variables between EORTC risk groups in this study revealed that low-risk patients were younger (p=0.005) and had higher ALT levels (p<0.001). Even so, preoperative the De Ritis ratio was similar across all groups.

The risks of recurrence and progression of NMIBC are determined using the EORTC risk table (3). Despite the risk stratification and use of intravesical therapy, there were high rates of recurrence (70%) and progression (30%), which poses a significant obstacle to the treatment of NMIBC (18). Pretreatment markers are required to predict the risks of recurrence and progression at the initial diagnosis and to identify misclassified or inadequately classified patients (19).

Although ALT is exclusive to the liver, AST is broadly expressed in various tissues, including the liver, brain, kidney, muscle, and even the heart (7). AST is preferentially used instead of ALT during anaerobic glycolysis; therefore, a higher De Ritis ratio is expected during periods of oxidative stress. The precise mechanism has not, however, been completely clarified (20,21,22). During frequent cell proliferation, such as in areas of tissue damage or tumours, an increase in AST is likely to increase the De Ritis ratio, which makes it an enticing potential biomarker (14). Although research on NMIBC is lacking, many recent studies have found that AST and ALT levels can help predict the development of upper urinary tract, colon, pancreatic, and lung cancers (11-14). In a study of the use of De Ritis ratio in NMIBC patients, Laukhtina et al. (23) observed a significant predictive value only in NMIBC patients with recurrence-free survival. The De Ritis ratio, according to the authors, did not influence the prognostic models.

In our study, no De Ritis ratio cut-off value could be identified that predicted a high risk. However, recent studies have reported different cut-offs for the prognosis of various types of cancer types. Patients with gastric cancer and a De Ritis ratio of greater than 0.8 have a better prognosis, according to Chen et al. (24). According to Tan et al. (13), individuals with distal cholangiocarcinoma should have a De Ritis ratio of >2.0 as a useful indicator of long-term survival. Additionally, the De Ritis ratio cut-off value that indicated survival in patients with urological malignancies ranged from 1.26 to 1.6. (25-27). Age (p=0.001), T-stage (p=0.001), and De Ritis ratio (cut-off value: 1.3) were thought to be independent predictive markers for the overall survival of patients with muscle-invasive bladder cancer after radical cystectomy by Gorgel et al. (28). In patients who underwent surgery for upper urinary tract urothelial carcinomas, Lee et al. (25) found that the De Ritis ratio (cut-off value: 1.5), age, T-stage, and lymph node involvement were related to cancer-specific survival and overall survival. Previous studies have shown that the De Ritis ratio correlated with lymph node involvement and recurrence-free survival in upper urinary tract malignancies, although we did not find correlations between the De Ritis ratio and tumour characteristics, recurrence, or progression scores (29,30). Tumour parameter analyses in our study, both univariate and multivariate, revealed that tumour parameters had no effect on the De Ritis ratio. Furthermore, no correlation was found between the EORTC recurrence and progression scores and

Table 2. Comparison of De Ritis ratio by EORTC risk groups				
	Low risk (n=70)	**Intermediate and high risk (n=142)**	**Total (n=212)**	**p-value**
Age	64 (24-87)	70 (23-89)	68 (23-89)	0.005
Recurrence probability	4 (0-9)	3 (0-9)	3 (0-9)	0.564
Progression probability	9 (0-18)	9 (0-18)	9 (0-18)	0.897
De Ritis ratio	1.26	Intermediate r. (1.17) - High r. (1.27)	1.25	0.908
AST	20 (7-68)	19 (10-56)	19.5 (7-68)	0.875
ALT	21 (8-69)	12 (3-27)	15 (3-69)	<0.001
EORTC: European Organization for Research and Treatment of Cancer, AST: Aspartate aminotransaminase, ALT: Alanine aminotransaminase, r: Range				

Table 3. Correlation between the De Ritis ratio and tumour characteristics				
	AST/ALT (Univariate)		**AST/ALT (Multivariate)**	
	Risk ratio	**p-value**	**Risk ratio**	**p-value**
Tumour diameter	0.895	0.715	0.826	0.620
The T category	0.870	0.616	0.794	0.547
Number of tumours	0.890	0.740	0.913	0.830
WHO Grade 1973	0.977	0.875	0.923	0.682
Associated CIS	1.167	0.879	1.099	0.931
AST: Aspartate aminotransaminase, ALT: Alanine aminotransaminase, WHO: World Health Organization, CIS: Carcinoma *in situ*				

Table 4. Correlation between De Ritis ratio and EORTC recurrence and progression scores	
	De Ritis ratio
Recurrence	r=0.020; p=0.770
Progression	r=0.032; p=0.639
EORTC: European Organization for Research and Treatment of Cancer, r: Spearman correlation coefficient	

the preoperative de RITIS ratio. Considering these findings, we conclude that the De Ritis ratio does not predict risk beyond the data provided by common clinical factors.

Study Limitations

The retrospective analysis of the prospectively acquired data and the lack of follow-up information regarding the specific recurrence and progression rates were the study's limitations. Moreover, undetected liver or other diseases may have affected the AST and ALT levels. The lack of additional systemic inflammatory indicators in our investigation, such as the neutrophil-lymphocyte ratio (NLR) or platelet-lymphocyte ratio, is a significant limitation. The primary goal of this study was to investigate the correlation between De Ritis ratio and NMIBC, although we discovered that the NLR value of the high-risk group was significantly higher (p=0.001) than that of the intermediate and low-risk groups.

Finally, variability in the skills of surgeons (i.e., quality of surgery) and pathologists (i.e., determination of T-staging, histological grading, and CIS evaluation) may have affected the results. Despite these limitations, our study is one of the few to look at the correlation among preoperative De Ritis ratio, disease risk categories, and tumour characteristics in NMIBC patients.

Conclusions

In NMIBC patients, the preoperative De Ritis ratio is not significantly correlated with disease risk categories, tumour characteristics, or recurrence or progression scores. As a result, the De Ritis ratio falls short of outperforms existing prognostic models. More robust results may be obtained from prospective studies with longer follow-up durations that also evaluate routine biochemical markers, such as albumin, C-reactive protein, and NLR, in various cancer types.

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Ethics

Ethics Committee Approval: The Medical Specialization Education Board of Samsun Training and Research Hospital granted clearance for this retrospective study with the number 203 dated 26.12.2017. The Dean of the Faculty of Medicine of the University of Health Sciences authorized this clearance with decision number 2018/4 dated 22.01.2018.

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Authorship Contributions

Concept: R.İ., Design: R.İ., A.B., Supervision: A.B., M.A., Data Collection-Processing: E.K., Analysis-Interpretation: M.A., Literature Review: M.K.A., L.İ., Writing: R.İ., Critical Review: M.K.A., L.İ.

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Original Article

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The Effect of Second TURBT on Recurrence and Progression in Primary Ta High-grade Bladder Cancers: A Multicenter Clinical Trial Comparing Long-term Outcomes

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Abstract

Objective: To evaluate the potential significance of the second transurethral resection of a bladder tumor (TURBT) in a population of patients whose primary pathology was high-grade pTa (Ta/HG) and who had received Bacillus Calmette-Guérin (BCG) treatment for at least 12 on oncological outcomes, based on the presence or absence of detrusor muscle.

Materials and Methods: Patients with primary Ta/HG tumors (n=207) that met the inclusion criteria were grouped based on the presence of muscle tissue in the first TURBT and whether the secondary TURBT was performed. Progression, recurrence, and disease-free survival rates were compared between the groups.

Results: Median follow-up period was 24 (12-205) months. In cases with muscle in the first TURBT, a second TURBT significantly increased the median disease-free survival time compared with those that did not undergo the second TURBT [32 months (12-83) vs 12 months (6-67); p<0.005]. In cases without muscle in the first TURBT, the second TURBT significantly reduced the rate of progression (p<0.05). Regression analysis showed that tumor size >3 cm [95% confidence interval (CI)=1.09-2.96, hazard ratio (HR)=1.79, p=0.021], presence of muscle tissue (95% CI=0.35-0.92, HR=0.57, p=0.022), and multiple tumor (95% CI=1.06-2.90, HR=1.75, p=0.028) were independent factors affecting disease relapse in primary Ta/HG tumor.

Conclusions: In patients with primary Ta/HG tumors, if there was no muscle in the first TURBT, a second TURBT should be performed to achieve lower progression rates. If there is muscle in the first TURBT, the second TURBT will only increase the median disease-free survival time.

Keywords: Bladder cancer, second look, urothelial carcinoma, second TURBT, BCG, pTa, high grade

Introduction

Up to 70 to 80% of all bladder neoplasms are non-muscle invasive bladder cancers (NMIBC). While 70% of NMIBCs are limited to the mucosa (Ta), 30% occupy the lamina propria (T1) (1). High-grade pTa tumors (Ta/HG) have a 10-15% higher risk of progression than low-grade pTa tumors (Ta/LG), but this risk is still lower than that of T1 tumors (2). When the classification proposed by the World Health Organization (WHO)/International Society of Urological Pathology in 2004 was widely adopted, all grade three bladder tumors and some previously grade two bladder tumors in the 1973 WHO classification were reclassified as high grade (3). Consequently, the high-grade pTa group was more heterogeneous than the pTaG3 group (4). This may lead to some differences in terms of clinical management and therefore the treatment guidelines for pTaG3 (WHO classification of 1973) may not apply to the pTa/HG group (5).

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Data on the indications and results of a second transurethral resection of a bladder tumor (TURBT) in Ta/HG tumors are limited and different approaches have been described in the literature (6-9). When we look at the guidelines, both the European Association of Urology and the National Comprehensive Cancer Network guidelines both suggest the second TURBT for pTa/HG urothelial carcinoma if there is no muscle tissue in the biopsy (10,11). However, American Urological Association guidelines did not make any recommendations regarding the need for the second TURBT in cases that had muscle in their first TURBT (12). Similarly, whether the presence of muscle changes the approach was not specified by the National Institute for Clinical Excellence (13).

In the literature, there is no consensus on different clinical approaches and results in the second TURBT of Ta/HG (6,8,14). Herr (8) noted that Ta/HG tumors are as deadly as T1 tumors and therefore should be treated with transurethral resection, intravesical therapy, and cystectomy in case of recurrence or progression, however they did not make any comment on the second TURBT. Dangi et al. (6) reported that the second TURBT increased median recurrence-free survival in primary Ta/HG tumors, while Tinay et al. (14) found that the second TURBT performed in patients with Ta/HG tumors resulted in longer median time to recurrence and progression and lower recurrence rates if the muscle tissue was absent at the first TUR and longer median time until the first recurrence if the muscle tissue was present at the first TUR.

This study aimed to determine the potential significance of the presence of detrusor muscle tissue at first TURBT in a population of patients whose primary pathology was Ta/HG and who were treated with Bacillus Calmette-Guérin (BCG) for at least 12 months. Additionally, we wanted to assess the effect of a second TURBT, performed on the basis of the presence or absence of detrusor muscle tissue, on recurrence and/or progression rates.

Materials and Methods

Following University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Clinical Research Ethics Committee approval (decision number: 2021/01-28, date: 25.01.2021), the data of patients, whose primary TURBT pathology result was Ta/HG NMIBC (reported according to the WHO 2004 classification) between January 2004 and February 2021, were retrospectively collected from four centers participating in the study. Patients' demographic and clinical characteristics [age, sex, body mass index (kg/m^2)], smoking status, comorbidities (hypertension, diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular disease), Charlson comorbidity index and occupational exposures were determined. The first TURBT features [number of tumors (single, multiple), tumor size, and pathological features], the second TURBT features (visual persistent tumor, pathological features), follow-up status, and relapse time (defined as recurrence or progression time) were recorded.

For patients who underwent a second TURBT, this procedure was performed between 2 and 6 weeks after initial TURBT. Follow-up visits occurred at three-monthly intervals during their first two years, and then biannually during their three subsequent years and then once a year afterwards by cystoscopy, cytology, and tumor resection, if any tumor was detected. Instances with Ta/HG in the first TURBT and T1/HG or T1/LG in the second TURBT were not evaluated as progression. The rates are expressed separately. Cases with Ta/LG or Ta/HG tumors in the bladder during the follow-up were considered recurrence, T1± CIS as progression, cases with recurrence ± progression were considered relapse. Pathologies seen in the second TURBT were also examined.

In total, the data of 4244 patients from 4 centers were evaluated. There were 372 patients whose primary pathology was Ta/HG. Among these, patients who received BCG induction therapy and at least 1-year BCG maintenance in accordance with the the Southwest Oncology Group (SWOG) protocol had a minimum 12-month follow-up, had no carcinoma *in situ* (CIS) in its primary pathology and had a complete first TURBT were included in the study. The flowchart is summarized in Figure 1. Those with variant histology (n=4) and tumor in the upper urinary tract (n=5) in the first TURBT, patients who did not receive at least 1 year of BCG maintenance therapy (n=64), and ones that did not meet the follow-up time (n=45) and other inclusion criteria [incomplete TURBT (n=47)] were excluded from the study. Two-hundred-seven patients who met the inclusion criteria were evaluated in 4 groups. Group 1 included patients who had detrusor muscle tissue at the first TURBT and underwent a second TURBT. Group 2 included patients who had detrusor muscle at the first TURBT but did not undergo a second TURBT. Group 3 consisted of patients that did not have detrusor muscle tissue at the first TURBT and did not undergo the second TURBT, while group 4 had patients that did not have detrusor muscle in the first TURBT, and underwent the second TURBT (Figure 1). Recurrence and progression rates, and time to progression were recorded in each group. The length of time that the patient survived without relapse after receiving BCG induction therapy and minimum 1 year maintenance BCG according to the SWOG protocol was evaluated as disease-free survival.

Statistical Analysis

The Kolmogorov-Smirnov test was used to analyze the normality of the data. The Pearson chi-square test and Fisher's exact test were used to compare categorical variables. Continuous variables with a normal distribution were presented as mean ± standard deviation and variables with non-normal distribution as median (range) for descriptive statistics in the study. Mann-Whitney U test was used for paired comparisons between groups. For quantitative data, one-way analysis of variance (ANOVA) is used for normally distributed variables and Kruskal-Wallis test with Bonferroni posthoc correction for others (15). For all tests, the likelihood of a type I error was α=0.05. Furthermore, Bonferroni adjustment was used to determine significant variants in the four groups. The Bonferroni cut value was calculated as 0.05/6.

We conducted univariable and multivariable Cox proportional hazard regression analysis to determine risk factors for recurrence in patients with pTaBG, calculating hazard ratios (HRs) and 95% confidence interval (CI). Kaplan-Meier survival curves with 95% CI determined the effect of a second TURBT and the presence of muscle tissue in the recurrent tumor specimen. Survival outcomes were compared between groups using the log-rank

test. IBM SPSS V.22 package software program was used for statistical analyses.

Results

The median follow-up was 24 (12-205) months. The primary pathology of 8.7% of patients was determined as Ta/HG. The demographic, clinical, and pathological characteristics of 207 patients who met the inclusion criteria are summarized in Table 1. Second TURBT was performed in 97 patients (46.8%) and persistent visual tumor was observed in the second TURBT in 15.4% in group 1 and in 55.6% in group 4 ($p<0.05$). The tumor detection rate in the second TURBT was significantly higher in group 4 than in group 1. Analysis of the bladder maps revealed a persistent tumor at the same site as the initial tumor in 61.6%, at other sites in 12.8% and both in 25.6%. In group 1, restaging after second TURBT indicated that there was no upstaging, whereas 3.8% of the patients had Ta/HG tumors, and 11.5% had Ta/LG tumors. The restaging in group 4 showed upstaging to T1/HG in 20% of patients, Ta/HG in 4 (8.8%) patients, and Ta/LG tumors in 18 (40%) patients ($p<0.05$) (Table 1).

During the follow-up among all groups, 11 patients (5.3%) had progression (T1/HG in 11 patients, concomitant CIS in 1 patient), but none progressed to muscle-invasive disease. The progression was significantly higher in group 3, which included patients that did not have muscle tissue involvement in primary TURBT and did not undergo second TURBT ($p<0.05$). When all groups were evaluated, the median relapse time was 17 (3-107) months. The time until the relapse was significantly longer in group 1 ($p<0.05$) (Table 1).

Multivariate Cox proportional hazards regression analysis showed that tumor size >3 cm (95% CI=1.09-2.96, HR=1.79, $p=0.021$), presence of muscle tissue (95% CI= 0.35-0.92, HR=0.57, $p=0.022$), and multiple tumors (95% CI=1.06-2.90, HR=1.75, $p=0.028$) were independent factors affecting disease relapse in primary Ta/HG tumor (Table 2).

Evaluation of the difference in disease-free survival between the groups showed a significant survival advantage in group 1, especially in the first 2 years. Group 3 was found to be the worst population in terms of disease-free survival ($p=0.015$, Figure 2a). The subgroup analysis of groups 1 and 2, both of which had the muscle tissue in the first TURBT, but had different status on the second TURBT, showed that the presence of muscle tissue positively affected disease-free survival, independently from the second TURBT ($p=0.008$, Figure 2b). When we examined whether the second TURBT, regardless of the presence of muscle tissue in the first TURBT (groups 1 and 4), provided the survival advantage, we saw that there was no statistically significant difference ($p=0.059$, Figure 2c).

Evaluation of difference in recurrence-free survival according to groups and all subgroups showed that there was no statistically significant difference. ($p>0.05$, Figure 3).

Assessment of difference in progression-free survival according to groups showed a significant survival advantage in group 1 and group 2. Group 3 was found to be the worst population in terms of progression-free survival ($p=0.004$, Figure 4a). The subgroup analysis of groups 1 and 2, both of which had the muscle tissue in the first TURBT, but had different status on the second TURBT, showed that the presence of muscle tissue positively affected

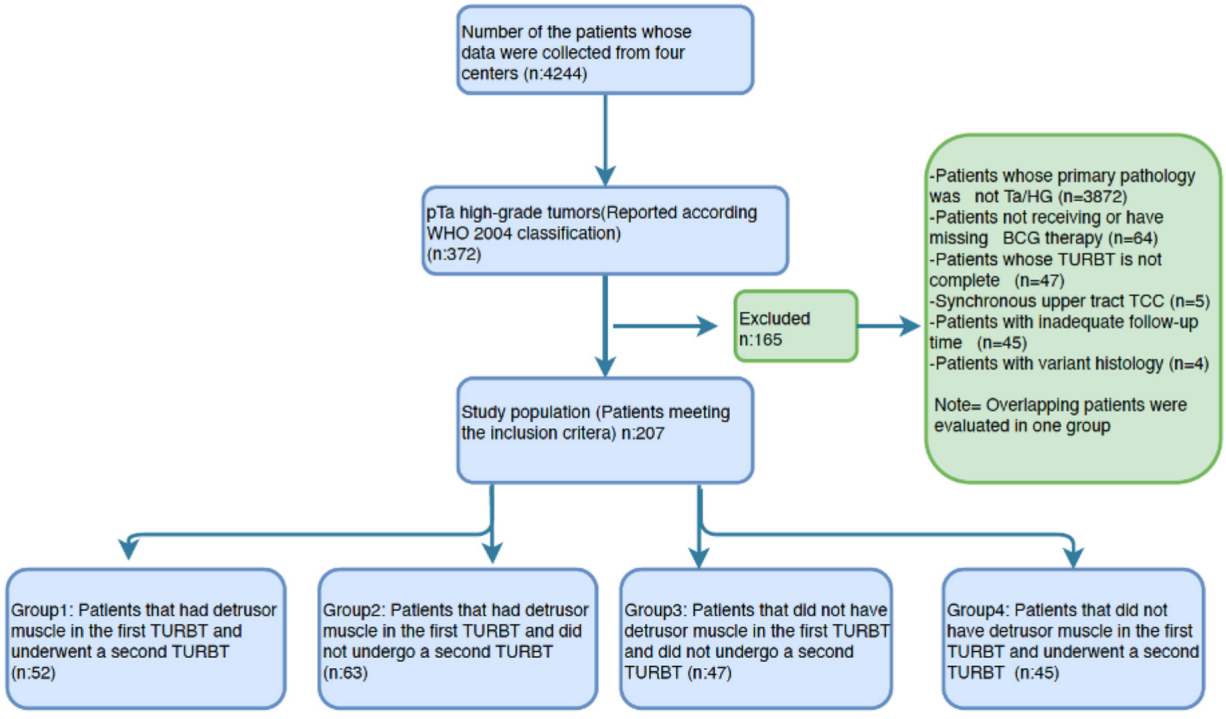

Figure 1. Study flow, detailing the process used to select cases for inclusion in the study

BCG: Bacillus Calmette-Guérin, WHO: World Health Organization, TURBT: Transurethral Resection of Bladder Tumor, TCC: Transitional cell carcinoma, Ta/HG: High-grade pTa tumors

progression-free survival, independently from the second TURBT (p=0.001, Figure 4b). When we examined whether the second TURBT, regardless of the presence of muscle tissue in the first TURBT (groups 1 and 4), provided the survival advantage, we saw that there was no significant difference (p=0.08, Figure 4c).

Discussion

There is uncertainty in the literature regarding the importance of detrusor muscle presence in the first TURBT, the need for the second TURBT, and data evaluating the effect of the second TURBT on tumor recurrence and progression in patients with maintenance BCG-treated primary Ta/HG (6,7,8,9). This study evaluated the potential significance of the second TURBT on oncological outcomes, based on the presence or absence of detrusor muscle in a population whose primary pathology was high-grade pTa (Ta/HG) and who had been treated with BCG for at least 12 months. Our results show that in patients with primary Ta/HG tumors, if there is no muscle in the first TURBT, a second TURBT should be performed to achieve lower progression rates. If there is muscle in the first TURBT, the second TURBT will only increase the median disease-free survival time.

Table 1. Distributions of diagnostic characteristics according to group

	Group 1 (n=52)	Group 2 (n=63)	Group 3 (n=47)	Group 4 (n=45)	p-value
Age, years (mean ± SD)	65.3±8.9	65.0±9.4	66.7±10.4	64.8±9.8	0.776[A]
Gender (M/F)	44/8	54/9	43/4	43/2	0.267[P]
BMI	25.9±4.7	26.6±4.3	25.3±4.4	25.3±2.9	0.356[A]
Charlson comorbidity index median (range)	3.2±1.5 3 (0-6)	3.0±1.8 3 (0-6)	3.2±1.9 3 (0-8)	3.0±1.4 3 (0-6)	0.911[A] 0.860[K]
Comorbidity number	1.1±0.8	1.1±1.2	1.0±1.1	1.0±0.8	0.839[A]
Smoking, n (%) Pack years (mean ± SD)	40 (76.9) 19.9±22.7	40 (63.5) 29.3±28.4	30 (63.8) 17.5±18.1	43 (95.6) 36.7±23.4	0.001[P] 0.001[A]
Comorbidity DM, n (%) HT, n (%) CVD, n (%) COPD, n (%)	 15 (28.8) 20 (38.5) 2 (3.8) 5 (9.6)	 17 (27) 22 (34.9) 6 (9.5) 8 (12.7)	 13 (27.7) 11 (23.4) 11 (23.4) 3 (6.4)	 14 (31.1) 16 (35.6) 4 (8.9) 6 (13.3)	 0.971[P] 0.412[P] 0.016[P] 0.664[P]
Occupational exposure, n (%) No Yes Unknown	 37 (71.2) 5 (9.6) 10 (19.2)	 36 (57.1) 3 (4.8) 24 (38.1)	 29 (61.7) 8 (17) 10 (21.3)	 28 (62.2) 4 (8.9) 13 (28.9)	0.138[P]
Number of tumors	1.9±1.4	2.0±1.5	1.5±0.7	2.2±3.3	0.284[A]
Tumor number, n (%) Single Multiple	 32 (61.5) 20 (38.5)	 39 (61.9) 24 (38.1)	 29 (61.7) 18 (38.3)	 24 (53.3) 21 (46.7)	0.793[P]
Tumor size, mm	3.0±1.8	3.1±2.2	2.5±1.6	3.3±1.5	0.154[A]
Visual persistent tumor, n (%)	8 (15.4)	-	-	25 (55.6)	0.004[P]
pT stage in the second TURBT, n (%) pT0 pTa pT1	 44 (84.6) 8 (15.4) 0	 - - -	 - - -	 14 (31.1) 22 (48.9) 9 (20)	<0.001[P]
Histological grade in the second TURBT, n (%) Benign Low grade High grade	 44 (84.6) 6 (11.5) 2 (3.8)	 - - -	 - - -	 14 (31.1) 18 (40) 13 (28.9)	<0.001[P]
Follow-up status, n (%) Disease-free Recurrence Progression	 39 (75) 13 (25) 0	 46 (73) 16 (25.4) 1 (1.6)	 26 (55.3) 14 (29.8) 7 (14.9)	 27 (60) 15 (33.3) 3 (6.7)	0.009[F] 0.094[P] 0.764[P] 0.016[F]
Follow-up total (months)	42 (12-83)[a,b,c]	20(12-62)[a,Ω,§]	24 (12-211)[b,Ω,q]	24 (12-132)[c,§,q]	0.023[K,M]
Relapse time (months)	32 (12-83)[†,‡,Δ]	16 (6-42)[†,ɣ,Σ]	15 (3-107)[‡,ɣ,ϕ]	12 (6-67)[Δ,Σ,ϕ]	<0.001[K,M]

[F]Fisher's exact test, [K]Kruskal-Wallis test, [M]Mann-Whitney U test, [P]Pearson chi-square test, [A]ANOVA.
[a]Group 1 vs group 2 p=0.005; [b]Group 1 vs group 3 p=0.014; [c]Group 1 vs group 4 p=0.292
[Ω]Group 2 vs group 3 p=0.932; [§]Group 2 vs group 4 p=0.146; [q]Group 3 vs group 4 p=0.257.
[†]Group 1 vs group 2 p<0.001; [‡]Group 1 vs group 3 p<0.001; [Δ]Group 1 vs group 4 p<0.001.
[ɣ]Group 2 vs group 3 p=0.338; [Σ]Group 2 vs group 4 p=0.672; [ϕ]Group 3 vs group 4 p=0.893.
[x]Group 2 vs group 3 p=0.854; [y]Group 2 vs group 4 p=0.033; [z]Group 3 vs group 4 p=0.102.
BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension, COPD: Chronic obstructive pulmonary disease, TURBT: transurethral resection of a bladder tumor, IVT: Intravesical treatment, M: Male, F: Female, SD: Standard deviation, CVD: Cardiovascular disease

In the literature, the pathology results of second TURBT after primary Ta/HG have been evaluated in various studies. In 2011, Herr (16) published a single-center study with 396 patients non-invasive grade 3 (TaG3) patients who underwent a second TURBT. Pathology results indicated pT0 in 35%, Ta/HG-CIS in 50%, pT1 in 10%, and pT2 in 5% of patients. In the study by Dangi et al. (6), 43 (38.3%) of 112 patients whose primary pathology was TaG3 underwent a second TURBT (only two of whom had no muscle in the first TURBT). In 7 of 37 patients whose first TURBT was complete, positive results (2 pTa LG lesions, 3 CIS, and 2 pTa HG lesions) were detected in the second TURBT, however no progression was found in any patient. Lazica et al. (7) performed a second TURBT in 61.3% of 142 patients with pTa/HG 97.1 days (the median) after the first TURBT and detected persistent tumors in 41.4%, progression to pT1/HG in 5.7%, and muscle-invasive tumors (T2) in none of the patients. Moreover, among 87 patients that had Ta/HG pathology, 38 had muscle tissue at the first TURBT, 5 did not have, and the presence of muscle at the first TURBT was not known in 44 patients (7). They recommended performing a second TURBT in these patients since the primary tumor site was the location for most of the persistent tumors (7). In another study by Hensley et al. (17), 104 of 209 patients with primary pathology Ta/HG underwent the second TURBT and residual disease was found in 39 patients (38%). The second TURBT was upstaged to pT1 in only one patient (1%). In our study, we found tumors in 39 (46.8%) of 97 patients who underwent the second TURBT, and this rate was significantly lower in group 1 than in group 4. During the second TURBT, a persistent visual tumor was observed in 8 (15.4%) patients in group 1, and 25 (55.6%) patients in group 4. Additionally, although there was no upstaging in group 1 with muscle involvement in the first round, we showed that there may be a tumor in the pathology specimen in the second TURBT, even with muscle involvement.

When considering the effect of the second TURBT on progression, recurrence and disease-free survival in primary TA/HG tumors, Dangi et al. (6) predicted median recurrence-free survival to be 76 months and 45 months for the groups that did and did not undergo second TURBT, respectively, and this difference was statistically significant. They suggested further large-scale studies investigating the second TURBT's role in this group (6). In a study by Tinay et al. (14) with 93 pTa/HG patients, they reported that in cases with muscle in the first TURBT, the median time to recurrence was increased significantly if the second TURBT was performed (77.6 vs 36.9 months, p=0.0086). Moreover, they reported that even in cases that did not have muscle at the first TURBT, the median time until recurrence (78.9 vs 42.7 months, p=0.0001) and median time until progression (22 vs 7 months, p=0.05) increased, while the recurrence rate (20% vs 66.7%, p=0.002) decreased in those that underwent a second round of TURBT compared to ones that didn't (14). Hensley et al. (17) reported that the second TURBT was associated with improved relapse-free survival (p=0.003) and progression-free survival (p=0.050) in all patients with non-stratified HG Ta. They noted that the second TURBT was associated with better results in all patients with Ta/HG, regardless of the stratified risk (17).

In our study, among all patients, 5.3% progressed to pT1 and none to pT2. Progression rates were significantly higher in group 3. Notably T1 pathology decreased in group 4 and progression was observed more in group 3, which emphasizing the importance of the second TURBT in cases without detrusor involvement in the first TURBT. Our results showed that having muscle tissue presence in the first TURBT significantly prolongs

Table 2. Univariate and multivariate Cox proportional hazards regression were performed to determine the factors that were associated with disease relapse

	Univariate model			Multivariate model		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	1.011	0.986-1.036	0.406			
Gender (ref: male)	0.531	0.210-1.338	0.179			
BMI	0.989	0.938-1.043	0.683			
CCI	1.056	0.916-1.216	0.454			
Occupational exposure	1.110	0.845-1.459	0.452			
Smoking (years)	1.001	0.992-1.011	0.768			
Multiple tumor	2.142	1.318-3.480	0.002	1.756	1.062-2.903	0.028
Tumor size	1.228	1.095-1.378	<0.001			
Tumor size >3 cm	2.157	1.330-3.497	0.002	1.798	1.092-2.963	0.021
Immediately IVT	1.668	0.946-2.943	0.077			
Presence of muscle tissues	0.535	0.332-0.862	0.010	0.572	0.354-0.923	0.022
Second TURBT	0.632	0.387-1.032	0.067			
Visual tumor on Second TURBT	1.210	0.632-2.316	0.566			
Second TURBT pT stage	1.166	0.977-1.391	0.088			
Second TURBT grade	1.648	0.707-3.841	0.247			

HR: Hazard ratio, CI: Confidence interval, BMI: Body mass index, CCI: Charlson comorbidity index, TURBT: transurethral resection of a bladder tumor, IVT: Intravesical treatment

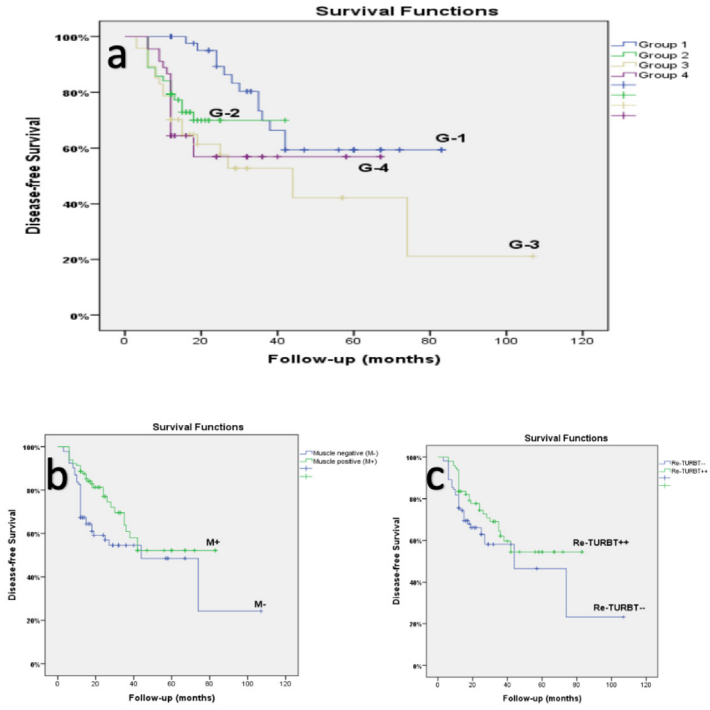

Figure 2. (a) Disease-free survival Kaplan-Meier curve according to groups. The log-rank method p-value was 0.015. The chi-square value was 10.455. **(b)** Disease-free survival Kaplan-Meier curve according to the presence of muscle in the specimen. The log-rank method p-value was 0.008. The chi-square value was 7.091, **(c)** Disease-free survival Kaplan-Meier curve according to the presence of the second TURBT. The log-rank method p-value was 0.059. The chi-square value was 3.558

TURBT: transurethral resection of a bladder tumor

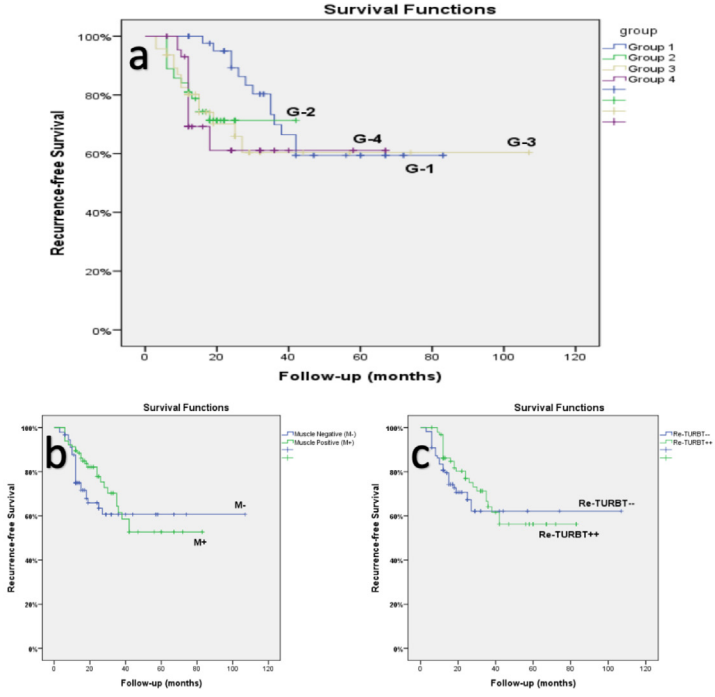

Figure 3. (a) Recurrence-free survival Kaplan-Meier curve according to groups. The log-rank method p-value was 0.157. The chi-square value was 5.217, **(b)** Recurrence-free survival Kaplan-Meier curve according to the presence of muscle in the specimen. The log-rank method p-value was 0.152. The chi-square value was 2.055, **(c)** Recurrence-free survival Kaplan-Meier curve according to the presence of the second TURBT. The log-rank method p-value was 0.202. The chi-square value was 1.631

TURBT: transurethral resection of a bladder tumor

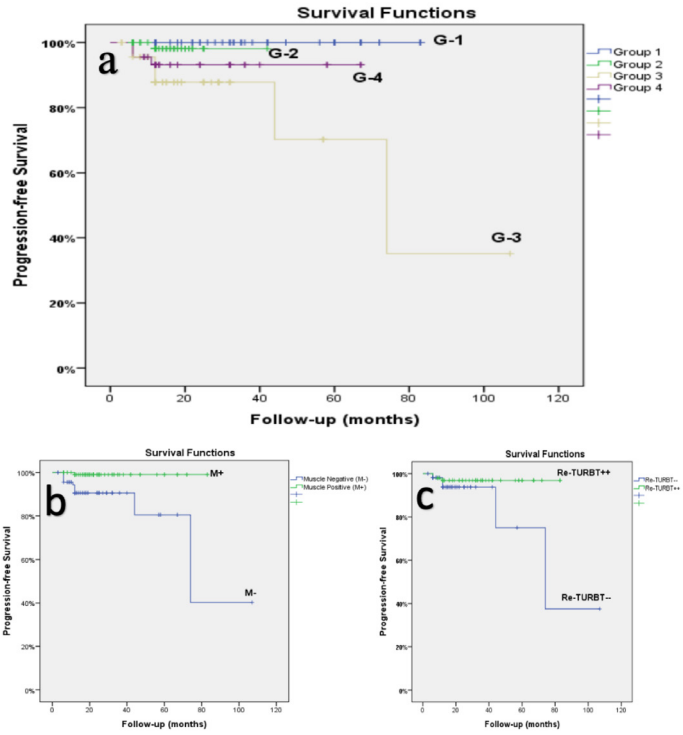

Figure 4. (a) Progression-free survival Kaplan-Meier curve according to groups. The log-rank method p-value was 0.004 the chi-square value was 13.342, **(b)** Progression-free survival Kaplan-Meier curve according to the presence of muscle in the specimen. The log-rank method p-value was 0.001. The chi-square value was 10.878, **(c)** Progression-free survival Kaplan-Meier curve according to the presence of the second TURBT. The log-rank method p-value was 0.084. The chi-square value was 2.994

TURBT: transurethral resection of a bladder tumor

progression-free survival and disease-free survival, independent of the second TURBT. When the effect of the second TURBT was evaluated independently, it was observed that it contributed positively to the disease-free survival approximately in the first 3 years even when it was not statistically significant. Although it was not significant, progression-free survival after the first 3 years favored the group in which the second TURBT was performed. Our study, which shows that if there is no muscle tissue present in the first TURBT, not performing the second TURBT significantly increased the likelihood of progression, supports the literature at this stage. An important point to be discussed in our results is that although it shows that when there is muscle in the first TURBT, the second TURBT does not have a significant effect on progression or recurrence rate, the second TURBT application increases median DFS (32 vs 16 months, p<0.001). Our study also showed that tumor size, presence of muscle tissue, and multiple tumors in primary TURBT are independent factors affecting disease relapse in primary Ta/HG tumor.

The mainstay of advanced therapy is adjuvant intravesical BCG in the NMIBC population, which has high-risk features in the second TURBT (18,19). In both the European Association of Urology and National Comprehensive Cancer Network guidelines, it's stated that priority intravesical BCG instillations are preferred or intravesical chemotherapy is recommended after TURBT in pTa grade 3/HG urothelial carcinoma (10,11). Studies on the importance of the second TURBT in Ta/HG patients revealed few reports of an insufficient number of BCG treatments as well and a limited number of patients (6,7,16). Lazica et al. (7) did not report on intravesical BCG treatment and recurrence/progression rates during the follow-up period. Dangi et al. (6), only 23.4% of their patients received at least 1 year of intravesical BCG treatment (5). Herr (16) stated that they did not use intravesical BCG therapy in their institutions and noted it as a limitation of their study. Only Tinay et al.'s (14) study was similar to ours in terms of providing maintenance BCG treatment in the Ta/HG NMIBC patient group and evaluating recurrence and progression rates, albeit with a smaller sample group.

Our study is important because it investigated the progression and recurrence rates in the Ta/HG patient group in relation to the presence of detrusor muscle, which is an unclear subject in the literature. It also is one of the rare studies conducted with a population of patients receiving BCG maintenance treatment for a minimum period of 1 year. Moreover, it is a multicenter study with the largest sample size to date. Lastly, the relatively homogeneous patient population is represented in our data.

Study Limitations

However, our study also has some limitations. These include retrospective design and the pathology reports not being interpreted by the same pathologists. The lack of a randomly allocated head-to-head study was another limitation.

Additionally, varying surgeons and surgeon experiences, the lack of genetic markers can be considered limitations.

Conclusion

Our study showed that in patients with a complete primary Ta/HG tumor treated with BCG, a second TURBT reduces the risk of progression if the detrusor muscle tissue is absent at the time of the first TURBT. If the muscle tissue is present at the first TURBT, second TURBT only increases median DFS, but does not affect progression or recurrence rates. It also showed that tumor size, presence of muscle tissue, and multiple tumors are independent factors affecting disease relapse. Further randomized trials are needed to confirm these findings.

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Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Clinical Research Ethics Committee (decision number: 2021/01-28, date: 25.01.2021)

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Authorship Contributions

Concept: U.M., E.K., Design: U.M., M.Ç.Ç., B.Ö., Supervision: B.Ö., E.K., R.G.A., A.Y., Data Collection or Processing: U.M., M.Ç.Ç., E.K., M.K., S.Ç., M.Ç., O.N.Y., M.Y.Y., E.Ka., Analysis-Interpretation: U.M., M.Ç.Ç., Literature Review: U.M., Writing: U.M., M.Ç.Ç., B.Ö., Critical Review: M.Ç.Ç., B.Ö., E.K., R.G.A., A.Y.

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Original Article

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Apparent Diffusion Coefficient Values as a Complementary Tool in Prostate Gland Disease: Retrospective Evaluation of Apparent Diffusion Coefficient Values with Pathological Data Guided by PI-RADSv2.1

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Abstract

Objective: This retrospective study reveals whether a lesion is a benign pathological process or malignant by measuring apparent diffusion coefficient (ADC) values following prostate imaging reporting and diagnostic system version 2.1 (PI-RADSv2.1) guide on multiparametric magnetic resonance imaging (MpMRI) examinations. Furthermore, this study aims to determine the cut-off ADC values (ADCv) that may exist to help identify and distinguish between benign and the malignant lesions. Additionally, the paper evaluates whether there is a correlation between malignant lesions' International Society of Urological Pathology (ISUP) score and ADCv, and whether ADCv provide information about prostate cancer (PCa) aggressiveness without requiring invasive procedures.
Materials and Methods: The study group consised of 243 patients. The lesions were diagnosed using transrectal ultrasound-guided cognitive MRI fusion. MpMRI images before the biopsy were evaluated according to PI-RADSv2.1 guideline by a radiologist. Three groups, benign prostatic tissue, prostatitis, and PCa were obtained according to the histopathological results.
Results: When the cut-off value for ADC was $780x10^{-3}$, sensitivity was 80%. When the cut-off value was taken as $668x10^{-3}$, the sensitivity and specificity were 72% and 62%, respectively. When the cut-off ADCv was taken as $647x10^{-3}$, the sensitivity was 83% and the specificity was 48.5%. ADCv varied significantly depending on the ISUP groups (p=0.003). It was determined that the ISUP 1 group was significantly higher compared to other groups. ADC group mean values were not significantly different between groups 2, 3, 4, and 5.
Conclusion: ADCv may be a suitable tool for estimating PCa aggressiveness, and it shows a significant potential to improve the diagnostic accuracy.
Keywords: Prostate cancer aggressiveness, magnetic resonance imaging, apparent diffusion coefficient value, PI-RADSv2.1

Introduction

Prostate cancer (PCa) shows a broad spectrum, ranging from low-grade organ-confined tumors to aggressive tumors that can metastasize and lead to death. Therefore, proper diagnosis and staging are essential (1). There are several treatment options for PCa, such as emergency radical surgery, hormonotherapy, and active surveillance (2). However, different treatments have different effects on the patients. For example, radical treatment decreases the quality of life with the risks of incontinence and impotence. The difficulty of managing PCa is to distinguish clinically significant cancers that should receive a radical treatment from clinically insignificant (3).

Multiparametric magnetic resonance imaging (MpMRI) has become the basic non-invasive examination for evaluating of the prostate gland (4,5,6). Diffusion-weighted imaging (DWI) is the basic sequence in MpMRI protocols in addition to conventional sequences, because it has advantages such as short exposure time, rapid acquisition, and creation of qualitative and quantitative measurements on apparent diffusion coefficient (ADC). The ADC value (ADCv) is a quantitative parameter of DWI representing water diffusion in the extracellular and extravascular spaces and capillary perfusion, also it has been shown to be decreased in malignant lesions. DWI is also the main sequence in the evaluation of peripheral zone (PZ) lesions,

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and its contribution to the final prostate imaging reporting and data system (PI-RADS) score in the transitional zone (TZ) has increased with the updated PI-RADS version 2.1 (PI-RADSv2.1) guide published in 2019 (7). To evaluate MpMRI data more accurately and objectively, this study suggests determining ADCv in addition to the visual signal assessment suggested in the PI-RADSv2.1. As we believe, this process can significantly contribute to standardize reporting results. Prior studies have reported that ADC cut-off values can be used as a diagnostic tool showing malignancy risk and tumor aggressiveness of focal lesions (8,9).

This retrospective study aims to reveal whether the lesion is benign or malign by measuring ADCv following PI-RADSv2.1 guide on MpMRI examinations and transrectal ultrasound (TRUS) guided cognitive fusion biopsy (CF-Bx). Additionally, the study evaluates whether there is a correlation between malignant lesions' pathological grade [International Society of Urological Pathology (ISUP) score] and ADCv and whether ADCv provide information about PCa aggressiveness without requiring invasive procedures. We determined the cut-off ADCv that may exist to identify and differentiate between benign and malignant lesions and to distinguish between cancers with an ISUP score ≥2 and with an ISUP score 1.

Materials and Methods

This retrospective study included 243 patients that were referred to the Radiology Clinic due to their elevated prostate-specific antigen (PSA) value (ng\mL) during the follow-up or positive digital rectal examination, or family history of PCa, MpMRI for PCa diagnosis and, screening between April 2019 and April 2020. There is no random selection of patients since we included all the male patients that were referred to radiology clinic for the above-mentioned complications or procedures. The ethical approval was obtained from the University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital Clinical Research Ethics Committee (decision no: 2021/199, date: 24.11.2021).

The inclusion criteria were to have a PI-RADSv2.1 score ≥3 lesion and to be examined by MRI-TRUS CF-Bx after MpMRI. Fifty-three patients who have PI-RADS <3 lesions; 15 patients with unsuitable image quality due to persistent rectal gas distension; 30 patients with bx performed previously, without CF-Bx in our hospital and with PCa treatment before testing; 10 patients with no tissue diagnosis due to refusing biopsy were excluded from the study. Finally, 135 patients and 152 lesions with a PI-RADSv2.1 score ≥3 were found eligible for our study, and they were diagnosed with MRI-TRUS CF-Bx in our urology clinic.

MRI Protocol

Prostate MpMRI images examined in the study were performed with a 1.5T Siemens Magnetom Aera (Siemens Healthcare, Erlangen, Germany) MRI device with 18 channels (body 18 A 1.5T Tim Coil) pelvic coil is used. DWI was obtained in the axial plane using 4 different b-values before contrast administration (b: 50-800-1200-1800 sec/mm^2). The b-2000 value was calculated and generated by the device itself, and the ADCv was calculated with a monoexponential model on a pixel-pixel basis using all b values. ADCv was obtained quantitatively from ADC maps. Different b-value distributions were applied which vary between 50 and 1800 sec/mm^2.

Evaluation of Images and Histopathological Correlation

MpMRI images were evaluated on the SYNGO.VIA workstation before biopsy according to PI-RADSv2.1 guideline by a radiologist with 5 years of experience in MpMRI evaluation. Patient age (years), serum PSA values (ng\mL), PSA density (PSAd) (ng/mL/cc), and prostate volume (cc) were recorded. The lesions in the TZ and PZ were scored according to the PI-RADSv2.1 guideline. All lesions with a PI-RADSv2.1 score ≥3 were included in this study. Localization, the largest diameter, and PI-RADS score of the tumors were recorded. The assessing radiologist chose the best suited ADC map image for each lesion and measured the ADCv of the lesions. Measurements were made retrospectively using an elliptical or circular region of interest (ROI) tool available on the SYNGO.VIA workstation using a field of view adjusted to prostate imaging from lesions and for comparison, measurements were taken avoiding borders in the parenchyma areas that appear homogeneous in all sequences without lesions in the PZ and TZ. The average of the measured ROI area was 15 mm2 (8 pixels). Measurements were performed twice for both PZ-TZ parenchyma and each lesion, and the lowest ADCv was used for the evaluation. In the radiology report, ADCv was defined as millimeter^{2}x10^{-3} per second. Relationships between patient age, serum PSA level, tumor ADCv, and Gleason score (GS) were investigated. Lesions with pathologically GS ≥6 were accepted as malignant. In our hospital, MRI-TRUS CF-Bx, 18G automatic tru-cut biopsy needle, and hypoechogenic-hyperechogenic foci were also considered and correlated with the foci identified in the MpMRI obtained before biopsy and marked on the sector map, and two samples were made from each lesion by 15 years experienced urologist. The radiologist and urologist made a consensus to decide the localization of the lesion together during the biopsy. Histopathological analysis of prostate specimens was performed by a urological pathologist with 20 years of experience. Three groups, which are benign prostatic tissue, prostatitis, and prostate cancer, were obtained according to the histopathological results. The malignant lesions were grouped according to the ISUP criteria (ISUP1, GS3+3; ISUP2, GS3+4; ISUP3, GS4+3; ISUP4, GS4+4; ISUP5, GS ≥9) (10).

Statistical Analysis

In the descriptive analysis, continuous variables are presented as mean ± standard deviation or median (25-75th percentile), and categorical variables as a percentage (%). The compliance of the data to the normal distribution was evaluated using the Shapiro-Wilk test. When the distribution of the data was normal, the t-test was used in the comparison of the two groups, and the Mann-Whitney U test was used under non-parametric conditions. One-way ANOVA or non-parametric Kruskal-Wallis test was used to compare continuous variables between three and more categories. The strength of the correlation between two continuous variables was evaluated using the Spearman correlation analysis. Accordingly, the correlation coefficient (r) values <0.2 show feeble or no correlation, values from

0.2-0.4 show weak correlation, from 0.4-0.6 show moderate correlation, 0.6-0.8 show a high correlation, and values >0.8 are interpreted as very high correlation. Receiver operating characteristic analysis was used to evaluate the success of the obtained variables in diagnosing PCa and to determine the cut-off values, and the area under the curve (AUC), sensitivity, and specificity were calculated. After confirming that the data were normally distributed, unpaired t-tests were used to determine significant differences in mean ADCv between normal and cancer regions in the prostate gland according to zones. The relationships between ADCv and tumor's GS were evaluated using the Spearman rank correlation coefficient (").

SPSS 22.0 (founded by SPSS Inc. in the USA) and MEDCALC (developed by Medcalc Software in 1993) programs were used for the statistical analysis. $p<0.05$ was considered statistically significant. Data are shown as mean ±95% confidence interval (CI).

Results

A total of 135 patients and 152 lesions were included in this study. The mean age of the patients was 63.7±7.12. The mean PSA values (ng\mL), prostate volume (cc) and PSAd (ng/mL/cc) of the individuals are 9.78±14, 65.83±35.07, 0.24±0.39, respectively. In the PI-RADS groups 3, 4, and 5, there were 84, 39, and 29 lesions identified respectively, and the PCa prevalence of them was 24.2%, 60%, and 93.4% respectively. Forty (26.3%) of 152 lesions obtained from individuals were diagnosed as benign prostatic tissue, 55 (36.2%) prostatitis, and 57 (37.5%) of them were diagnosed with PCa (Table 1). Sixteen lesions were identified as ISUP1 and 41 of the lesions had higher ISUP grades.

When PCa-non-PCa lesions and PCa-prostatitis lesions were evaluated according to age, PSA, prostate volume, and PSAd; the mean PSA values were not statistically different (p=0.051 and p=0.256). Mean age and PSAd were higher in the PCa group, and the prostate volume was lower (Table 1). Age showed a low-level positive correlation (r=0.308, p=0.004) with the mean PSA. While a weak positive correlation between PSA and prostate volume (r=0.275, p=0.011); a moderate positive correlation (r=0.617, p<0.001) was observed with the PSAd. A moderate negative correlation was found between prostate volume and PSAd (r=-0.502, p<0.001).

The mean ADCv for the normal PZ was 1174.22±178.19x10^{-3} [minimum-maximum (min-max): 739.0-1537.0x10^{-3}], the mean ADCv for the normal TZ was 920.27±158.27x10^{-3} (min-max: 312.4-1521.0x10^{-3}) (Graphic 1). While there was a weak negative correlation between PZ ADCv and PSAd (r=-0.236, p=0.036), a weak positive correlation was observed between TZ ADCv and PSAd (r=0.326, p=0.003).

When cancer and non-cancerous lesions were compared, ADCv were found to be significantly different (Table 2). Mean ADCv for pCa were 598.8±145.3 x10^{-3} and Mean ADCv for non-pCa were 758.9636±146.4 x10^{-3}.

When the mean ADCv of the malignant lesions according to the zones are evaluated, it is 629.97±151.77 for the PZ and 614.75±152.23 for the TZ, and the difference between them is not statistically significant (p=0.830) (Table 3). ADCv of benign prostatic tissue, prostatitis, and PCa groups showed a statistically significant difference (p=0.001).

To determine the group in which the difference originated, paired comparisons were made. No significant difference was found between the benign prostatic tissue and prostatitis group ADCv (p=0.076).

Table 1. Descriptive statistics of patients who have PCa or nonPCa or prostatitis

Variables	PCa positive n=51	non-PCa n=84	Prostatitis n=59	p-value	p-value*
Age (years) Mean ± SD	65.23±7.8	62.06±6.90	61.41±7.04	0.051	0.048
PSA (ng/mL) Median (25p-75p)	7.36 (5.23-11.16)	7.22 (4.20-9.76)	9.96 (4.77-11.19)	0.250	0.256
Prostat volume (cc) Median (25p-75p)	40.37 (31.00-51.23)	71.50 (44.85-99.75)	74.75 (44.90-102.0)	<0.001	0.003
PSA density (ng/mL/cc) Median (25p-75p)	0.21 (0.11-0.33)	0.10 (0.07-0.147)	0.11 (0.08-0.13)	<0.001	0.012
ADC Median (25p-75p)	544.50 x10^{-3} (485.0-727.83)	679.48 x10^{-3} (620.8-812.5)	788.39 x10^{-3} (663.05-905.25)	0.003	<0.001

P-value refers to comparison in between PCa and non-PCa, p-value* refers to comparison in between PCa and prostatitis
p and p* values were calculated using independent t-test for age;
p and p* values were calculated using the Mann-Whitney U test for the others
Prostate Volume and PSAd values are statistically significant for PCa and prostatitis lesion differentiation
PCa: Prostat cancer, n: Number of lesions, SD: Standard deviation PSA: Prostate spesific anjigen, PSAd: PSA density, ADC: Apparent diffusion coefficient

Table 2. Mean ADC values according to the pathological diagnosis

Pathological definitive diagnosis					
Variables		**Benign prostatic tissue (n=40)**	**Prostatitis (n=55)**	**PCa (n=57)**	**p-values**
ADC	**Mean ± SD**	707.34±131.04 x10^{-3}	790.51±148.15 x10^{-3}	598.82±145.35 x10^{-3}	<0.001
	Median (25p-75p)	679.48 x10^{-3} (608.00-820.76)	788.39 x10^{-3} (663.05-905.25)	544.50 x10^{-3} (485.0-727.83)	

ADC: Apparent diffusion coefficient, PCa: Prostate cancer, n: Number of lesions, SD: Standard deviation, p-value less than 0.05 considered as statistically significant. P-values were calculated using Kruskal-Wallis test

The ADCv of the PCa lesions (598.82±145.35 x10^{-3}) were found to be significantly lower than the prostatitis group (790.51±148.15 x10^{-3}) (p=0.011) and the benign prostatic tissue group (707.34±131.04 x10^{-3}) (p≤0.005). AUC is 0.796 (0.702-0.890) for the ADCv in diagnosing PCa, (p<0.001).

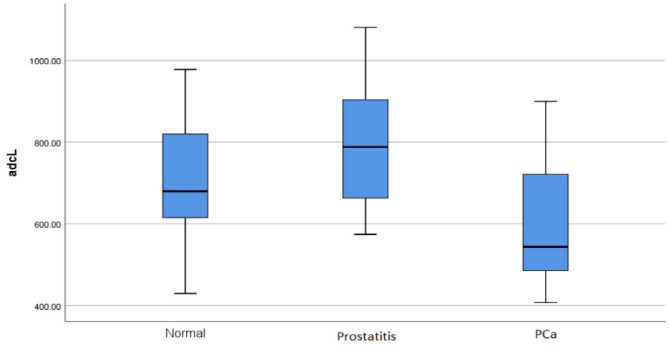
When the cut-off value for ADC was 780x10^{-3}, sensitivity was 80% and specificity was 45.5%. When the cut-off value was taken as 668x10^{-3}, the sensitivity was found to be 72% and specificity 62%. When the cut-off value was taken as 633.7 x10^{-3}, the sensitivity was found to be 70.5% and specificity 80.7%. AUC was 0.775 (0.686-0.864), p<0.001 for ADCv in diagnosing prostatitis. When the cut-off ADCv was taken as 647x10^{-3}, the sensitivity was 83% and the specificity was 59,4%. When the cut-off ADCv was taken as 697.5 x10^{-3}, the sensitivity was 64.9% and the specificity was 67.2%. When the cut-off value for ADC was 773x10^{-3}, the sensitivity was 53% and specificity was 75.0% (CI was 95%) (Graphic 2,3,4).

ADCv varied significantly according to the ISUP groups (p<0.001). In paired comparisons, it was determined that ISUP 1 group was significantly higher than each other group (Graphic 4). The cut-off value for ADC was found to be 584.59 to distinguish the ISUP grade 1 from >1 [sensitivity, 81.3%; specificity, 92.6%, AUC (95% CI): 0.863 (0.734-0.993)]. ADC group mean values were not significantly different between group 2, 3, 4, and 5 (Table 3, Figure 1,2).

Table 3. The Asssociation between ADC values and ISUP grades

	ISUP	Mean ± SD	p-value
ADC	1 (n=16)	726.71±143.08 x10^{-3}	0.003
	2 (n=9)	558.03±132.98 x10^{-3}	
	3 (n=10)	496.21±73.69 x10^{-3}	
	4 (n=12)	508.67±27.94 x10-^{3}	
	5 (n=10)	527.16±63.48 x10^{-3}	

ADC: Apparent diffusion coefficient, ISUP: International Society of Urological Pathology, SD: Standard deviation, p-value less than 0.05 considered as statistically significant



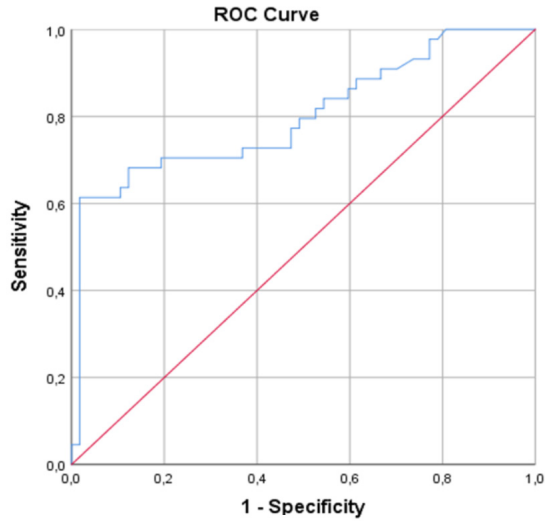
Graphic 1. Distribution of ADC values of pathological results in the prostate gland

The mean ADC value for the normal peripheral zone is 1174.22±178.19 x10^{-3} (min-max: 739.0-1537.0 x10^{-3}), the mean ADC value for the normal transitional zone is 920.27±158.27 x10^{-3} (min-max:312.4-1521.0 x10^{-3})

ADC: Apparent diffusion coefficient, Min-max: Minimum-maximum

Discussion

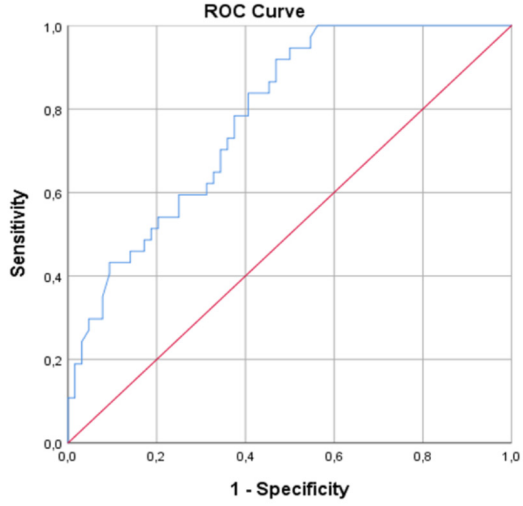
PCa itself is a disease with a very heterogeneous clinical course, 5-year survival ranging from 100% to 29% for the localized disease (11,12,13). The ISUP score is a widely accepted histopathological grading system for PCa, it reveals a 5-year survival rate of patients after radical prostatectomy (10).



Graphic 2. ROC curves of ADC values that showed for PCa

The cut-off value for ADC was found for 780x10^{-3} (sensitivity 80%, specificity 45.5%); for 668x10^{-3} (sensitivity 72%, specificity 62%); for 633.7x10^{-3} (sensitivity 70.5%; specificity 80.7%), AUC (95% CI): 0.796 (0.702-0.890) for PCa (p<0.001)

ROC: Receiver operating characteristic, ADC: Apparent diffusion coefficient, PCa: Prostate cancer, CI: Confidence interval, AUC: Area under the curve



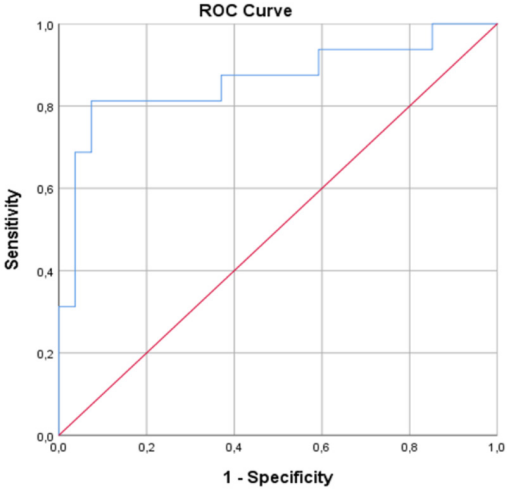
Graphic 3. ROC curves of ADC values that showed for prostatitis

The cut-off value for ADC was found for 647 x10^{-3} (sensitivity 83%, specificity 59.4%); for 697.5x10^{-3} (sensitivity 64.9%, specificity 67.2%); for 773x10^{-3} (sensitivity 53%; specificity 75%), AUC (95% CI): 0.775 (0.686-0.864) for prostatis (p<0.001)

ADC: Apparent diffusion coefficient, CI: Confidence interval, ROC: Receiver operating characteristic, AUC: Area under the curve

Differentiating a low-grade (ISUP-1) tumor, which is not expected to have a significant effect on 5-year survival, from significant (ISUP 2-5) PCa, may decrease prebiopsy and pretreatment risk stratification of the patient (14). It will save the patient from the morbidities of radical prostatectomy that decrease the quality of life e.g., incontinence, especially in very elderly patients, and may lead the clinician to prefer more conservative treatments. It is a delicate balance to be able to distinguish between PCa cases that do not require any intervention and patients who will undergo radical treatment, and it can only be established using the correct auxiliary modalities. Advances in the MpMRI technique increase the diagnostic accuracy in detecting clinically significant PCa (15).

DWI and ADC are two important milestones in PI-RADSv2.1 for evaluating the PZ, where PCa is the most common, and TZ (16). It is a known fact that highly cellular cancers have smaller interstitial space and lower ADCv (17). The healthy prostate tissue observed in the PZ of the prostate contains rich tubules and allows the diffusion of the water. ADCv is high in this area. On ADC maps, lower ADCv are detected because PCa destruct the normal tissue and invades the ducts of the gland (18). Several previous studies have revealed that ADCv is negatively correlated with GS and may show PCa aggressiveness (19,20). However, absolute ADCv varies considerably depending on individual factors such as selected b-values and patient demographics (21). There is no consensus on the cut-off ADCv in distinguishing PCa from healthy parenchyma. Also, no agreed ADCv correspond to the ISUP grades. However, a range between 750-900 mm^2/s is suggestive for PCa in PI-RADSv2 (22). The mean ADCv of the lesions included in our study was 629.97±151.77 for the PZ and 614.75±152.23 for the TZ. Currin et al. (23) reported that malign cells within the aggressive PCa produce duct and acini and pushing normal prostatic secretions and have marked nucleomegaly, this may be the reason for ISUP 2 or 3 tumors to demonstrate the characteristic features of high-risk PCa on MRI. Wu et al. (24) revealed that higher ADCv ($0.830x10^{-3}$ mm^2/s) was related to low-risk PCa (GS 6 disease). Alessandrino et al. (13) found that quantitative values obtained from ADC (median ADC, and ADC ratio) are inversely correlated with the ISUP score. In another study, ADCv can distinguish GS 6-7 PCa from 8-10, but there was no statistical difference between GS 3+4 and 4+3 PCa (25). Hambrock et al. (26) found that ADCv can perfectly differentiate low-grade vs intermediate grade vs high-grade PCa from each other. In another study, ADCv reduced the false-negative rate of MpMRI (PI-RADS <3) for clinically significant PCa (27). In a meta-analysis in which Shaish et al. (28) evaluated the studies on ADCv recently published in the literature; 13 studies were included, providing 1107 tumor foci in 705 patients. They reported that ADCv demonstrates moderate accuracy in distinguishing clinically significant PCa from insignificant. They further reported that a significant bias may occur in these studies, therefore the performance of ADCv in distinguishing high-grade cancers from low-grade cancers may have been exaggerated, and that there was substantial heterogeneity in the results. In fact, the results of our study also support this broad meta-analysis. In paired comparisons, it was determined that the ISUP 1 group was significantly higher than each of the other group. Mean ADCv did not show a statistically significant difference between groups 2, 3, 4, 5. Our study shows that ADCv are successful in distinguishing cancers with an ISUP 1, which are defined as silent diseases, from cancers with a clinically important (ISUP ≥2). Thus, in elderly patients



Graphic 4. The cut-off value for ADC was found to be 584.59 for ISUP grade 1

ADC: Apparent diffusion coefficient, ISUP: International Society of Urological Pathology, ROC: Receiver operating characteristic

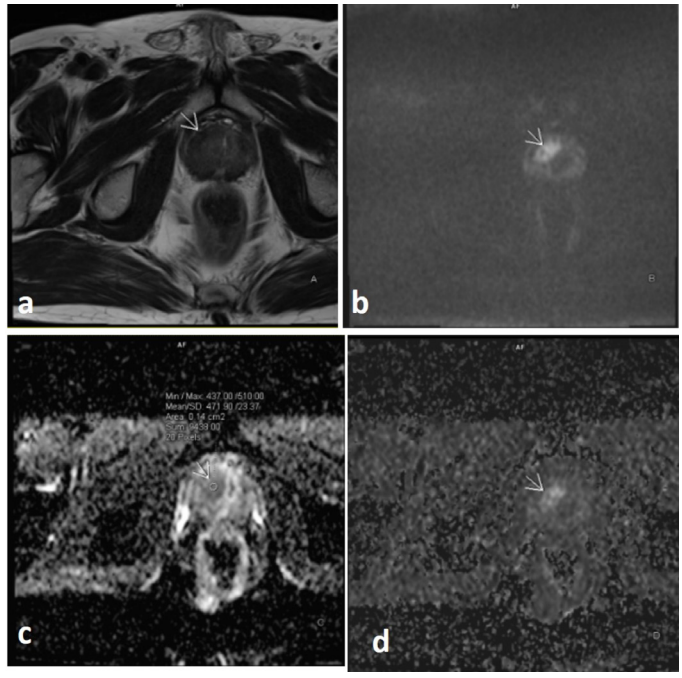


Figure 1. A 68-year-old male patient whose serum PSA level was 6.7 ng/mL. (a) On the T2W axial view; a prominent hypointense lesion (17x12x10 mm in size) located in the right middle part of the peripheral zone is seen. (b) on DWI axial image (b=1800 s/mm^2); lesion is markedly hyperintense, (c) ADC map shows markedly hypointense lesion and ADC value measured as $471.90x10^{-3}$ mm^2/s. (d) on DWI axial image (b=2000 s/mm^2); lesion is markedly hyperintense. Lesion evaluated as PI-RADS score=5 and histopathologically confirmed as ISUP grade 5 PCa

PSA: Prostate-specific antigen, ADC: Apparent diffusion coefficient, DWI: Diffusion-weighted imaging, PI-RADS: Prostate imaging reporting and diagnostic system, ISUP: International Society of Urological Pathology, PCa: Prostate cancer

where radical prostatectomy will not change the 5-year survival rate, with a simple measurement of ADCv, we can predict clinically insignificant (ISUP 1) PCa before surgery. And we can protect these patients' groups from the possible morbidity of radical prostatectomy, such as incontinence, by choosing a more conservative treatment plan. In a recent study, Sokmen et al. (29) found that the ADC coefficient of variation value as a tissue texture parameter can be a new biomarker to assess tumor aggressiveness in patients with PCa.

The effectiveness of ADCv in differentiating PCa from benign processes is known fact. In our study, when PCa and non-cancerous lesions were compared, ADCv was significantly different. DWI and ADC mapping demonstrated that the tissue cellularity of the prostate parenchyma are basic sequences that can provide vital information. Threshold values are enabled us to distinguish between prostatitis and benign lesions, and these values can be obtained with ADC mapping since it reflects the internal architecture and localization of the pathological process within the prostate (30). PCa and chronic prostatitis are associated with variable clinical manifestations and presentation may interfere. Unfortunately, there are no specific diagnostic laboratory tests to distinguish them from each other (31). In another study, the accuracy of MRI was observed in the differentiation of PCa from other prostatic disorders, such as benign prostatic hyperplasia, acute bacterial prostatitis, and chronic bacterial prostatitis. The sensitivity to differentiate PCa from benign disorders was high, but they found that the accuracy of detecting bacterial prostatitis was low compared with other prostatitis groups (32). Prostatitis has two forms known as acute and chronic prostatitis. Low signal intensity on T2-weighted images and early enhancement on dynamic MRI is both observed in PCa and prostatitis. Esen et al. (31) reported that ADCv is highly effective in differentiating PCa from prostatitis, but there was no significant difference between normal prostate parenchyma and prostatitis.

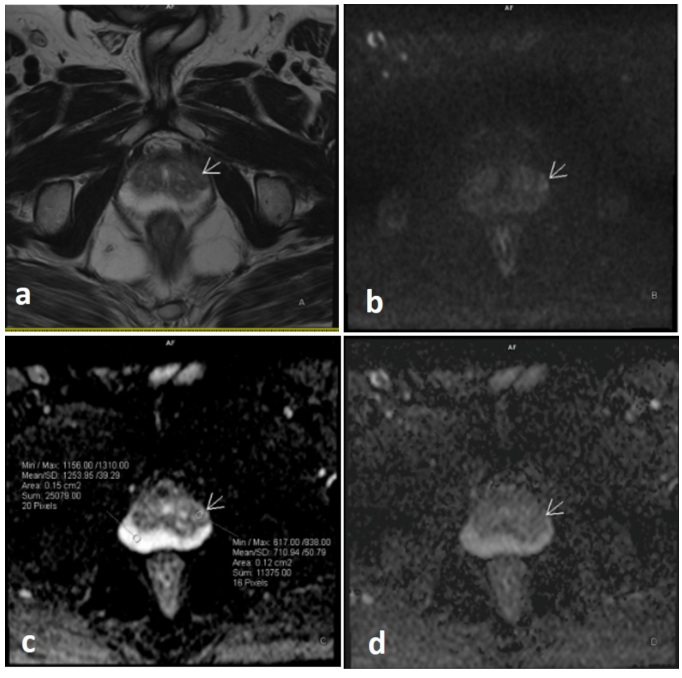


Figure 2. A 55-year-old male patient whose serum PSA level was 5.6 ng/mL. (a) On the T2W axial view; a prominent hypointense lesion (7x8x10 mm in size) located in the left middle part of the peripheral zone is seen. (b) on DWI axial image (b=1800 s/mm^2); lesion is mildly hyperintense, (c) ADC map shows markedly hypointense lesion and ADC value measured as 710,94x10-^{3} mm^2/s. (d) on DWI axial image (b=2000 s/mm^2); there is no abnormal signal. Lesion evaluated as PI-RADS score=3 and histopathologically confirmed as ISUP grade 1 PCa

PSA: Prostate-specific antigen, DWI: Diffusion-weighted imaging, ADC: Apparent diffusion coefficient, PI-RADS: Prostate imaging reporting and diagnostic system, ISUP: International Society of Urological Pathology, PCa: Prostate cancer

Similarly, in our study, no significant difference was found between benign prostatic tissue and prostatitis group ADCv, but a significant difference was observed between normal prostate tissue and benign prostate disease ADCv as well as between normal prostate tissue and PCa.

Study Limitations

Our study had some limitations; first, the reference ADCv did not investigate different b-values. In our study, only the most preferred b-values in the routine were used and, normal ADC reference values were not compared according to the b-value used. It is left for further studies to investigate its effect. The significant disadvantages of TRUS-guided CF-Bx are that success rates are highly dependent on the operator's experience and lack of standardization (12). In our study, the false-negative rate of TRUS-guided CF-Bx, especially in clinically insignificant tumors, was not considered. This present study was performed with one type and a 1,5T MRI. Other manufacturers' devices should be investigated and compared. Also, interobserver variability was not evaluated in our study, and we suggest a larger scale of a prospective study to be conducted.

Conclusions

In conclusion, ADCv is a potent and non-invasive imaging method that can provide useful information about the tissue structure in the prostate parenchyma. Creating a reference range for pathological ADCv accepted by all radiologists in the differentiation of PCa from normal prostate parenchyma and prostatitis is also promising and has become a necessity. ADCv can be used as a complementary imaging method for clinically distinguishing insignificant PCa from significant tumors. Considering the presence of operator-dependent false-negative results in TRUS-guided biopsy and CF-Bx, particularly in the elderly patient group, demonstrating clinically insignificant PCa before surgery with accuracy may protect this patient group from possible complications of radical prostatectomy. Also, in distinguishing PCa from normal prostate parenchyma and prostatitis, ADCv shows significant potential and may improve the diagnostic accuracy. Similar to our study, the importance of ADCv has been shown in the latest version of PI-RADS, and we believe that ADCv should be used in the upcoming version of the PI-RADS.

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Ethics

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Authorship Contributions

Surgical and Medical Practices: G.Y.O., E.Ş., Concept: G.Y.O., Design: Z.H.A., Data Collection or Processing: G.Y.O., Analysis or Interpretation: E.Ş., Literature Search: G.Y.O., Writing: G.Y.O., F.Z.A.

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Original Article

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Rare Atypical Adrenal Pathologies: Single-center Experience

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Abstract

Objective: To share the clinical, radiological and biochemical features of rare atypical pathologies in our adrenalectomy series.
Materials and Methods: Patients with atypical adrenal pathology among patients who underwent open or laparoscopic adrenalectomy for various indications were retrospectively reviewed. the hormonal behavior, radiological and pathological features of rare atypical adrenal pathologies in our series are demonstrated. Information about the postoperative follow-up and surveillance of the patients is given.
Results: Rare adrenal pathologies were detected in 17 (11.6%) of 146 patients who underwent adrenalectomy. Adrenal cysts (6), cavernous hemangioma (3), ganglioneuroblastoma (1), ganglioneuroma (2), ectopic thyroid tissue (1), schwannoma (1), arteriovenous malformation (1), sarcomatoid carcinoma (1), and primary adrenal lenfoma (1) were the rare atypical adrenal pathologies in our series.
Conclusion: Although there are no specific laboratory or radiological findings for most atypical adrenal pathologies, it should be kept in mind that such pathologies with a benign course can also be encountered by the clinician.
Keywords: Adrenalectomy, atypical pathologies, adrenal gland

Introduction

The prevalence of adrenal mass is quite common in the general population, and it is 3-5% in autopsy series, while the detection rate in contrasted abdominal computed tomography (CT) examinations ranges from 0.5-10% (1,2). The prevalence of adrenal adenomas increases with increasing age (3).

Adrenal masses can be presented to the clinician in four different scenarios. The first is patients admitted with adrenal-induced endocrinological complaints, as in some adrenocortical adenomas and carcinomas. These symptoms may include virilization, central obesity in Cushing's syndrome or hypertension, flushing, and headache in pheochromocytoma, or symptoms due to adenomas producing aldosterone. Secondly, they can be detected because of non-specific symptoms such as pain, weakness, weight loss, or intra-abdominal mass sensation caused by the adrenal mass. Thirdly, they may appear as adrenal metastasis in the staging screening of another malignancy. Finally, they can be detected incidentally in examinations with unrelated complaints; this condition is called adrenal incidentaloma (4).

In this study, we presented the rare pathological diagnoses found in pathological examinations performed after adrenalectomies which were performed by a single surgeon with different indications.

Materials and Methods

The data of 146 open and laparoscopic adrenalectomy cases that we performed between January 2005 and February 2020 in our urooncology clinic were retrospectively analyzed. Although our standard approach is laparoscopic, the open method has been preferred in large masses, in patients who are not suitable for laparoscopy and who are suspected of invasive carcinoma. Hormone tests in blood and urine were performed for each patient in whom adrenal mass was detected by CT or

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magnetic resonance imaging (MRI). Patients with suspected malignancy or metastasis were also evaluated with additional scans. After the completion of the evaluation of adrenal masses, patients were divided into two groups: those with non-functional adrenal mass and those with functional adrenal mass. Adrenalectomy was performed in patients who were hormonally active or suspected of malignancy, or who were symptomatic due to the size of the mass. Adrenalectomy pathologies were analyzed retrospectively. Because of the analysis, rare adrenal pathologies were evaluated considering the current literature. The study protocol was approved by the Clinical Research Ethics Committee of Gazi University Faculty of Medicine (decision no: 804, date: 26.11.2020).

Statistical Analysis

The SPSS 15.0 (SPSS Inc., Chicago, IL, USA) program was used to calculate median and percentage values.

Results

Of the 146 patients, 97 (66.4%) were female and 49 (33.6%) were male. The median age was 47 (18-73) years. Open transperitoneal adrenalectomy was performed in 24 (16.3%) patients, and laparoscopic transperitoneal adrenalectomy was performed in 122 (83.7%). In the preoperative period, 54 (36.6%) patients were evaluated by abdominal MRI, 36 (24.6%) patients by abdominal CT, and 56 (38.3%) patients by both methods. An 18-fluorodeoxyglucose Positron emission tomography/CT scan was performed on 14 (9.5%) patients with suspected malignancy or metastasis. Pathology types, numbers, and ratios are shown in Table 1. Benign epithelial cysts, endothelial cyst, pseudocyst, cavernous hemangioma, ganglioneuroblastoma (GNB), ganglioneuroma (GN), ectopic thyroid, schwannoma, arteriovenous malformation (AVM), sarcomatoid carcinoma and primary adrenal lymphoma (PAL) cases were evaluated as atypical adrenal pathologies. The various characteristics of these patients are placed in Table 2.

In our study, a total of six patients had adrenal cysts. According to their histological specifications, they were divided. Three were endothelial cysts with surrounding flat endothelial cells adjacent to the adrenal parenchyma (Figure 1b), two were pseudocysts with endothelium like epithelium on the wall of the cyst (Figure 1c), and the last was a benign epithelial cyst with mesothelial cells surrounding the multiple cystic cavities of the lesion filled with a serous fluid (Figure 1d). All six cases were metabolically inactive, three cases were asymptomatic, and one case of endothelial cyst (weakness) and two cases of pseudocyst (abdominal pain) were symptomatic. CT and MRI scans revealed cystic lesions with no contrast enhancement. In one case of endothelial cyst, MRI showed mural nodular hyperintensity on T1 weighted images due to hemorrhage. Also one case pseudocyst, CT revealed a large cystic mass with thin wall calcification. All six patients operated with the indication that the mass dimensions were larger than 40 mm (40, 45, 45, 45, 55, and 65 mm).

Another atypical adrenal pathology is the cavernous hemangioma. Three patients in our series were metabolically inactive, which was detected incidentally and operated on with the indication that the mass dimensions were larger than 40 mm (60, 75, and 90 mm). The CT and MRI scans showed large heterogeneous masses with intralesional hemorrhage and thin capsular enhancement after contrast material administration. A histological image is shown in Figure 1a.

The GNB case in our series was a 56-year-old male patient with a 65 mm solid mass detected in the right adrenal gland on CT scan performed due to abdominal pain. Hormonal examination revealed that it was not metabolically active; thus, open right adrenalectomy was performed because of suspected malignancy. A pathological examination showed GNB-intermixed (Schwannian stroma-rich). The background component of the tumor was mostly composed of ganglion cells and areas of naked neuropil, but intermixed with small round blue cell tumor cells (neuroblasts) in clusters (Figure 1e). The patient had no metastasis at the time of diagnosis. During his six-year follow-up, there was no local recurrence or distant metastasis.

There were two GN cases in our series. While one of the two patients was hormonally inactive, the other was shown to secrete catecholamine in a preoperative metabolic examination. While the hormonally inactive mass was operated on suspicion of malignancy, the mass synthesizing catecholamine was operated with a preliminary diagnosis of pheochromocytoma. Their morphologies were similar and both were mature GN. There were no naked neuropils, and the stroma was filled with mature ganglion cells (Figure 1f). Both patients were followed up without local or systemic recurrence.

Table 1. Numerical distribution of pathological subtypes

Pathology type	Frequency	Percent (%)
Adrenocortical adenoma	78	53.4
Adrenocortical hyperplasia	6	4.1
Adrenocortical carsinoma	9	6.1
Benign pheochromocytoma	22	15.1
Malignant pheochromocytoma	3	2.05
Renal cell carcinoma metastasis	1	0.68
Paraganglioma	2	1.36
Myelolipoma	6	4.1
Normal adrenocortical tissue	2	1.36
Benign epithelial cyst	1	0.68
Endothelial cyst	3	2.1
Pseudocyst	2	1.36
Cavernous hemangioma	3	2.05
Ganglioneuroblastoma	1	0.68
Ganglioneuroma	2	1.36
Ectopic thyroid	1	0.68
Schwannoma	1	0.68
AVM	1	0.68
Sarcomatoid carcinoma	1	0.68
Lymphoma	1	0.68
Total	146	100.0

AVM: Arteriovenous malformation

Table 2. Various characteristics of the patients							
Diagnosis	**Age**	**Gender**	**Symptom**	**Side**	**Maximum size (cm)**	**Hormonal hypersecretion**	**Operation type**
Endothelial cyst	24	female	weakness	right	4.5 cm	no	laparoscopic
Endothelial cyst	27	female	asymptomatic	right	4.5 cm	no	laparoscopic
Endothelial cyst	23	female	asymptomatic	right	6.5 cm	no	laparoscopic
Pseudocyst	55	female	abdominal pain	right	4 cm	no	laparoscopic
Pseudocyst	66	female	abdominal pain	left	4.5 cm	no	laparoscopic
Benign epithelial cyst	56	male	asymptomatic	left	5.5 cm	no	open
Cavernous hemangioma	32	male	asymptomatic	left	6 cm	no	laparoscopic
Cavernous hemangioma	49	female	asymptomatic	left	9 cm	no	laparoscopic
Cavernous hemangioma	70	female	abdominal pain	left	7.5 cm	no	laparoscopic
Ganglioneuroblastoma	56	male	abdominal pain	right	6.5 cm	no	open
Ganglioneuroma	55	male	asymptomatic	right	7 cm	no	open
Ganglioneuroma	42	male	tachycardia	right	6.5 cm	yes (catecholamine)	laparoscopic
Ectopic thyroid tissue	57	female	hyperhidrosis	right	2 cm	yes (catecholamine)	open
Schwannoma	42	female	asymptomatic	left	5 cm	no	laparoscopic
AVM	64	female	abdominal pain	right	7 cm	no	open
Sarcomatoid carcinoma	52	female	abdominal pain	bilateral	10.5/6.5 cm	no	open
Lymphoma	56	female	asymptomatic	right	7 cm	no	open
AVM: Arteriovenous malformation							

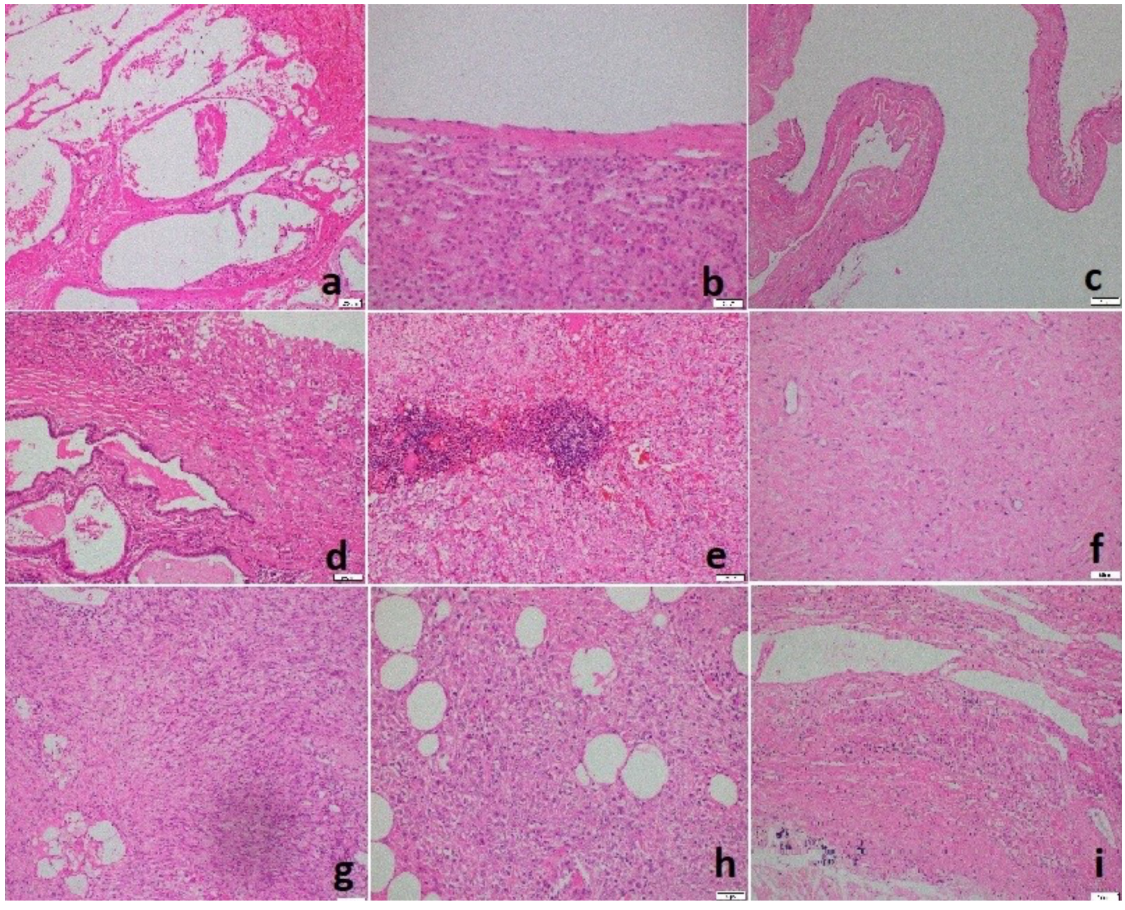

Figure 1. Histological features. (a) cavernous hemangioma, (b) endothelial cyst, (c) pseudocyst, (d) benign epithelial cyst, (e) ganglioneuroblastoma, (f) ganglioneuroma, (g) schwannoma, (h) sarcomatoid carcinoma, (i) arteriovenous malformation

The ectopic thyroid case was 57 years old woman who had undergone subtotal thyroidectomy because of hyperthyroidism 30 years ago. A 20 mm minimally enhancing mass with calcifications was found in the right adrenal gland incidentally on CT scan. The patient was considered pheochromocytoma in the metabolic evaluation. Right adrenalectomy was performed, and ectopic thyroid tissue (ETT) was detected on pathological examination.

The Schwannoma case in our series was a female with a 50 mm mass in the left adrenal gland that was detected incidentally and is non-functional in metabolic evaluation. Pathological examination revealed spindled cells arranged in hyper (Antoni A) and hypocellular (Antoni B) areas and mild lymphocytic infiltration with peculiar vascular spaces here and there (Figure 1g). No recurrence was observed in the five-year follow-up.

The AVM case was a 64-year-old woman who presented with complaint of abdominal pain. CT and MRI examinations revealed an 80 mm peripherally enhancing cystic mass originating from the right adrenal gland. Metabolic examination showed that the mass did not release hormones. Adrenalectomy was performed given that a mass size was larger than 40 mm and a suspected malignancy. The pathological feature of the lesion are large numbers of vessels of different sizes, including veins and arteries, with a dominant vein counterpart (Figure 1i). As it can be frequently accompanied, an organized hematoma was detected also. No recurrence was observed during the patient's 10-year follow-up.

A sarcomatoid carcinoma case was of a 52-year-old woman who CT and MRI scans revealed bilateral heterogeneous contrast-enhanced cystic masses with areas of hemorrhage, fluid-fluid levels and irregular borders. Also, our patient had liver invasion at the time of diagnosis, and bilateral adrenalectomy, liver lobectomy, left nephrectomy, and distal pancreatectomy surgeries were performed. The mass of infiltrative sheets of neoplastic cells with frequent mitoses, areas of necrosis and hemorrhage. Two components could be observed in the tumor. The first component showed the epithelioid cells in a syncytial pattern with large vesicular nuclei, reddish nucleoli and an eosinophilic cytoplasm with distinct borders. The second component mostly contains spindle cells and multinuclear giant cells. Both compounds were stained with vimentin and pankeratin. EMA, S-100, chromogranin, PGP 9.5, Factor-VIII, CD31 and desmin were focally stained in different areas (Figure 1h). One month after surgery, the patient died because of multiorgan failure.

The PAL case in our series, a 56-year-old woman, was investigated for a rash, while a 70 mm mass originating from the right adrenal gland was detected incidentally. This mass was metabolically inactive. After open right adrenalectomy, diffuse large B-cell lymphoma was diagnosed. It had a germinal center B subtype phenotype. The patient is on postoperative 3rd month follow-up and continues adjuvant chemotherapy treatment.

Discussion

Regardless of the indication for adrenalectomy, atypical pathologies can be encountered. In our 146-patient adrenalectomy series, atypical pathology was detected in 17 (11.6%) patients. A total of 11 different types of adrenal pathology were observed in these 17 patients.

Adrenal cysts are rare pathologies, and the incidence in autopsy series is 0.064-0.18% (5,6). Adrenal cysts are generally asymptomatic and metabolically inactive (7). More than 600 patients have been reported in the literature (4). Adrenal cysts form a subcategory that can be divided into endothelial cysts, epithelial cysts, pseudocysts, and parasitic cysts (8). The dispersion in the 220 case series published in 1966 is as follows: endothelial cysts (45%), pseudocysts (39%), epithelial cysts (9%), and parasitic cysts (7%) (9). Both endothelial cysts and pseudocysts are considered variants of adrenal vascular cysts based on immunohistochemical and ultrastructural evidence. The non-vascular adrenal cysts include epithelial cysts and parasitic cysts (10). Usually, they present as thin-walled cystic lesions with internal low-density and no contrast enhancement on CT and MRI scans (10). In a series of 41 cases, 66% of patients were reported to be symptomatic (typically, abdominal pain or gastrointestinal complaints), and 44% were asymptomatic (11). A review of more than 600 cases showed that the malignancy rate of adrenal cysts was 7% (12). The probability of malignancy is typically high in pseudocysts (5,13). Although there is no generally accepted protocol for follow-up, we believe that especially benign cysts can be followed up with ultrasound.

Adrenal cavernous hemangiomas are unusual tumors that originate in the endothelial layer of blood vessels (14). They are a rare, non-functional mass of the adrenal gland that are often diagnosed postoperatively (15). A literature review published in 2019 on adrenal cavernous hemangioma cases found 66 cases reported in the literature. Pre-operative metabolic evaluation was performed in 51 of these 66 patients, and 45 (88.2%) of them were found to be metabolically inactive (16). Although CT and MRI scans are helpful in the diagnosis, imaging findings are usually non-specific. These tumors mostly present as large complex heterogeneous masses with variable amounts of bleeding and calcification. On contrast-enhanced CT, characteristic peripheral patchy and centripetal enhancement may be found (8). On MRI, adrenal cavernous hemangiomas tend to be marked hyperintense on T2-weighted images and have focal hyperintensity on T1-weighted images due to hemorrhage and calcification (8,9). However, the preoperative diagnosis of adrenal cavernous hemangiomas is difficult, and definitive diagnosis is usually made by pathological examination of a surgical specimen. The histological of cavernous hemangioma is common all around the body and is characterized by proliferation of blood vessels with cystic dilatations in their lumens. It is generally benign, and there is no reported recurrence after excision. Large masses can cause life-threatening spontaneous retroperitoneal bleeding (17). Surgical resection is generally required to exclude malignant disease, resolve pressure-related symptoms, and prevent retroperitoneal hemorrhage. Although the prognosis of cavernous hemangiomas is excellent after excision, patients should be followed up with CT and endocrinological tests.

Peripheral neuroblastic tumors (PNTs) are a group of tumors that originate from sympathetic ganglion cells. In two-thirds of the cases, PNTs arise in the adrenal gland or the retroperitoneal paravertebral ganglia. They represent one of the most common

solid tumors in children, while the occurrence in adults is very rare (18). The International Neuroblastoma Pathology Classification separates four pathological groups with respect to the different proportions of ganglion and Schwann cells: neuroblastoma (Schwannian stroma-poor, undifferentiated/poorly, and differentiated/differentiating), GNB intermixed (Schwannian stroma-rich), GN (Schwannian stroma-dominant), and GNB nodular (composite Schwannian stroma-rich/stroma-dominant/stroma-poor) (19). GNB is a rare cause of adrenal tumors in adults. The preoperative suspicion is difficult, and the definitive diagnosis is often made by the pathologist after surgical excision (18). Thus far, 19 adrenal GNBs have been reported in the literature in the adult age group (20), and this number will be 20 in our case. There is no specific presentation; there may be symptoms such as pain due to abdominal mass compression. While only four of the cases in the literature were detected with catecholamine secretion, others were metabolically inactive. Nearly half of the patients had metastases at the time of diagnosis. Cases with metastases to the liver, lymph node, and bones have been reported (18). Most of the patients were treated only with surgery and showed no recurrence during follow-up. Adjuvant chemo-radiotherapy can be administered to patients with metastasis. In one patient who had bone metastasis and did not accept adjuvant chemo-radiotherapy, recurrence was observed 2.5 years after the operation. In only one patient, recurrence developed in the adrenalectomy field two years after the operation, and metastasis occurred in the lumbar vertebrae (21). The patient in our series had no recurrence or metastasis during six years follow-up. Due to the potential for metastasis and the possibility of being hormonally active, patients should be followed up with contrast-enhanced CT and endocrinological tests.

GNs are benign masses that originate from the neural crest and are composed of ganglion cells, mature Schwann cells, and nerve fibers. They are most commonly seen in the adrenal gland (29.7%), followed by the mediastinal sympathetic ganglia (21.8%), retroperitoneum (20.8%), and neck (10.9%), respectively (22). Most GNs are sporadic, but they can also be hereditary and associated with neurofibromatosis type II and multiple endocrinologic neoplasia type II (23). Adrenal ganglioneuromas are rare pathologies representing less than 6% of adrenal masses (24). Imaging findings are usually not distinctive. Most frequently, it appears as a homogeneously minimally enhanced solid mass with smooth borders (25). In our cases, the CT scan showed a heterogeneous solid mass containing central cystic areas and calcification. Usually, GN are metabolically inactive. In some rare cases, a GN can secrete hormones, primarily catecholamines, androgens, and vasoactive intestinal peptide (26). While one of the two masses in our series was releasing catecholamine, the other was hormonally inactive. We believe that patients should be followed up with ultrasound and endocrinological tests because of the possibility of NBs being hormonally active.

The frequency of ETT is approximately 1 in 100,000-300,000. ETT usually occurs in the base of the tongue, but it may also develop in the mediastinum or in the subdiaphragmatic organs. Additionally, the ETT in the adrenal gland (ETTAG) is an extremely rare condition (27). In our literature review, we found that 15 ETTAGs have been reported so far. This number will be increased to 16 with one patient in our series. The subdiaphragmatic ectopic thyroid mechanism was not fully revealed. The most important differential diagnosis of this entity is the metastasis of a cystic papillary thyroid carcinoma. Some researchers also considered that thyroid carcinoma could be a metastasis to the adrenal gland or ETT malignant transformation (28,29). No malignancy of the thyroid gland was detected in the post-operative examinations in the patient we reported.

Schwannomas are very rare, benign tumors that originate from the myelin sheaths of peripheral autonomic or cranial nerves. The head and neck or flexor surface of the extremities are the most related anatomic locations (30). Schwannomas originating from the retroperitoneum are much rarer and constitutes 3-5% of all schwannoma cases (31). Additionally, adrenal schwannomas account for 0.7% of all adrenal masses (32). These masses do not release hormones and are clinically asymptomatic. Thus, preoperatively, they are often misdiagnosed as non-functioning adrenal adenoma. The imaging features of schwannomas are not specific. Schwannomas appear as a well-defined solid mass with cystic degenerative changes. Our case showed a heterogeneous solid mass with central cystic necrotic areas with contrast enhancement. Almost all schwannomas display benign behavior, except for melanotic schwannoma, a rare subtype that has not been clearly identified (33). No cases in the literature have reported recurrence after resection. We think that ultrasound is sufficient in the postoperative follow-up of the patients.

In our literature review, we found that two cases of adrenal AVM have been reported to date (34,35). There are now three with one patient in our series. The pathological feature of the lesion is a large numbers of vessels of different sizes, including veins and arteries, with a dominant vein counterpart. As it can be frequently accompanied, an organized hematoma was detected also.

Adrenal sarcomatoid carcinoma is an extremely rare malignancy mass, and 21 cases have been reported in the literature to date. Only two of these cases are bilateral; one is from our adrenalectomy series and was previously published as a case report (36). Typical symptoms are mass pressure-related abdominal pain, lumbago, and weight loss. The primary treatment modality is surgery. These tumors are aggressive, and their prognosis is very poor. Primary adrenal sarcomatoid carcinomas tend to produce distant metastases, and patients usually die within two years (37). In the literature, at the time of diagnosis, two patients had liver, one patient had lung, and one patient had vena cava metastasis (36,38-40). They are generally metabolically inactive; but hormone-releasing adrenal sarcomatoid carcinoma cases have been reported (39).

PAL is extremely rare and there are fewer than 200 cases reported in the literature. It generally tends to occur in older male patients, and 70% of all cases are bilateral (41,42). Patients usually present with local pain or systemic symptoms such as weakness, weight loss, fever (41). The diagnosis is usually established using imaging-guided biopsy, surgical excision, or on autopsy (43). Immunodeficiency, Epstein-Barr virus, and mutations in the p53 and c-kit genes play a role in pathogenesis

(44,45). The most commonly reported subtype is Diffuse B-cell lymphoma, anaplastic large cell and T-cell types are rarely reported (46-49). PAL shows a poor prognosis, responds well to treatment early, but long-term complete remission is rarely observed after chemotherapy (46). The patient in our series is at postoperative 3rd month follow-up and continues adjuvant chemotherapy treatment.

Study Limitations

The small number of patients in most pathological subtypes and the short follow-up period of some of them are limitations of the study.

Conclusion

Adrenal originated masses can be encountered with different clinical findings. It is quite difficult to establish the differential diagnosis of particularly hormonally inactive masses with preoperative laboratory and radiological examinations. Surgical resection is indicated in patients with potential for malignancy, risk of spontaneous hemorrhage, increase in size over time, or symptoms of mass compression. While a surprise is not expected in pathological diagnosis after resection in hormonally active masses, it should be remembered that rare atypical pathologies can be encountered in hormonally inactive masses.

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Ethics

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Informed Consent: Retrospective study.

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Authorship Contributions

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

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Case Report

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Rare Primary Signet Ring Cell Carcinoma of the Bladder Cancer

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Abstract

Primary signet ring cell carcinoma of the bladder is a rare tumor and it has a poor prognosis and is more mortal than the urothelial cell carnioma. However, most patients apply with painless macroscopic hematuria; rarely do they could apply with urinary tract infection or lower urinary tract symptoms. In this study; a 47-year-old male was referred to our clinic with dysuria, which was antibiotic therapy and symptomatic treatment. In ultrasonography, bladder wall thickening has been seen then patient underwent with cystoscopy. After atypical lesions were seen on the bladder mucosa, random punch biopsies were taken. A pathological examination revealed infiltrative urothelial carcinoma with a poorly differentiated signet ring cell component.

As in this case report, patients with signet ring cell bladder cancer, which is rare and has an aggressive course, might only present with non-specific complaints such as dysuria. If atypical lesions are observed during the diagnostic cystoscopy procedure, the threshold should be kept low to decide on biopsy.

Keywords: Adenocarcinoma, lower urinary tract symptoms, urinary bladder neoplasms

Introduction

Bladder adenocarcinoma; colloid, clear cell, colonic, signet ring cells and many unclassifiable histological subtypes, is an extremely rare carcinoma among bladder cancers. Primary signet ring cell carcinoma of the bladder is one of poor prognosis, mortal and treatment-resistant subtype of bladder adenocarcinoma (1). Most patients may present with painless macroscopic hematuria, but they can also be associated with lower urinary tract symptoms (2). These tumors are diagnosed with histological examination of biopsy which is performed with cystoscopy. Unfortunately, treatment options for this tumor are limited due to its rare occurrence among bladder cancers and its aggressive and poor prognosis. In this tumor, where radiotherapy and chemotherapy are not effective enough, the most effective treatment is radical cystectomy in the early stage (3). In this case report, we drew attention to the fact that dysuria may be the only symptom of signet ring cell bladder cancer and the necessity of biopsy in patients with atypical cystoscopy findings.

Case Report

A 47-year-old male patient presented with dysuria that has been continuing for 3-4 months without hematuria. It was learned that cystoscopy was performed in another urology clinic about 2 weeks ago; suspicious areas were evaluated as lokoplakia, fulgurization was performed, antibiotherapy and analgesic treatment was applied, and he was referred to our clinic because his complaints continued. In his medical history, smoking for 10 pack years and 2 cystolithotomy operations were performed 25 and 30 years ago. There was no abnormal sign in his genitourinary and rectal examinations. Other system examinations were evaluated as normal. In the biochemical evaluation of the patient, creatine was 1.5 mg/dL and other values were normal. In his urinalysis, there were 30 erythrocytes, 49 leukocytes and leukocyte esterase positivity were detected. Grade 2-3 pyelocalcial dilatation and increased diffuse bladder wall thickness were detected by urinary ultrasonography and computerized tomography (CT) (Figure 1). A diagnostic cystoscopy was performed. Cystoscopy revealed that; areas compatible with bladder trigonal leukoplakia, and bullous edematous areas on the posterior wall. The right

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ureteral orifice was not seen. The left ureteral orifice was seen, but the ureteral catheter could not be advanced through this orifice. After taking cold biopsies from the suspicious areas, the procedure was terminated. In the postoperative period, bilateral 8F nephrostomy catheter was inserted by the interventional radiology clinic. Pathological evaluation revealed that; atypical cells with narrow cytoplasm, prominent nucleoli, and hyperchromatic nuclei, individually and in small clusters, without a clear pattern. The pathology report of the patient was T1 high-grade signet ring cell component and poorly differentiated carcinoma (Figure 2). After the pathological evaluation, it was considered that the patient might have a primary gastrointestinal system malignancy. Gastrointestinal system was performed and no foci of malignancy were detected. Contrast-thoracoabdominal tomography was performed for staging, and 5x4 mm nodular lesions in the bilateral lungs and solid lesions of 18x16 mm and 52x43 mm in the right lobe of the liver were detected. Radiological images were evaluated and no other primary focus was detected in the gastrointestinal tract. Lesions detected in the liver were evaluated as hemangioma. Radical cystoprostatectomy, bilateral lymph node dissection (obturator and iliac) and ileal loop diversion were performed. The patient did not have any problems in the postoperative period; the right abdominal drain was removed on the 6th postoperative day, the pelvic drain was removed on the 9th postoperative day, and the left abdominal drain and bilateral nephrostomy catheters were removed on the postoperative 12th day. Pathology was reported during the same period and the tumor infiltrated the surrounding tissue of the bladder, there was lymphovascular and perineural invasion and involvement in bilateral iliac and obturatory lymph nodes is seen in the report. Also left ureter surgical margin was positive. The patient was clinically staged as T3N2M0. In the immunohistochemical examination, it was seen that the tumor cells were stained positively with CK7, panCK, and GATA-3 and partially stained positively with CK20. The patient was evaluated as having undifferentiated bladder carcinoma with a primary signet ring cell component (Figure 3). Adjuvant chemotherapy was planned and the patient was discharged on the postoperative 15th day. The patient died from neutropenic fever and pulmonary thromboembolism while receiving the 6th course of gemcitabine and cisplatin chemotherapy in the 6th postoperative month. Informed consent was obtained from the patient.

Discussion

Signet ring cell bladder cancer is a rare subtype of bladder cancer and it is diagnosed in 0.12-0.6% of bladder cancers (1,4). Signet ring cell cancers are mostly detected in geographic information systems (GIS) as the stomach, colon, gallbladder, or breast adenocarcinoma. Therefore, primary adenocarcinomas of these organs should be investigated and excluded before the diagnosis of primary bladder signet ring cell cancer. Signet ring cell cancer of the bladder has a progressive course and high mortality. It metastasized at a rate of 50%, at the time of diagnosis. It may also present with ureteral invasion (3).

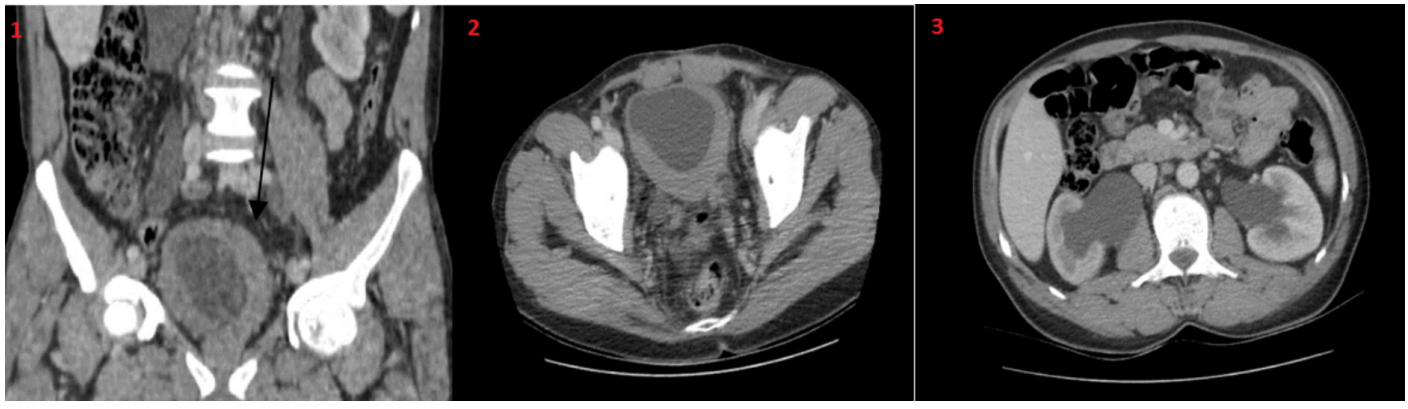

Figure 1. (1-2) Diffuse bladder wall thickness increase in preoperative computed tomography, (3) bilateral hydronephrosis view

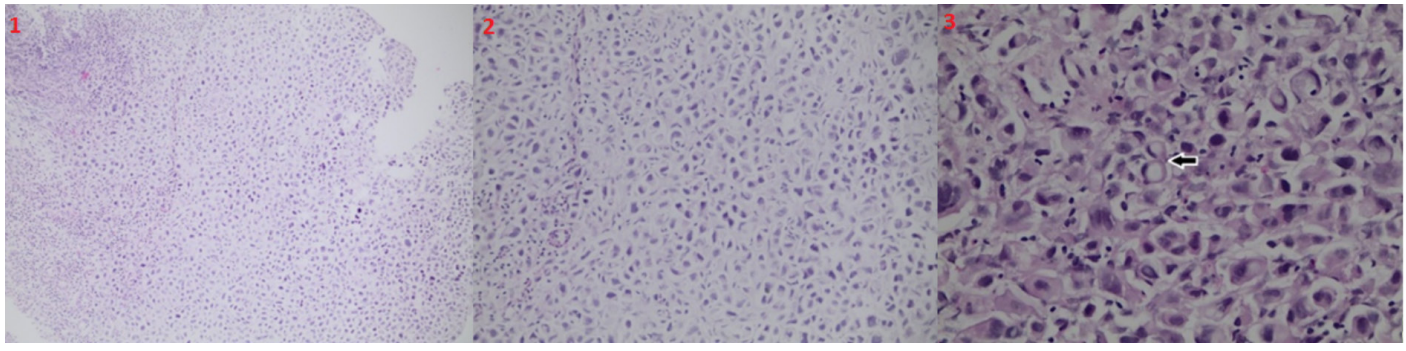

Figure 2. There are atypical cells and signet ring cells with a hyperchromatic nuclei with a narrow cytoplasm, prominent nucleoli, and individual and small clusters, which do not have a clear pattern (cold-cup biopsy) (signet ring cell) (1: HEX10, 2: HEX20, 3: HEX40)

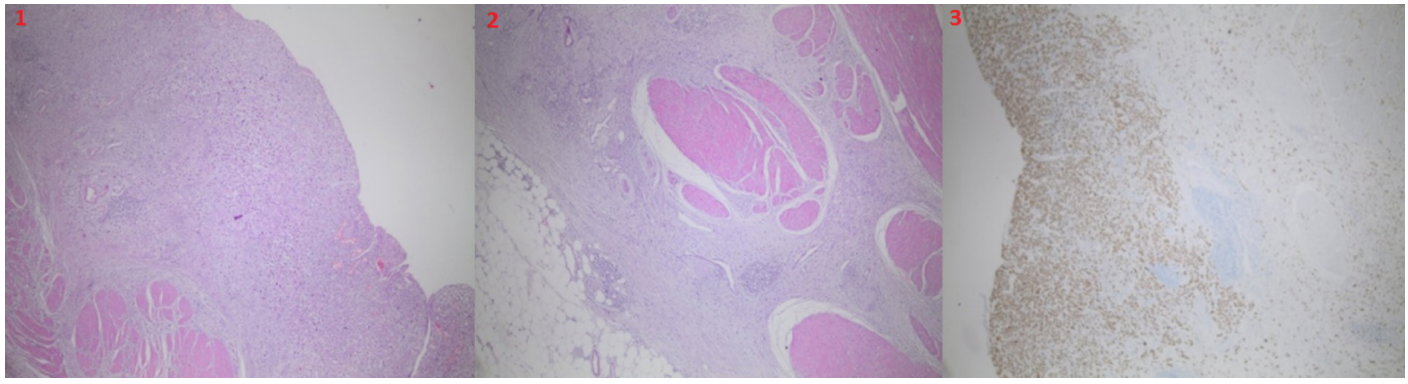

Figure 3. (1-2) Tumor cells appear to have crossed the muscularis propria and invaded the perivesical adipose tissue. Epithelial, muscular and perivesical adipose tissue invasion is seen in the same pathology preparation (1: HEX4, 2: HEX4, 3: panCKX4), (3) Tumor cells staining positive with panCK in radical cystectomy material

The disease is mostly seen in middle-aged men and it is usually accompanied by complaints of hematuria, dysuria and lower urinary tract symptoms. As in our case, there were findings resembling urinary tract infection or infravesical obstruction. Gaurav et al. (2) primary signet ring cell bladder cancer was detected in the patient whom they examined with the complaints of pollakiuria, nocturia, and incomplete urination without hematuria. Yamamota et al. (5) also detected signet ring cell bladder cancer in a patient who presented with oliguria and renal failure without the complaint of hematuria. These authors reported that signet ring cell bladder cancer may progress silently and asymptomatically, or may present with bladder irritation findings, flank pain, oliguria, and acute renal failure.

For staging of signet ring cell bladder carcinoma thoracic, abdominopelvic computed tomography could be performed and CT urography may be performed for the examination of the upper urinary tract. Upper gastrointestinal endoscopy, colonoscopy, mammography, and gynecological examination should be performed to exclude any other possible primary site. Our case was also evaluated according to the results of GIS endoscopy and imaging studies, and no other possible primary focus was found.

When cystoscopic findings are examined, there are no specific findings of signaling ring cell bladder cancer. It could be seen on cystoscopy as a prominent mass to the peduncle and ulceroinfiltrative lesions. Grignon et al. (6) In a study conducted, because of the cystoscopic examination of 34 primary signet ring cell bladder cases, no mass protruding into the lumen was seen in the bladder in 47.1% of the cases. The most prominent findings encountered in the cystoscopic examination of the cases were reported as mucosal edema, erythematous or granular mucosa (6). No significant mass formation was seen also in our case. Cystoscopy revealed trigonal leukoplakia and diffuse bullous mucosal edema. Cold-cup biopsies were taken from suspicious areas because no obvious solid mass or papillary formation detected. In signet ring cell bladder cancers, subepithelial invasion of the disease may cause full-thickness involvement of the bladder wall, ureter invasion, and bilateral hydronephrosis, as in our patient (6). Bladder wall irregularity, increased thickness, and/or hydronephrosis may be seen on computed tomography or intravenous pyelography. In our patient, a spread in the form of infiltrative and diffuse bladder wall thickness increase and bilateral hydronephrosis was seen.

Treatment options in primary signet-ring cell bladder cancer include surgical treatment such as transurethral resection, radical cystectomy and lymph node dissection, radiotherapy and chemotherapy and a combination of these. However, chemotherapy or radiotherapy is an option in treatment; its effectiveness is quite limited (3,5,6,7). Primary signet ring cell bladder cancer is usually diagnosed in advanced stages and a 5-year survival is 27-30% (8). For treating these patients, a multidisciplinary approach is required and urology, medical oncology, radiation oncology and pathology departments should work together. In non-metastatic and non-invasive cases, the most effective method of treatment is complete resection of the tumor. In cases with invasive, diffuse and intramural spread such as our case, radical cystectomy along with ileal loop diversion and lymph node dissection are considered the most effective treatment methods (3,5).

Conclusion

Primary signet ring cell bladder cancer is a rare disease and it has a high mortality. Asymptomatic and insidiously progressive, it may cause symptoms similar to urinary infection or infravesical obstruction and this could make it difficult to diagnose early. In cases with suspected signet ring cell carcinoma and non-specific cystoscopic findings, subepithelial infiltrative spread should be considered and biopsy should be performed.

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Case Report

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Solitary Metachronous Drop Metastasis of a Rare Variant of Renal Cell Carcinoma to Ipsilateral Ureteric Stump - A Case Report

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Abstract

Metachronous metastasis of renal cell carcinoma (RCC) to its ureter has been scarcely reported. All such reports have involved clear cell RCC. We report the first ever case of an oncocytic variant of papillary RCC (OPRCC) - an extremely rare variant that spreads to the ipsilateral ureter. A sixty-five-year-old man, diagnosed to have non-metastatic left RCC with renal vein thrombus, underwent radical nephrectomy. Histopathology revealed large cells in papillary and tubular arrangements with abundant granular cytoplasm. On immunohistochemistry, cells strongly expressed Alpha-methylacyl-CoA racemase and were negative for CD10, C-kit, TFE3, and Melan A, hence a diagnosis of OPRCC, type 2 was given. During follow-up six months, he had a fluorodeoxyglucose avid lesion of size 2.8 cm in the proximal aspect of the left ureteric stump. Therefore, we performed robotic excision of the left ureteric stump and bladder cuff with pelvic node dissection. Pathological examination showed a ureteric mass infiltrating the muscularis propria and periureteric adipose tissue with features of OPRCC, similar to the nephrectomy specimen. It was Pax 8 positive with negativity for the urothelial markers Gata 3, uroplakin and p63, consistent with drop metastasis in a known case. Thus, clinicians must bear in mind that ureteric masses are not always of transitional cell variety and non-clear cell RCC can also metastasize to the ureter. This should be considered by pathologists while evaluating kidney specimens showing oncocytic features. This is the first case report of non-clear cell variety of drop metastasis of a rare histological variant of RCC to the ipsilateral ureter.

Keywords: Drop metastasis, papillary RCC, oncocytic, ureteric metastasis

Introduction

Ureteral metastasis is an uncommon entity. Breast and stomach are the common primary malignancies, which spread to the ureter (1). Renal cell carcinoma (RCC), mainly of the clear cell variety, spreads via hematogenous and lymphatic pathways to the lung, liver and bones. Although, few case reports of renal adenocarcinoma metastasizing to the ureteric stump have been reported, all have been of clear cell carcinoma variety (2). We present the first-ever case of drop metastasis of a rare variant of RCC to the ipsilateral ureter.

Case Report

A sixty-five-year-old diabetic and hypertensive male presented with hematuria in May 2020. On imaging, he had an eight cm left renal mid pole tumor with renal vein thrombus without distant metastasis. He underwent left robotic radical nephrectomy with para-aortic and hilar lymph node dissection. On gross examination, the tumor was unencapsulated, multinodular, solid, soft and friable with a yellowish-brown cut surface and extended into the renal sinus fat. The renal vein branch also showed a tumor thrombus and the mass did not infiltrate into perinephric fat. On histology, the tumor was composed of large cells arranged in papillary and tubular arrangements (Figure 1). The tumor cells showed a pleomorphic grade 3 nuclei and abundant granular cytoplasm. Focal cytoplasmic clearing, rhabdoid morphology, areas of necrosis and a few tumor giant cells were seen, however, sarcomatoid morphology was not seen. On immunohistochemistry, the tumor cells expressed Alpha-methylacyl-CoA racemase (AMACR) strongly and

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diffusely. They were negative for Ca 9, CD10, cytokeratin-7 (CK-7), C-kit, TFE3 and Melan A (Figure 2). A diagnosis of oncocytic variant of papillary RCC (OPRCC), type 2 with focal rhabdoid features, International Society of Urological Pathology nuclear grade 3 and pathological stage pT3aN0 was given. Ureteric and vascular margins were free. At six months, follow-up ultrasonography showed a three cm hypoechoic lesion in the left iliac fossa. In view of a raised creatinine level of 2.41 mg/dL, fluorodeoxyglucose, positron emission tomography (PET) computerized tomography (CT) scan without contrast was performed. It showed an avid soft tissue lesion of size 2.8 cm in the proximal aspect of the left ureteric stump abutting the left psoas muscle (Figure 3). Urine cytology was negative for malignant cells. In view of increased avidity for PET scan, it was decided to excise the mass. The patient underwent robotic excision of the left ureteric stump with bladder cuff excision and left pelvic lymph node dissection. Pathological examination revealed a tumor in the left ureteric wall filling up the lumen similar in appearance to the previously excised left renal tumor (Figure 4). The immunohistochemistry profile was similar to the renal tumor and it was Pax 8 positive with negativity for the urothelial markers Gata 3, uroplakin and p63. A diagnosis of an OPRCC type 2 infiltrating muscularis propria of the ureter and periureteric adipose tissue was given, consistent with drop metastasis in a known case. The pelvic nodes were negative for metastasis. His post-operative recovery was uneventful. Currently, he is doing well on a one-year follow-up. Written valid informed consent has been obtained from the patient for the publication of this manuscript.

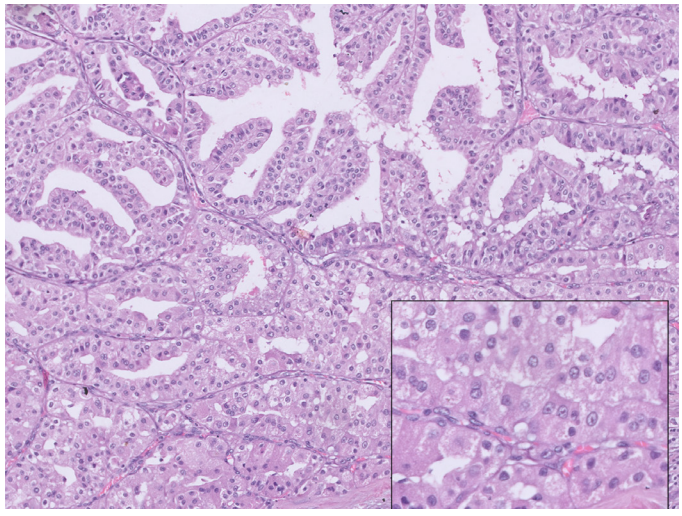

Figure 1. Left renal tumor 10x - Composed of cells arranged in papillary and acinar formations

Inset - 40x: The tumor cells show abundant eosinophilic granular cytoplasm. The nuclei showed conspicuous nucleoli (grade 3)

Discussion

The unpredictable nature of RCC with regard to its presentation, spread and metastasis is well known. Although the majority of the metastases are widespread, up to 10% can be solitary as well (3). RCC metastasizing to the ureter is an uncommon entity. There have been 57 cases of RCC metastasizing to ureter in the literature (4). Several mechanisms responsible for cancer spread are the hematogenous route, retrograde spread through

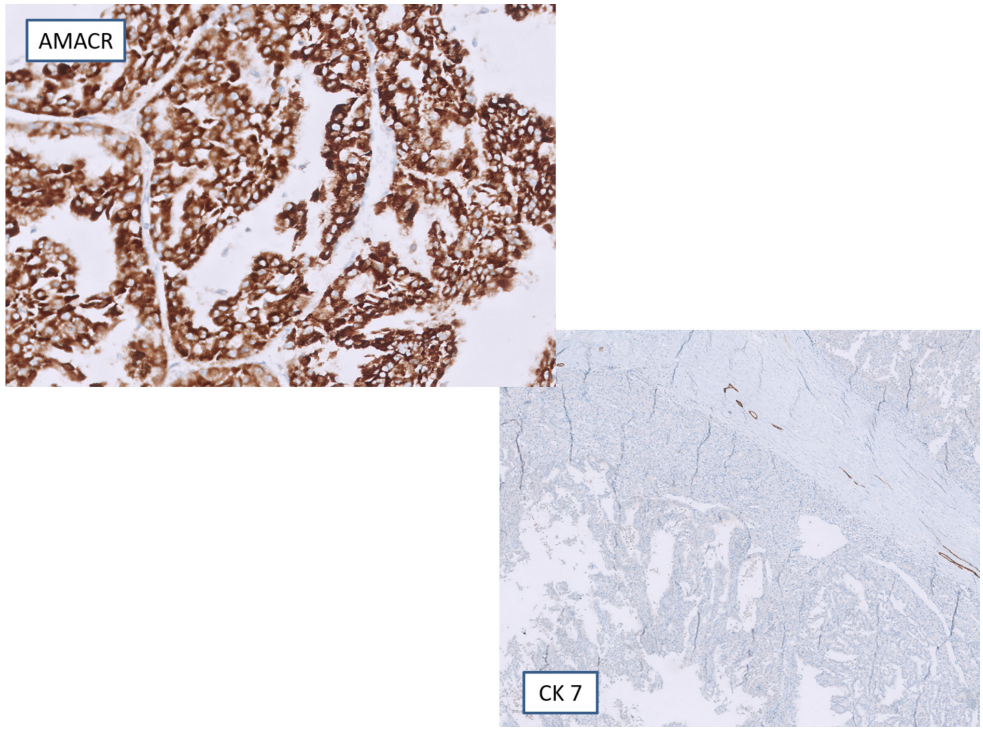

Figure 2. The tumor cells show strong and diffuse AMACR expression and are negative for CK-7

AMACR: Alpha-methylacyl-CoA racemase

veins and lymphatic channels and direct spread by seeding of urothelium (2). Any mechanism could be responsible for the solitary ureteral metastasis in the current case.

Our patient was incidentally found to have a ureteric mass on a routine follow-up after radical nephrectomy. Since PET CT showed uptake, the differential diagnoses were metastatic RCC or transitional cell carcinoma of the ureter. Generally, a surgical approach is preferred for solitary renal cancer metastasis due to high resistance to chemotherapy and radiotherapy and metastasectomy provides the best shot at cure (5). Thus, we performed robotic excision of the ureteric stump and bladder cuff along with left pelvic lymph node dissection much like Bhoopathy et al. (6) who performed a similar case robotically in a metastatic clear cell carcinoma. The histopathology reports of both, the radical nephrectomy specimen and ureteric stump were similar with regards to histological subtype (OPRCC), presence of necrosis and immunohistochemical features.

Although clear cell carcinoma is a common renal malignancy, papillary subtypes can be found in 10 to 15% cases (7). Papillary RCC (PRCC) has traditionally been divided into types 1 and 2 based on the nuclear features (8). The new 2016 edition of the World Health Organization Classification of Tumors of the Urinary and Male Genital Organs has mentioned an oncocytic variant (9). It was reported for the first time in 2005 in a series of 10 cases. The tumor is uncommon and there is a lack of understanding of its immunohistochemical features

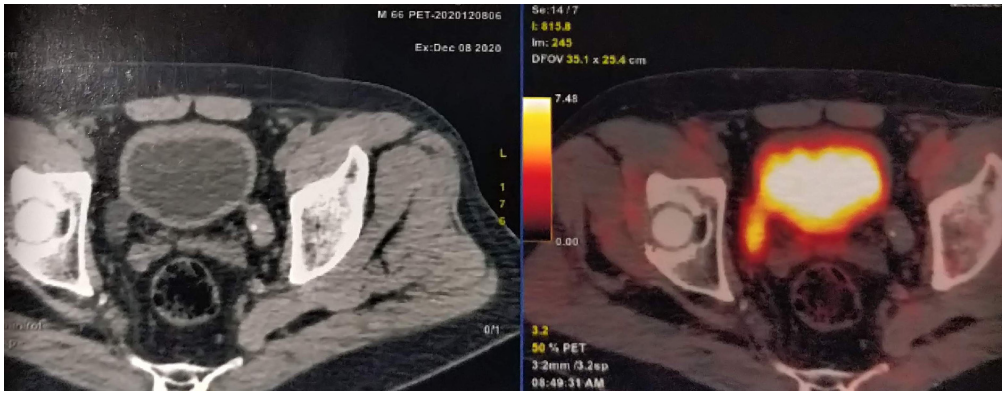

Figure 3. Avidity seen in the right ureteric stump on fluorodeoxyglucose positron emission tomography computerized tomography scan

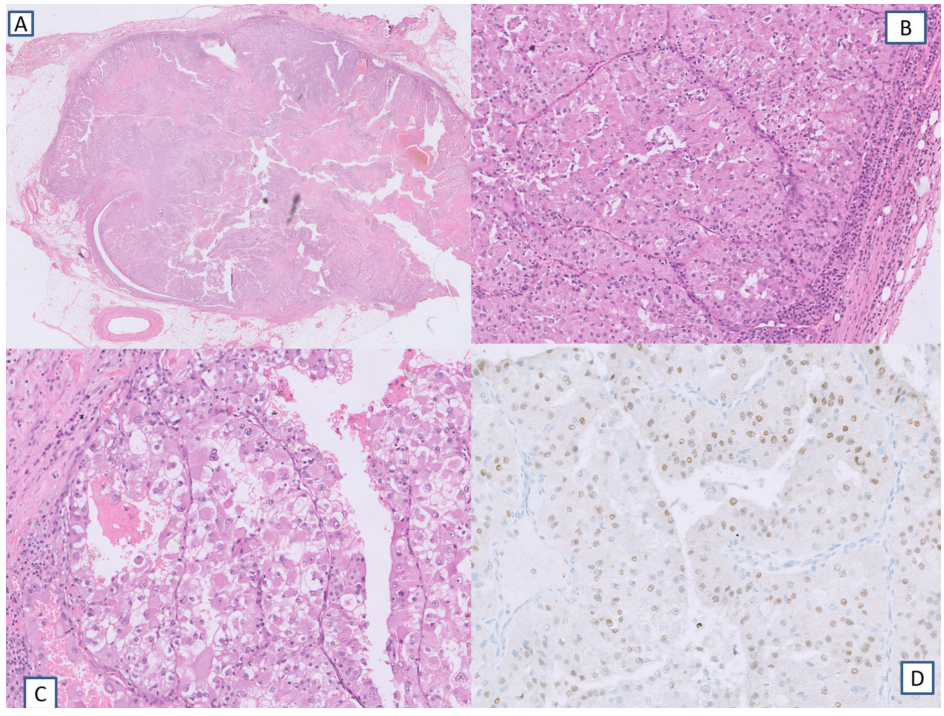

Figure 4. Left ureteric tumor

A- 4x tumor completely fills up the lumen

B&C- 20X and 40X -Eosinophilic tumor cells are similar in appearance to the renal tumor

D- The tumor cells express Pax 8

that makes the classification controversial (10). In 2016, Han et al. (11) characterized ORPCC as having a papillary structure with a single layer of cells with round or polygonal nuclei and eosinophilic granular cytoplasm. On immunohistochemistry, above 90% of the cells were positive for AMACR, whereas a few showed positivity for CD10 and vimentin (11). In this study, these pathological findings were mirrored, although CD10 was negative and vimentin immunostaining was not performed. The presence of rhabdoid features and areas of necrosis are associated with a poor prognosis. Until now, only 3 cases of metastatic OPRCC have been reported, none of them to the ureter (11). The current case, despite not having sarcomatoid features, metastasized to the ipsilateral ureter metachronously within six months of nephrectomy, highlighting the rarity of the case. The presence of renal vein thrombus, large areas of necrosis and partial rhabdoid morphology in the radical nephrectomy specimen were indicators of aggressive pathology and likely contributed to early metastasis. All of the previously reported cases of RCC metastasis to the ureteric stump have been of the clear cell type, which have occurred in a time interval ranging from four months to 12 years from nephrectomy (2).

Conclusion

The new oncocytic variant of PRCC is not well studied and can have serious metastatic implications. Clinicians must bear in mind that non-clear cell RCC can also metastasize to the ureter and ureteric masses are not always of transitional cell variety. This should be considered by pathologists while evaluating any kidney-related specimen showing oncocytic features. This is the first case report of non-clear cell variety of drop metastasis of a rare histological variant of RCC to the ipsilateral ureter. Further studies should help characterize and predict this uncommon variant.

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