E-ISSN 2667-4610

# bulletin of UROONCOLOGY

galenos yayinevi

UROONCOLOGY ASSOCIATION - 1999

June
2021
Volume
20(2)

The Official Journal of Urooncology Association of Turkey

# Editorial Board






Galenos Publishing House
**Owner and Publisher**
Derya Mor
Erkan Mor

**Publication Coordinator**
Burak Sever

**Web Coordinators**
Fuat Hocalar
Turgay Akpınar

**Graphics Department**
Ayda Alaca
Çiğdem Birinci
Gülşah Özgül

**Finance Coordinator**
Sevinç Çakmak

**Project Coordinators**
Aysel Balta
Duygu Yıldırım
Gamze Aksoy
Gülay Akın
Hatice Sever
Melike Eren
Meltem Acar
Özlem Çelik Çekil
Pınar Akpınar
Rabia Palazoğlu

**Research&Development**
Melisa Yiğitoğlu
Nihan Karamanlı

**Digital Marketing Specialist**
Seher Altundemir

**Publisher Contact**
**Address:** Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Türkiye
**Phone:** +90 (212) 621 99 25 **Fax/ Faks:** +90 (212) 621 99 27
**E-mail:** info@galenos.com.tr
**Web:** www.galenos.com.tr **Publisher Certificate Number:** 14521
**Publication Date:** April 2021
E-ISSN 2667-4610
International scientific journal published quarterly.

# About Us

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

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

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

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

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

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

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

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

Scientific and ethical responsibility for the manuscripts belongs to the authors.

**Open Access Policy**

This journal provides immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge.

Open Access Policy is based on the rules of Budapest Open Access Initiative (BOAI) (http://www.budapestopenaccessinitiative.org/). By "open access" to peer-reviewed research literature, we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, index, or link to the full text of these articles, enter them as data into software, and use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. The only constraint on reproduction and distribution, and the only role for copyright in this domain, is that the authors retain control over the integrity of their work and should be properly acknowledged and cited.

**Subscription**

To subscribe to the journal, please contact the Turkish Urooncology Association.

**Advertising**

The application for advertising should be made to the Editorial of Bulletin of Urooncology. The advertisers (person or institution) are responsible for the advertisements' content.

**Instructions to Authors**

Instructions to authors section can be reached at www.uroonkolojibulteni.com/instrustions-to-authors.

**Editorial Office of Bulletin of Urooncology**

H. Kamil ÇAM, MD

Editor in Chief

Address: Şerif Ali Mevkii, Pakdil Sokak, No: 5, 34775, Yukarı Dudullu, Ümraniye, İstanbul, Turkey

E-mail: bulten@uroonkolojibulteni.com

Tel: +90 (216) 594 52 85

Fax: +90 (216) 594 57 99

**Publisher**

**Galenos Yayınevi**

**Address:** Molla Gürani Mah. Kaçamak Sk. No:21 34093 Fındıkzade, İstanbul, Turkey

**E-mail:** info@galenos.com.tr

**Phone:** +90 212 621 99 25

**Fax:** +90 212 621 99 27

# Instructions to Authors

## 1. General Information

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

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

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.

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

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

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

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

Turkish Society of Urooncology owns the copyright of all published articles. All manuscripts submitted must be accompanied by the "Copyright Transfer and Author Declaration Statement Form" available at www.uroonkolojibulteni.com. By signing this form by all authors and sending it to the journal, they 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.

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

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

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

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

We disapprove of unethical practices such as plagiarism, fabrication, duplication, and salami slicing, as well as inappropriate acknowledgements. In such cases, sanctions will be applied in accordance with the Committee on Publication Ethics (COPE) rules. We use Crossref Similarity Check powered by iThenticate to screen all submissions for plagiarism prior to publication.

It is the authors' responsibility to ensure their manuscript meets full ethical criteria detailed at www.uroonkolojibulteni.com/Peer-Review-and-Ethic.

## 2. Manuscript Submission

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

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

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

## 3. Peer-Review Process

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

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

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

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

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

## 4. Editorial Policies

**-Scientific Responsibility:**

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

(1) conception and design of the study, acquisition of data, or analysis and interpretation of data,

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

(3) final approval of the version to be submitted.

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

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

**-Abbreviations:**

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

-Units of Measurement:

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

**-Statistical Evaluation:**

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

## A. Copyright Transfer and Author Declaration Statement Form

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

## B. Title Page

The title page should include the following:

-Full title

-Running title

-Authors' names and institutions

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

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

## C. Main Text (without authors' credentials)

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

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

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

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

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

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

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

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

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

## Examples for writing references:

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

Example:

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

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

Example:

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

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

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

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

## D. Tables and Figures

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

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

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

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

## E. Acknowledgements Form

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

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

Acknowledgements are given for contributors who may not be listed as authors, or for grant support of the research. Any technical or financial support or editorial contributions (statistical analysis, English evaluation) to the study should appear at the end of the article. IF YOU DID NOT RECEIVE ANY FUNDING FOR THIS WORK, PLEASE STATE "THE AUTHOR(S) RECEIVED NO SPECIFIC FUNDING FOR THIS SUBMISSION."

A statement of financial, commercial or any other relationships of a declarable nature relevant to the manuscript being submitted, (i.e., associations/relationships with the sponsors or any other associations which might lead to a potential conflict of interest), must be included in this section. OTHERWISE THIS SECTION SHOULD INCLUDE THIS STATEMENT: "THE AUTHOR(S) DECLARES(S) THAT THERE IS NO CONFLICT OF INTEREST".

## 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

1) Copyright Transfer and Author Declaration Statement Form

2) Title Page

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

First page (Title- 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

2) Title Page

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

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

4) Table(s)

5) Figure(s)

6) Acknowledgements Form

## C-Review Article

1) Copyright Transfer and Author Declaration Statement Form

2) Title Page

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

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

4) Table(s)

5) Figure(s)

6) Acknowledgements Form

## D. Literature Review

1) Copyright Transfer and Author Declaration Statement Form

2) Title Page

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

First page (Title- abstract – keywords), Introduction, 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

## Correspondence

**Bulletin of Urooncology**
**Editor in Chief**
Prof. H.Kamil Çam, M.D.
Department of Urology, Marmara University School of Medicine, İstanbul, Turkey
**Editor**
Associate Prof.
Nihat Karakoyunlu, M.D.
Department of Urology, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey
**Editor**
Bahadır Sahin, M.D.
Department of Urology, Marmara University, School of Medicine, İstanbul, Turkey
**Editorial Office**
Şerif Ali Mevkii, Pakdil Sokak, No: 5, 34775, Yukarı Dudullu, Ümraniye, İstanbul, Turkey
+90 216 594 52 85
+90 216 594 57 99
bulten@uroonkolojibulteni.com
**Publisher**
Galenos Publishing House
Molla Gürani Mahallesi Kaçamak Sokak No: 21 34093 Fındıkzade, İstanbul, Turkey
+90 212 621 99 25
+90 212 621 99 27
info@galenos.com.tr

# Contents

bulletin of
UROONCOLOGY

BEST REVIEWER of ISSUE
Dr. Volkan İzol

BEST REVIEWER of 2020
Dr. İlker Tinay

*Review*

DOI: 10.4274/uob.galenos.2019.1455

*Bull Urooncol 2021;20(2):73-82*

# *Approach to Prostate Cancer Treatment in Elderly Patients with High Comorbidity*

Hasan Hüseyin Tavukçu[1], Mustafa Kaplan[2]

[1]*University of Health Sciences Turkey, Sultan 2. Abdülhamid Han Training and Research Hospital, Clinic of Urology, İstanbul, Turkey*
[2]*Vega Hospital, Clinic of Urology, Tekirdağ, Turkey*

**Abstract**

The incidence of prostate cancer increases with age, and elderly patients often have other accompanying diseases. The most important clinical prediction for deciding on curative treatment in localized prostate cancer treatment is the 10-year survival status of the patient. In advanced prostate cancers, treatment is usually decided according to the comorbidity and age of the patients. Guidelines and consensus reports recommend that patients' general health status should be determined by validated health status screening forms in deciding on treatment for prostate cancer in elderly patients. After evaluating the health status, the treatment options recommended by the guidelines should be presented to the patients according to the risk group of the patient and the treatability of the existing diseases, regardless of their age. Patients who are found to be healthy as a result of the evaluation should be included in the standard treatment applied to non-elderly patients. For patients who are frail but have treatable disease, standard treatment is recommended after correction or improvement of comorbidities. Supportive treatment and adapted treatment options should be offered to the patients who are in a frail state.
**Keywords:** Comorbidity, prostate cancer, health status, elderly

## Introduction

Life expectancy is increasing in the world and in our country, so the majority of the patients who encounter with prostate cancer (PC) are older patients. The median age of patients diagnosed as having prostate cancer is 66 in the world. Mostly metastatic PC is diagnosed at a later age and the median age of death is reported as 80 (1). The proportion of patients over the age of 65 who will be diagnosed as having PC in the United States in 2030 is estimated to be 70% (2). There is a similar increase in expectation for Europe (3). Early and late PC treatment in elderly patients will increase gradually in the coming decades and will become a common public health problem (4).

In the United States of America, curative treatment is applied to only 41% of patients in the intermediate and advanced risk group in men over 75 years of age, while curative treatment is applied to 88% of patients aged 65-74 (5). Life expectancy of more than 10 years in treatment of localized PC is a key clinical factor for benefit from local treatment. This is due to the impact of existing comorbidities on life years. Studies report that the presence of comorbidity is a more important factor than age in predicting death from localized PC (6). At the end of a decade, most patients with a Charlson comorbidity index >2 die due to comorbid diseases, regardless of age or cancer aggressiveness.

In this review, comorbidity-weighted recommendations and treatment approaches in the treatment approach of elderly patients with PC and high comorbidity will be reviewed.

## History

The International Society for Geriatric Oncology (SIOG) has published several different guidelines on the management of PC in elderly patients since 2010 (7,8,9,10). Although none of these literature reviews are systematic, they are all reported as consensus reports that include multidisciplinary expert opinions (4). Their purpose can be basically expressed as defining the "elderly frail" patient group in urology and oncology. These guidelines have accepted patients over 70 years of age as the elderly.

In the first SIOG article, the most important geriatric factors such as dependency, comorbidity, and nutritional status were discussed (7). The most important result was that the treatment should be made not according to chronological age, but should be made according to different tools that scanned the general

**Cite this article as:** Tavukçu HH, Kaplan M. Approach to Prostate Cancer Treatment in Elderly Patients with High Comorbidity. Bull Urooncol 2021;20(2):73-82

**Address for Correspondence:** Hasan Hüseyin Tavukçu, University of Health Sciences Turkey, Sultan 2. Abdülhamid Han Training and Research Hospital, Clinic of Urology, İstanbul, Turkey
**Phone:** +90 216 542 20 20 **E-mail:** hhtavukcu@yahoo.com **ORCID-ID:** orcid.org/0000-0003-0956-7460
**Received:** 14.10.2019 **Accepted:** 26.11.2019

health status and according to methods such as "comprehensive geriatric assessment" (CGA) for detailed examination. This working group published the first SIOG recommendations in the same year (8). In the updated guideline in 2014 (10), they suggested that simple geriatric evaluation with Geriatric 8 (G8) health status screening tool (11) or CGA in geriatric clinics in some patients should be performed to identify patients and distinguish those who would benefit from treatment. The 2017 update contained 2 important perspectives: Screening the cognitive status disorder (with the Mini COG™ tool) and the introduction of early palliative care (9).

The second important date was the full adoption of the SIOG guidelines by the European Association of Urology (EAU) in 2017 (The EAU/ESTRO/SIOG Guidelines) (12). In 2018, the same working group made a new update. This update is very comprehensive and includes surgery, minimally invasive treatments and follow-up, radiotherapy (RT) and brachytherapy, health status assessment, and geriatric oncological conditions in low-middle-income countries (4) (Table 1).

### The Assessment of General Health Status

The basic approach in PC is to decide according to the biological age and current general health status rather than the chronological age of the patient (12). For this purpose, a standard clinical evaluation and the Eastern Cooperative Oncology Group Performance score are generally used in the clinic to distinguish healthy individuals from unhealthy individuals (13) (Table 2). CGA can be used to define health status and predict treatment risks (14). The SIOG strongly recommends that CGA be included in the treatment plan for elderly patients (15). However, CGA will be applied with difficulty as it will be both costly and time consuming for clinicians who do not have a geriatric clinic and do not have sufficient experience in this field. Therefore, it may not be necessary to fill CGA in all elderly patients. It will be more appropriate to determine the patients who will require advanced geriatric examination. If necessary, CGA should be performed after geriatric screening and examinations. Since the health status of elderly patients may change over time, evaluations should be repeated at every step (4).

### 1. Geriatric Scanning

The G8 screening is the most common and short-lasting screening method to identify patients who will require geriatric evaluation (11,16). G8 is an easy assessment method that can be completed in 4 minutes (Tables 3 and 4). It has been specially developed for patients with cancer and includes nutritional status, body mass index, mobility, neuropsychiatric problems, multiple drug use, self-health status and age. The highest score is 17 and score ≤14 is considered abnormal. The use of G8 screening is also recommended by EAU guidelines (17). The 2017 SIOG guidelines recommends Mini-COG™ to evaluate cognitive functions together with the G8 screening (9). Mini-COG™ has been determined to be the most compatible test with Mini Mental State Examination among 10 different cognitive screening tests (18,19). When the result is abnormal, further investigations should be performed to provide a complete cognitive assessment of the patient. Mini-COG™ consists of three-word- recall test and clock drawing test and can be completed in 5 minutes. Values ≤3/5 indicate that the patient needs to be guided for fully evaluation of potential dementia (4).

### 2. Comprehensive Geriatric Assessment (CGA)

CGA should be applied to patients with G8 score ≤14/17. CGA, which is the gold standard for geriatric health status assessment, includes a comprehensive, interdisciplinary diagnostic process to determine the care needs of frail elderly patients, plan care and improve outcomes (20,21). CGA includes functional status, fatigue, cognitive status, comorbidity, mental status, social support, nutrition, and geriatric syndromes (22). In elderly patients with cancer, CGA can predict survival and treatment-related adverse effects, influence treatment choice, and reflect patients' values and treatment goals, as well as their decision-making capacity (15).

### 3. The Geriatric Assessment

It may be necessary to conduct a relevant multidisciplinary study for each problem detected in CGA. It is recommended that the multidisciplinary team includes nurses, psychologists, dieticians, social workers, pharmacists and other relevant therapists (4). However, although CGA is recommended for all patients with cancer, it has been reported that its clinical application has been investigated in very few studies (23,24,25). Many studies are currently ongoing, and higher level of evidence will be reported with their results (4,26).

As the number of elderly patients with cancer is increasing all over the world, the need for a healthcare team trained in geriatrics will indirectly increase. This team will need electronic evaluation forms that can be used more quickly to inquire about the health status of elderly patients (27). There are 3 electronic CGA forms available today (28,29,30). Although it is stated that these forms can be easily used even in the most crowded oncology clinics, they need to be supported by larger series (4).

The latest American Society of Clinical Oncology (ASCO) guidelines recommend integrating CGA into daily practice in elderly patients receiving chemotherapy, and recommend the use of a validated tool listed in ePrognosis to estimate non-cancer life expectancy in the adjuvant and treatment setting (31,32). Schonberg and Lee indexes are also well validated usable forms. These indices include both comorbidities and functional status (4). The ASCO guidelines recommended the use of different screening tools, but especially the use of CGA, in addition to screening tests such as G8 and the geriatric assessment (31).

In summary, when the ASCO guidelines recommendations are adapted to SIOG guidelines;

- First, elderly patients with PC should be screened using the G8 and Mini-COG™.
- Estimated non-cancer survival should be determined using ePrognosis in early stage PC, especially Shonberg and Lee indexes contribute to decision making.

| **Table 1. The International Society for Geriatric Oncology's recommendations for the treatment of elderly patients with prostate cancer** |
|---|
| **Assessment of health status**<br>• Treatment should be based on health status, rather than age, and also on the patient's preference. |
| • It is recommended to scan for frailty using the G8 tool and to scan for cognitive impairment with Mini-COG™. In patients with Mini-COG™ score ≤3/5, a more detailed cognitive assessment is required. |
| • Assessment of dependence, comorbidity, and nutritional status in patients with a G8 score ≤14/17 classifies patients into three health status groups: (1) "healthy" or "fit" patients; (2) "vulnerable" patients; and (3) "frail" patients. Vulnerable and frail patients are candidates for geriatric evaluation and geriatric examinations. |
| • Patients benefit most from a geriatric assessment when identified as frail because geriatric management allows for a more appropriate treatment plan. |
| **Management of localized prostate cancer in elderly patients**<br>• Prostate cancer (PC) risk should be determined according to the D'Amico classification. |
| • Healthy elderly patients with PC in the D'Amico high-risk group who have a chance of living for more than 10 years are more likely to benefit from curative treatment. |
| • Elderly patients with moderate to low risk PC are likely to benefit from active surveillance or a watchfull waiting, depending on their individual expected survival time. A curative approach should be discussed with intermediate risk patients with a life expectancy of at least 10 years. |
| • The balance between the benefits and harms of androgen deprivation therapy (ADT) for localized PC should be carefully considered. It should be noted that the risk of diabetes, cardiovascular complications, osteoporosis, bone fractures and cognitive dysfunction may increase. Adjuvant ADT should only be used in moderate and especially high risk diseases. In patients who are symptomatic or asymptomatic but in the high risk D'Amico group, ADT monotherapy should only be discussed with patients who are unwilling or who cannot receive any local treatment. |
| • A validated tool such as Schonberg or Lee index can aid in predicting life expectancy independent of PC. |
| **Advanced prostate cancer treatment in elderly patients**<br>**• Metastatic castration sensitive prostate cancer**<br>1. Six cures of docetaxel concurrent with ADT is the first recommended treatment in "healthy" patients with newly diagnosed hormone sensitive metastatic PC. It is only suitable for the treatment of high volume diseases. The use of primary prophylaxis with granulocyte colony stimulating factor (G-CSF) should be considered. |
| 2. ADT + abiraterone is another recommended first-line treatment. It is indicated in "healthy" men with newly diagnosed hormone sensitive metastatic PC with high risk disease. The use of abiraterone in the M1 indication should be carefully evaluated against possible side effects and costs. |
| 3. In all other cases, only ADT remains standard. |
| 4. Patients treated with ADT should be evaluated for bone densitometry and should receive calcium (if dietary intake is insufficient) and vitamin D supplements. For those at high risk of falling or having fractures, it is recommended to use denosumab 60 mg subcutaneous injection every 6 months at osteoporosis prevention/therapy approved doses. In settings where denosumab is not available, osteoporosis prevention/therapy approved doses of bisphosphonates should be used. Fracture risk is best assessed using a validated scale. |
| 5. Primary radiotherapy to the prostate is a standard treatment option for healthy men with newly diagnosed disease with low metastatic burden. |
| **Advanced prostate cancer treatment in elderly patients**<br>**• Metastatic castration resistant prostate cancer**<br>1. In metastatic castration resistant prostate cancer (mCRPC), docetaxel 75 mg/m$^2$ every 3 weeks is suitable for elderly patients with good health status. Geriatric evaluation and examination results should be considered for frail elderly patients, and the bi-weekly regimen should be considered in those who cannot take the three-week regimen. It is recommended that primary prophylaxis with G-CSF be used in a three-week regimen. |
| 2. Abiraterone and enzalutamide are other first-line drugs in mCRPC. |
| 3. Options for patients who have previously received docetaxel include cabazitaxel, abiraterone and enzalutamide. |
| 4. The optimum sequence of treatments is subject to investigation. After the failure of a new hormonal agent, agents with another mechanism of action, including taxanes or radium-223 (i.e. in cases of bone metastasis), should be the preferred choice due to cross-resistance between androgen- deprivation agents. |
| 5. Elderly patients need careful evaluation of drug interactions and proactive management of side effects. It is important to first perform cardiac evaluation, treat pre-existing high blood pressure, correct hypokalemia, and monitor hemogram, aspartate aminotransferase, alanine aminotransferase, potassium, glycemia, and blood pressure. Prospective evaluation of the side effects of new hormone therapy should be made in routine clinical practice. |
| 6. Patients who have received first line treatment, patients with no visceral and dense lymph node metastasis, with bone metastasis, and with docetaxel failure are eligible for radium-223. |
| 7. Palliative treatments include radiotherapy, radiopharmaceuticals, bone-sparing treatments, palliative surgery, medical treatments for pain and other symptoms.<br>• Basically, early palliative approaches should be applied in mCRPC<br>• Adapted physical activity is recommended at all stages of prostate cancer management; further clinical studies are required in elderly patients. |

• The use of a frailty index suggested by the geriatric assessment or a similar tool predicts mortality and classifies elderly patients into healthy, vulnerable or fragile groups. The SIOG working group decided to use the health status category in 2014. Accordingly; (1) Healthy elderly is defined as an elderly with a G8 screening score of >14/17, without comorbidity, dependency, malnutrition or impairment in cognitive status, (2) Vulnerable elderly is defined as an elderly who is unable to perform some daily activities, with moderate malnutrition or comorbidity, and (3) Frail elderly are patients who are debilitated, dependent,

| Table 2. Eastern cooperative oncology group performance scoring (ECOGPS) | | | |
|---|---|---|---|
| **Karnofsky status** | **Karnofsky grade** | **ECOG score** | **ECOG status** |
| Normal, no complaint | 100 | 0 | Normal. Able to continue normal activities before the disease |
| The patient can continue his/her normal activity, there may be several symptoms or signs of the disease. | 90 | 1 | Can continue his/her daily life with tolerable tumor findings |
| The patient continues his/her normal activities with some difficulties, there are minor signs and symptoms of the disease. | 80 | | |
| The patient can take care of himself/herself and cannot do his/her normal activity and job. | 70 | 2 | Having disturbing tumor findings but spending more than 50% of his/her time out of bed |
| Patient can meet his/her needs, rarely needs help, needs some help | 60 | | |
| Help and medical attention are often required. | 50 | 3 | Severely ill and forced to stay bed-bound more than 50% of his/her time |
| Special care and assistance are required. | 40 | | |
| Disabled enough to require hospital care, but no risk of death | 30 | 4 | Being in a very ill condition and spending all the time tied to the bed |
| Severely ill, need active supportive care in the hospital. | 20 | | |
| About to die | 10 | | |
| Dead | 0 | 5 | Dead |
| ECOG: Eastern cooperative oncology group | | | |

| Table 3. Geriatric 8 (G8) health status screening criteria | | |
|---|---|---|
| | **Question** | **Answer (Score)** |
| A | In the last 3 months, was there digestive problems, a decrease in appetite, and a decrease in nutrition due to chewing or swallowing difficulties? | 0 = severe decrease in nutrition<br>1 = moderate decrease in nutrition<br>2 = no decrease in nutrition |
| B | Was there any weight loss in the last 3 months? | 0 = More than 3 kg<br>1 = Did not know<br>2 = Loss of 1-3 kg<br>3 = No weight loss |
| C | Mobility | 0 = Dependent on bed or chair<br>1 = Can get out of bed or chair, but cannot go out<br>2 = Can go out |
| E | Neuropsychological problem? | 0 = Severe dementia or depression<br>1 = Mild dementia<br>2 = No psychological problems |
| F | Body mass index (BMI) | 0 = BMI <19<br>1 = BMI 19-21<br>2 = BMI 21-23<br>3 = BMI ≥23 |
| H | Prescripted drug use less than 3 | 0 = Yes<br>1 = No |
| P | How does the patient feel when compared to other people of the same age? | 0.0 = Not good<br>0.5 = Did not know<br>1.0 = Same<br>2.0 = Better |
| | Age | 0:>85<br>1 = 80-85<br>2 = <80 |
| | **Total score** | 0-17 |

unable to perform many daily activities, have severe comorbidity and severe malnutrition. Vulnerable and frail patients should be treated with detailed geriatric assessment (Figure 1).

## Prostate Cancer Treatment in the Elderly and Patients with Comorbidity

### Localized Prostate Cancer - Active Monitoring

In elderly patients with poor health status, surgical treatment provides a low rate of cancer-specific and overall survival advantage, however, with increasing age, side effects of surgery are more common. Elderly patients over the age of 65 and with poor health status have year gain with a better quality of life with active follow-up (33). Active surveillance or watchfull waiting can be applied to patients in the low risk group. However, the risk of dying from PC or any other concomitant cause should be carefully evaluated and active surveillance should be decided accordingly (34). Although there was no difference in terms of cancer-specific survival between radical prostatectomy (RP), RT and active surveillance groups at the end of the 10 years of the ProtecT study, the highest quality of life was reported in the active surveillance group. Of the population group of the study; 60% were low-risk group patients and 40% were medium-risk group patients (35).

### Localized Prostate Cancer-Radical Prostatectomy

Although advanced PC and higher rates of cancer-specific mortality are observed in elderly patients, most of the causes of death are other accompanying diseases. Those with high-risk diseases actually constitute the group of patients who take or will take the most benefit from RP (36). There is no significant difference in terms of cancer-specific mortality in high-risk patients over 70 years of age or below who have undergone RP at the end of 10 years of follow-up (37). The benefit of surgery in terms of cancer-related death is higher than active surveillance in patients with localized PC under the age of 65 years. However, in elderly patients, RP reduces the risk of metastasis and the use of androgen deprivation therapy (ADT) (38). In another study,

| Table 4. Cumulative illness rating scale-geriatric (CISR-G) | | | |
|---|---|---|---|
| **"Cumulative illness rating scale-geriatric" score** | | | |
| **Name** | **Age** | **Date** | **Scorer** |
| **Scores** | | | |
| 0 | | None | |
| 1 | | Mild (or past serious health problem) | |
| 2 | | Moderate (moderately significant disability, requiring level 1 treatment) | |
| 3 | | Severe (persistent marked disability/uncontrolled chronic illness) | |
| 4 | | Advanced severe (need for immediate treatment/end-stage organ failure/severe functional impairment | |
| | | Score: | |
| Cardiac | | | |
| Vascular | | | |
| Respiratory | | | |
| Eye, ear, nose, throat, larynx | | | |
| Upper gastrointestinal tract | | | |
| Lower gastrointestinal tract | | | |
| Hepatic | | | |
| Kidney | | | |
| Genitourinary | | | |
| Musculoskeletal system | | | |
| Neurological | | | |
| Endocrine/metabolic | | | |
| Psychiatric | | | |
| Total score | | | |

RP (with adjuvant therapies) in high-risk disease resulted in cancer-specific survival rates of 91%. Survival was reported as 95% if any of the risk factors [Gleason >7, >T2, prostate-specific antigen (PSA) >20 ng/mL], and 79% if all three were present (39). The risk of early complications after RP is associated with increased comorbidity compared to age. On the other hand, in the long term, the risk of urinary incontinence and erectile dysfunction is affected more by increasing age (40,41,42).

### Localized Prostate Cancer-Radiotherapy

With RT applied with the appropriate dose (>72 Gy) and technique, similar cancer control and treatment-related comorbidity rates with RP are achieved, regardless of age (43). Studies on RT using hypofractionated techniques in recent years give high biochemical control rates in all risk groups (44,45,46,47,48). However, routine use of RT is not recommended in patients in the low risk group due to the increase in late complications (4,48). In addition, although most of these studies involve patients over the age of 70, no specific results have been reported for these age groups, so definitive interpretations can not be made for the elderly group. Although dose escalation studies on brachytherapy have been widely conducted in recent years, age-specific results have not been reported as in hypofractionated techniques. In addition, the procedure requires anesthesia, although less side effect rates have been reported (49,50,51,52,53,54). Administration of ADT together with RT increases the morbidity and mortality of pre-existing heart disease in elderly patients. Patients with moderate and severe comorbidity can not obtain a significant life-year benefit from ADT with RT. However, it has been reported that high-risk patients with no or less comorbidity benefit from ADT (55). In the medium-risk patient group, the combination of short-term ADT and RT is recommended (55,56).

### Localized Prostate Cancer-Minimally Invasive Treatments

Minimally invasive-ablative therapies are still experimental and there is currently insufficient evidence to recommend them in elderly patients and patients with comorbidities.

### Localized Prostate Cancer-Androgen Deprivation Therapy

ADT alone should not be used in patients with localized PC without metastasis. Patients with locally advanced disease (T3-T4), PSA value higher than 50 ng/mL and PSA doubling time less than 12 months benefit from early ADT (57,58). In patients with high-risk diseases and in very frail patients, early initiation of ADT provides little overall survival advantage, but cancer-specific or symptom-free survival benefit has not been reported (57).

### Metastatic Prostate Cancer-Castration Sensitive Disease

The first-line treatment is ADT in the elderly with hormone sensitive PC. Bone densitometry is recommended to determine basal bone mineral density in elderly patients and calcium and vitamin D supplements are recommended to protect from osteoporosis (10).

In recent years, with the LATITUDE study, it has been reported that the addition of abiraterone to the ADT has significantly improved overall survival and radiological progression-free survival in the elderly (>70 years old) patient group. However, the strength of this study was found to be insufficient to make comments for patients >75 years old, and toxicity was not reported by special age groups (59,60). In the STAMPEDE study, it was stated that the addition of abiraterone had a significant effect on overall survival in patients >70 years of age, and toxicity was found to be similar in this patient group compared to the group aged <70 years. However, patients with a history of cardiovascular disease were not included in this study (61).

With the early addition of docetaxel to ADT in the group of metastatic patients susceptible to castration, significantly higher overall survival rates were reported in CHAARTED, STAMPEDE and GETUG-15 studies, especially in high-volume disease [≥4 bone metastases (one of them should be in spine bone) or pelvic bone and/or visceral metastasis] (62,63,64). The addition of docetaxel was reported to be beneficial in patients younger

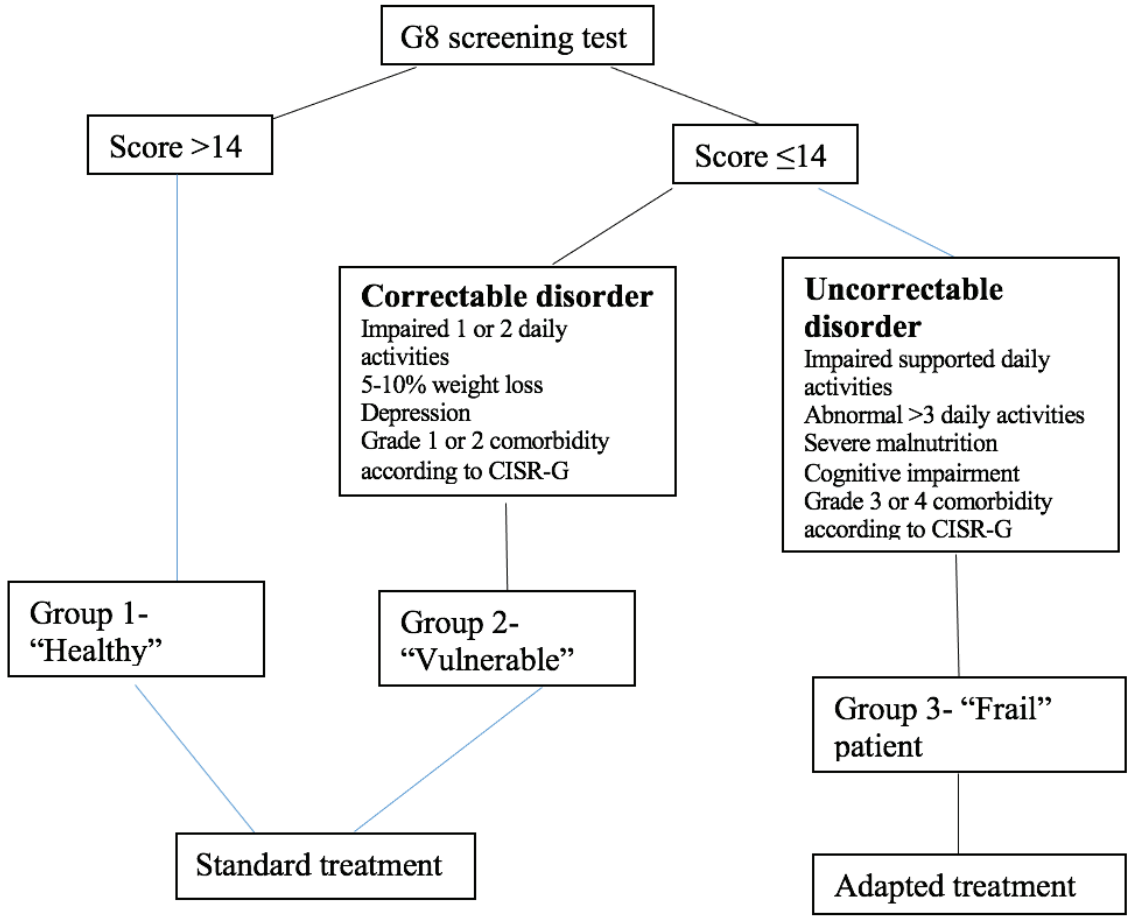


**Figure 1.** Decision tree in prostate cancer treatment according to health status
CIRS-G: Cumulative illness rating scale-geriatric

than 70 years of age or over (65). When evaluated as to whether there was a superiority between docetaxel and abiraterone, there was no difference in terms of the cancer-specific survival in the STAMPEDE study, while another metaanalysis reported that abiraterone was more effective in terms of overall survival (66,67). However, since the rate of patients aged >70 years is 29% in these studies, this makes it difficult to interpret for the elderly patient group (4).

In the subsequent study of STAMPEDE, the groups with metastatic PC with and without primary RT were compared. In the subgroup analysis, it was reported that RT significantly contributed to overall survival in low volume metastatic patients (68). Primary RT was recommended as a standard in newly diagnosed metastatic PC with low metastatic load. However, the data in the study were not reported specific to age (4).

There is not enough information about the toxicity of abiraterone and docetaxel in the castration sensitive group and the elderly patient group (4). However, in docetaxel chemotherapy, especially in the elderly patient group, toxicity related to neutropenia was reported to be more frequent in castration-resistant patients (69).

Routine use of bisphosphonates or denosumab is not recommended to prevent skeletal complications in this patient group unless there is a suspicion of fracture or castration-resistant disease with bone metastases (70).

## Metastatic Prostate Cancer-Castration Resistant Disease

The standard treatment for patients with castration-resistant metastatic PC and tolerable comorbidity is docetaxel chemotherapy, with similar results to younger patients (71). It was reported that in older and more frail patients, granulocyte colony stimulating factor prophylaxis with docetaxel could be given to protect the patient from febrile neutropenia, every 2 weeks (50 mg/kg for four weeks) or weekly instead of every 3 weeks (75 mg/kg) (72).

It was reported that the use of cabazitaxel as the first choice in castration-resistant disease was not superior to docetaxel (73). In the same study, overall survival was not found different, and toxicity was reported less with the dose of 20 mg/m$^2$ than 25 mg/m$^2$. In second-line use, less toxicity was reported with the dose of 20 mg/m$^2$ than 25 mg/m$^2$ and a lower efficiency in terms of overall survival was not reported (74). It is recommended to prefer low doses in elderly patients as a better approach (4). In

two different studies, it was suggested that administration of cabazitaxel at different doses and days would reduce toxicity rates and that the use of granulocyte colony stimulating factor could be applied concurrently with treatment (75,76). In eligible patients cabazitaxel increases the life years in elderly patients receiving chemotherapy and susceptible to chemotherapy, similar to abiraterone acetate, enzalutamide, and sipuleucel-T (77,78,79,80,81,82,83).

Radiopharmaceutical agents are generally less toxic than chemotherapy agents, so they may be more suitable for elderly patients. Studies with Ra223 have shown that hospitalization due to bone problems decreases and that they generally cause less toxicity as a result of its positive effects on bone lesions with early administration programs (84,85,86,87). It has been reported that Ra223 can only be used with ADT and should not be used with other chemotherapeutic agents. Early results of the study of another new agent 177Lu-PSMA indicated that it was an effective treatment and its side effects were low (88).

In general, besides the side effects of ADT treatments, it has been reported that they are not generally associated with cognitive dysfunction as a result of the latest meta-analysis (89). Care should be taken in terms of the most important side effects of ADT, such as myocardial infarction, cerebrovascular disease, metabolic syndrome, diabetes, obesity, and dyslipidemia, and precautions should be taken, especially in elderly patients (90).

The general approach to PC in elderly patients, which is prepared based on the recommendations of the SIOG study group, is summarized in Table 1.

### Future Approaches

There are many unknown questions about the treatment of metastatic PC, especially in elderly patients. However, the successive use of abiraterone and enzalutamide, regardless of age and health status, can develop a high rate of cross-resistance, on the other hand, taxanes are considered highly effective drugs that can be used easily after new hormonal treatments (4).

Although it has been reported that poly ADP-ribose polymerase-1 inhibitors such as olaparib and ipilimumab as immunotherapy do not have a distinctly different side effect profile in the elderly patient group, the results of new studies are expected for more accurate interpretations (91,92).

## Conclusion

The choice of treatment should be decided in elderly patients with PC according to their general health status. Age affects the treatment less than comorbidity, and general health status should be determined with a validated screening form such as G8 and comorbid disease assessment scales. Geriatric evaluation should be made in patients according to their existing comorbidities. The health status of the patient should be determined according to the biological age and current comorbidity, not the chronological age. The standard treatment recommended by the guideline according to the current PC stage should be given to the patients without comorbidities, and standard PC treatment should be given after the evaluation of vulnerable patients and the geriatric examination-recovery. Only palliative and supportive treatments should be applied to elderly patients who are found to be frail.

### Acknowledgements

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

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

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

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

### Ethics

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

### Authorship Contributions

Concept: H.H.T., Design: H.H.T., Data Collection and Processing: H.H.T., Analysis and Interpretation: H.H.T., Literature Search: M.K., Writing: H.H.T., M.K.

## References

1. National Cancer Institute. SEERCancer Stat Facts: prostate cancer. 2018. Available from: https//seercancergouv/statfacts/html/prosthtml2018. 2018.
2. Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol 2009;27:2758-2765.
3. Arnold M, Karim-Kos HE, Coebergh JW, et al. Recent trends in incidence of five common cancers in 26 European countries since 1988: analysis of the European Cancer Observatory. Eur J Cancer 2015;51:1164-1187.
4. Boyle HJ, Alibhai S, Decoster L, et al. Updated recommendations of the International Society of Geriatric Oncology on prostate cancer management in older patients. Eur J Cancer 2019;116:116-136.
5. Hamilton AS, Albertsen PC, Johnson TK, et al. Trends in the treatment of localized prostate cancer using supplemented cancer registry data. BJU Int 2011;107:576-584.
6. Albertsen PC, Moore DF, Shih W, et al. Impact of comorbidity on survival among men with localized prostate cancer. J Clin Oncol 2011;29:1335.
7. Droz JP, Balducci L, Bolla M, et al. Background for the proposal of SIOG guidelines for the management of prostate cancer in senior adults. Crit Rev Oncol Hematol 2010;73:68-91.
8. Droz JP, Balducci L, Bolla M, et al. Management of prostate cancer in older men: recommendations of a working group of the International Society of Geriatric Oncology. BJU Int 2010;106:462-469.
9. Droz JP, Albrand G, Gillessen S, et al. Management of prostate cancer in elderly patients: recommendations of a task force of the International Society of Geriatric Oncology. Eur Urol 2017;72:521-531.
10. Droz JP, Aapro M, Balducci L, et al. Management of prostate cancer in older patients: updated recommendations of a working group of the International Society of Geriatric Oncology. Lancet Oncol 2014;15:e404-e414. doi: 10.1016/S1470-2045(14)70018-X.
11. Soubeyran P, Bellera C, Goyard J, et al. Screening for vulnerability in older cancer patients: the ONCODAGE Prospective Multicenter Cohort Study. PLoS One 2014;9:e115060. doi: 10.1371/journal.pone.0115060.
12. Droz JP, Boyle H, Albrand G, et al. Role of geriatric oncologists in optimizing care of urological oncology patients. Eur Urol Focus 2017;3:385-394.

13. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.
14. Wedding U, Kodding D, Pientka L, et al. Physicians' judgement and comprehensive geriatric assessment (CGA) select different patients as fit for chemotherapy. Crit Rev Oncol Hematol 2007;64:1-9.
15. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol 2014;32:2595-2603.
16. Decoster L, Van Puyvelde K, Mohile S, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendationsdagger. Ann Oncol 2015;26:288-300.
17. Mottet N BJ, Bolla M, Briers E, et al. EAU e ESTRO e ESUR e SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017;71:618-629.
18. Tsoi KK, Chan JY, Hirai HW, et al. Cognitive Tests to Detect Dementia: A Systematic Review and Meta-analysis. JAMA Intern Med 2015;175:1450-1458.
19. Borson S, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia: validation in a population-based sample. J Am Geriatr Soc 2003;51:1451-1454.
20. Solomon DH. Geriatric assessment: methods for clinical decision making. JAMA 1988;259:2450-2452.
21. Reuben DB, Fishman LK, McNabney M, Wolde-Tsadik G. Looking inside the black box of comprehensive geriatric assessment: a classification system for problems, recommendations, and implementation strategies. J Am Geriatr Soc 1996;44:835-838.
22. Ellis G, Gardner M, Tsiachristas A, et al. Comprehensive geriatric assessment for older adults admitted to hospital. Cochrane Database Syst Rev 2017;9:CD006211. doi: 10.1002/14651858.CD006211.pub3
23. Puts MTE, Sattar S, Kulik M, et al. A randomized phase II trial of geriatric assessment and management for older cancer patients. Support Care Cancer 2018;26:109-117.
24. Schmidt H, Boese S, Lampe K, et al. Trans sectoral care of geriatric cancer patients based on comprehensive geriatric assessment and patient-reported quality of life - Results of a multicenter study to develop and pilot test a patient-centered interdisciplinary care concept for geriatric oncology patients (PIVOG). J Geriatr Oncol 2017;8:262-270.
25. Magnuson A, Lemelman T, Pandya, et al. Geriatric assessment with management intervention in older adults with cancer: a randomized pilot study. Support Care Cancer 2018;26:605-613.
26. NCI clinical trials. 2018. https://ClinicaltrialsGouv/Ct2/Results?Terms=cancer+and+ geriatric assessment&search.
27. Kalsi T, Babic-Illman G, Ross PJ, et al. The impact of comprehensive geriatric assessment interventions on tolerance to chemotherapy in older people. Br J Cancer 2015;112:1435-1444.
28. McCleary NJ, Wigler D, Berry D, et al. Feasibility of computer-based self-administered cancer-specific geriatric assessment in older patients with gastrointestinal malignancy. Oncologist 2013;18:64-72.
29. Hurria A, Akiba C, Kim J, et al. Reliability, validity, and feasibility of a computer-based geriatric assessment for older adults with cancer. J Oncol Pract 2016;12:e1025-e1034. doi: 10.1200/JOP.2016.013136.
30. Shahrokni A, Tin A, Downey RJ, et al. Electronic Rapid Fitness Assessment: A Novel Tool for Preoperative Evaluation of the Geriatric Oncology Patient. J Natl Compr Canc Netw 2017;15:172-179.
31. Mohile SG, Dale W, Somerfield MR, Hurria A. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology summary. J Oncol Pract 2018;14:442-446.
32. University of california eprognosis: electronic tools. 2018. https://EprognosisUcsfEdu/IndexPhp.
33. Liu D, Lehmann HP, Frick KD, Carter HB. Active surveillance versus surgery for low risk prostate cancer: a clinical decision analysis. J Urol 2012;187:1241-1246.
34. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA 2005;293:2095-2101.
35. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016;375:1415-1424.
36. Scosyrev E, Messing EM, Mohile S, Golijanin D, Wu G. Prostate cancer in the elderly: frequency of advanced disease at presentation and disease-specific mortality. Cancer 2012;118:3062-3070.
37. Briganti A, Spahn M, Joniau S, et al. Impact of age and comorbidities on long-term survival of patients with high-risk prostate cancer treated with radical prostatectomy: a multi-institutional competing-risks analysis. Eur Urol 2013;63:693-701.
38. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med 2014;370:932-942.
39. Joniau S, Briganti A, Gontero P, et al. Stratification of high-risk prostate cancer into prognostic categories: a European multi-institutional study. Eur Urol 2015;67:157-164.
40. Begg CB, Riedel ER, Bach PB, et al. Variations in morbidity after radical prostatectomy. N Engl J Med 2002;346:1138-1144.
41. Stanford JL, Feng Z, Hamilton AS, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. JAMA 2000;283:354-360.
42. Kundu SD, Roehl KA, Eggener SE, et al. Potency, continence and complications in 3,477 consecutive radical retropubic prostatectomies. J Urol 2004;172:2227-2231.
43. Kupelian PA, Elshaikh M, Reddy CA, et al. Comparison of the efficacy of local therapies for localized prostate cancer in the prostate-specific antigen era: a large single-institution experience with radical prostatectomy and external-beam radiotherapy. J Clin Oncol 2002;20:3376-3385.
44. Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 2016;17:1047-1060.
45. Incrocci L, Wortel RC, Alemayehu WG, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2016;17:1061-1069.
46. Arcangeli G, Saracino B, Arcangeli S, et al. Moderate hypofractionation in high-risk, organ-confined prostate cancer: final results of a phase III randomized trial. J Clin Oncol 2017;35:1891-1897.
47. Catton CN, Lukka H, Gu CS, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. J Clin Oncol 2017;35:1884-1890.
48. Lee WR, Dignam JJ, Amin MB, et al. Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. J Clin Oncol 2016;34:2325-2332.
49. Shahid N, Loblaw A, Chung HT, et al. Long-term toxicity and health-related quality of life after single-fraction high dose rate brachytherapy boost and hypofractionated external beam radiotherapy for ıntermediate-risk prostate cancer. Clin Oncol (R Coll Radiol) 2017;29:412-420.
50. Joseph N, Taylor C, O'Hara C, et al. A combined single high-dose rate brachytherapy boost with hypofractionated external beam radiotherapy results in a high rate of biochemical disease free survival in localised intermediate and high risk prostate cancer patients. Radiother Oncol 2016;121:299-303.

51. Morris WJ, Tyldesley S, Rodda S, et al. Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): an analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and ıntermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017;98:275-285.
52. Rodda S, Tyldesley S, Morris WJ, et al. ASCENDE-RT: an analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and ıntermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017;98:286-295.
53. Rodda S, Morris WJ, Hamm J, Duncan G. ASCENDE-RT: an analysis of health-related quality of life for a randomized trial comparing low-dose-rate brachytherapy boost with dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017;98:581-589.
54. Hoskin P, Rojas A, Ostler P, et al. Single-dose high-dose-rate brachytherapy compared to two and three fractions for locally advanced prostate cancer. Radiother Oncol 2017;124:56-60.
55. D'Amico AV, Chen MH, Renshaw AA, et al. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. JAMA 2008;299:289-295.
56. Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med 2011;365:107-118.
57. Studer UE, Collette L, Whelan P, et al. Using PSA to guide timing of androgen deprivation in patients with T0–4 N0–2 M0 prostate cancer not suitable for local curative treatment (EORTC 30891). Eur Urol 2008;53:941-949.
58. Studer UE, Whelan P, Albrecht W, et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) trial 30891. J Clin Oncol 2006;24:1868-1876.
59. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017;377:352-360.
60. Chi KN, Protheroe A, Rodriguez-Antolin A, et al. Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naive prostate cancer (LATITUDE): an international, randomised phase 3 trial. Lancet Oncol 2018;19:194-206.
61. James ND, de Bono JS, Spears MR, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med 2017;377:338-351.
62. Kyriakopoulos CE, Chen YH, Carducci MA, et al. chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol 2018;36:1080-1087.
63. Gravis G, Boher JM, Joly F, et al. Androgen Deprivation Therapy (ADT) plus docetaxel versus adt alone in metastatic non castrate prostate cancer: impact of metastatic burden and long-term survival analysis of the randomized phase 3 GETUG-AFU15 trial. Eur Urol 2016;70:256-262.
64. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;387:1163-1177.
65. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373:737-746.
66. Sydes MR, Spears MR, Mason MD, et al. Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol. Ann Oncol 2018;29:1235-1248.
67. Wallis CJD, Klaassen Z, Bhindi B, et al. Comparison of abiraterone acetate and docetaxel with androgen deprivation therapy in high-risk and metastatic hormone-naive prostate cancer: a systematic review and network meta-analysis. Eur Urol 2018;73:834-844.
68. Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018;392:2353-2366.
69. Italiano A, Ortholan C, Oudard S, et al. Docetaxel-based chemotherapy in elderly patients (age 75 and older) with castration-resistant prostate cancer. Eur Urol 2009;55:1368-1375.
70. Aapro M, Saad F. Bone-modifying agents in the treatment of bone metastases in patients with advanced genitourinary malignancies: a focus on zoledronic acid. Ther Adv Urol 2012;4:85-101.
71. Berthold DR, Pond GR, Soban F, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol 2008;26:242-245.
72. Kellokumpu-Lehtinen PL, Harmenberg U, Joensuu T, et al. 2-Weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: a randomised, phase 3 trial. Lancet Oncol 2013;14:117-124.
73. Oudard S, Fizazi K, Sengelov L, et al. Cabazitaxel Versus Docetaxel As First-Line Therapy for Patients With Metastatic Castration-Resistant Prostate Cancer: A Randomized Phase III Trial-FIRSTANA. J Clin Oncol 2017;35:3189-3197.
74. Eisenberger M, Hardy-Bessard AC, Kim CS, et al. Phase III study comparing a reduced dose of cabazitaxel (20 mg/m(2)) and the currently approved dose (25 mg/m(2)) in postdocetaxel patients with metastatic castration-resistant prostate cancer-PROSELICA. J Clin Oncol 2017;35:3198-3206.
75. Climent MA, Perez-Valderrama B, Mellado B, et al. Weekly cabazitaxel plus prednisone is effective and less toxic for 'unfit' metastatic castration-resistant prostate cancer: Phase II Spanish Oncology Genitourinary Group (SOGUG) trial. Eur J Cancer 2017;87:30-37.
76. Hui MM, Clement CI. Evaluation of the early to mid-term efficacy and safety of deep sclerectomy without an ıntrascleral spacer for open-angle glaucoma in an Australian population. J Curr Glaucoma Pract 2018;12:107-112.
77. Sternberg CN, de Bono JS, Chi KN, et al. Improved outcomes in elderly patients with metastatic castration-resistant prostate cancer treated with the androgen receptor inhibitor enzalutamide: results from the phase III AFFIRM trial. Ann Oncol 2014;25:429-434.
78. De Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Eng J Med 2011;364:1995-2005.
79. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187-1197.
80. De Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147-1154.
81. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012;13:983-992.
82. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411-422.
83. Bahl A, Oudard S, Tombal B, et al. Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. Ann Oncol 2013;24:2402-2428.
84. Prior JO, Gillessen S, Wirth M, et al. Radiopharmaceuticals in the elderly cancer patient: Practical considerations, with a focus on prostate cancer therapy: A position paper from the International Society of Geriatric Oncology Task Force. Eur J Cancer 2017;77:127-139.

85. Parker C, Zhan L, Cislo P, et al. Effect of radium-223 dichloride (Ra-223) on hospitalisation: An analysis from the phase 3 randomised Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) trial. Eur J Cancer 2017;71:1-6.
86. Vogelzang NJ, Coleman RE, Michalski JM, et al. Hematologic Safety of Radium-223 Dichloride: Baseline Prognostic Factors Associated With Myelosuppression in the ALSYMPCA Trial. Clin Genitourin Cancer 2017;15:42-52.
87. Dan TD, Eldredge-Hindy HB, Hoffman-Censits J, et al. Hematologic Toxicity of Concurrent Administration of Radium-223 and Next-generation Antiandrogen Therapies. Am J Clin Oncol 2017;40:342-347.
88. Brauer A, Grubert LS, Roll W, et al. (177) Lu-PSMA-617 radioligand therapy and outcome in patients with metastasized castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging 2017;44:1663-1670.
89. Sun M, Cole AP, Hanna N, Mucci LA, et al. Cognitive Impairment in Men with Prostate Cancer Treated with Androgen Deprivation Therapy: A Systematic Review and Meta-Analysis. J Urol 2018;199:1417-1425.
90. Ahmadi H, Daneshmand S. Androgen deprivation therapy: evidence-based management of side effects. BJU Int 2013;111:543-548.
91. Mateo J, Carreira S, Sandhu S, Miranda S, et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N Engl J Med 2015;373:1697-1708.
92. Beer TM, Kwon ED, Drake CG, Fizazi K, et al. Randomized, Double-Blind, Phase III Trial of Ipilimumab Versus Placebo in Asymptomatic or Minimally Symptomatic Patients With Metastatic Chemotherapy-Naive Castration-Resistant Prostate Cancer. J Clin Oncol 2017;35:40-47.

*Original Article*

DOI: 10.4274/uob.galenos.2020.1695

*Bull Urooncol 2021;20(2):83-86*

# *Association Between Prostate Biopsy Results and Serum Vitamin D Levels*

Oktay Özman[1], Fethi Ahmet Türegün[2], Muhammed Fatih Şimşekoğlu[3], Uğur Aferin[3], Çetin Demirdağ[3]

[1]*University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, İstanbul, Turkey*
[2]*Güney Hospital, Clinic of Urology, İstanbul, Turkey*
[3]*İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Urology, İstanbul, Turkey*

## Abstract

**Objective:** This study investigates the relationship between pathological findings of prostate biopsy and serum 25 (OH) D levels.
**Materials and Methods:** Demographic, clinical and pathological data of 147 eligible patients were included in the study. All patients underwent transrectal ultrasound-guided prostate biopsy. Patients were divided into two groups; those with biopsy-proven prostate cancer (group 1) and those with only benign pathological findings (group 2). Later, two subgroups were formed among the patients diagnosed with prostate cancer (group 1); patients with serum 25 (OH) D levels above and below 20 ng/mL. All groups and subgroups were compared regarding clinical and pathological parameters. Finally, patients were divided according to International Society of Urological Pathology (ISUP) grade groups.
**Results:** Serum 25 (OH) D level of patients with prostate cancer (group 1: 15.6±7.0 ng/mL) was slightly lower than the non-cancer group (group 2: 16.0±9.2 ng/mL) (p=0.38). On analysis of variance, there was a statistically significant difference between ISUP grade 1, grade 2-3 and grade 4-5 (p=0.012). Patients with clinically insignificant prostate cancer (ISUP grade 1) had significantly higher serum 25 (OH) D levels than other prostate cancer patients (p=0.023). There was a weak negative correlation between serum 25 (OH) D levels and ISUP grades (r=-0.319, p=0.01).
**Conclusion:** There was no association between the diagnosis of prostate cancer and vitamin D deficiency. However, promising results have been obtained in favour of prostate cancer aggressiveness in vitamin D deficiency.
**Keywords:** Prostate cancer, vitamin D, biopsy

## Introduction

Prostate cancer is the second most common cancer in men worldwide, according to current data of the GLOBOCAN study (1). Many endogenous and exogenous factors' effects on the pathogenesis of prostate cancer have been investigated. Since the hypothesis explaining cancer's development with daylight-vitamin D has been proposed by Garland and Garland (2) 40 years ago, many biochemical, genetic, epidemiological and clinical studies have been conducted on the relationship between vitamin D and prostate cancer. A secondary analysis of the VITAL study suggests that vitamin D supplementation may reduce prostate cancer incidence (3).

Despite the promising results from the VITAL study at the end of 40 years, vitamin D deficiency's role in prostate cancer pathophysiology has not been fully elucidated. It is emphasised that mitochondrial activation of vitamin D in prostate cells is also a process that affects mitochondrial metabolism (4). Vitamin D deficiency develops a metabolic tendency in favour of oxidation in mitochondrial functions. There are also biochemical studies that try to explain the prostate cancer's pathophysiology through vitamin D's regulatory effect on androgen intracrinology (5).

A meta-analysis investigating vitamin D deficiency cases in Turkey was published recently (6). The prevalence of vitamin D deficiency was high (58.9% to 66.6%). It was emphasised that community-based follow-up and supplementation were necessary. Studies investigating the relationship between pathological findings and vitamin D deficiency in patients with prostate cancer in our country are insufficient. This study investigates the relationship between pathological findings of prostate biopsy and serum 25-hydroxyvitamin D [25 (OH) D] levels.

## Materials and Methods

After ethical approval (İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, number: 83045809/604.01/02-107680),

**Cite this article as:** Özman O, Türegün FA, Şimşekoğlu MF, Aferin U, Demirdağ Ç. Association Between Prostate Biopsy Results and Serum Vitamin D Levels. Bull Urooncol 2021;20(2):83-86

**Address for Correspondence:** Oktay Özman, University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, İstanbul, Turkey
**Phone:** +90 212 945 30 00 **E-mail:** ozmanoktay@hotmail.com **ORCID-ID:** orcid.org/0000-0003-2499-8947
**Received:** 22.03.2020 **Accepted:** 02.07.2020

the data of 151 patients who underwent prostate biopsy due to increased serum prostate-specific antigen (PSA) levels and/or positive rectal examination findings were prospectively evaluated and collected. Patients with the following exclusion criteria were excluded from the study:

1. Patients receiving vitamin D and calcium supplementation
2. Patients with known liver or kidney dysfunction
3. Biopsies diagnosed with ASAP and/or HGPIN but without prostate cancer
4. Patients with other malignancy

Demographic, clinical and pathological data of 147 eligible patients were included in the study. All patients underwent transrectal ultrasound-guided prostate biopsy. All biopsies were performed as previously described in the literature (7). Six cores were obtained from patients with a high probability of prostate cancer by the clinical diagnosis (e.g. PSA >100 ng/dL or imaging findings favouring prostate cancer). Twenty-eight core biopsy specimens were obtained from patients who underwent repeat biopsy and 16 cores from patients with transrectal prostate volumes of 60 mL or more. Standard 12 cores were taken from all other patients. All samples were evaluated by the same uropathologist.

According to the published evidence, 25 (OH) D is considered the best marker for body vitamin D status (8). After patient consent was obtained, serum 25 (OH) D levels of all patients were measured in the same laboratory, with venous blood samples taken before the biopsy. All blood samples were taken in the summer or spring for serum vitamin D measurements. Serum samples were sent to the biochemistry laboratory as soon as they were received. Samples were stored at room temperature before measurement. Serum 25 (OD) D was measured by the liquid chromatography-tandem mass spectrometry method (9). The 20 ng/mL level defined by the World Health Organisation and recommended by the Institute of Medicine was considered the cut-off value for "vitamin D deficiency" (10,11).

Patients were divided into two groups according to the presence of prostate cancer on biopsy; those with prostate cancer (group 1) and those with only benign pathological findings, such as chronic prostatitis and benign prostatic hyperplasia (group 2). Groups were compared for age, body mass index (BMI), serum PSA, 25 (OH) D levels and prostate volumes (Table 1). Later, two subgroups were formed among the patients diagnosed with prostate cancer (group 1); patients with serum 25 (OH) D levels above and below 20 ng/mL. The subgroups were compared regarding PSA, digital rectal examination findings, prostate volume and pathological findings (Table 2). Finally, patients with prostate cancer were classified according to International Society of Urological Pathology (ISUP) grade groups. Serum 25 (OH) D levels of ISUP grade 1, grade 2-3 and 4-5 patients were compared. In addition, grade 1, which is considered clinically insignificant, was compared with the other groups (Table 3).

**Table 1. Demographic and clinical characteristics of groups**

| Variables (means) | PCa cases (n=62) Group 1 | Negative biopsies (n=85) Group 2 | p-value |
|---|---|---|---|
| Age, years (median, range) | 65.6±7.8 (66, 43-81) | 61.9±7.9 (63, 41-83) | **0.007** |
| BMI, kg/m$^2$ | 26.1±4.2 | 26.6±3.6 | 0.48 |
| Serum PSA, ng/dL | 27.8±61 | 8.5±6.9 | **0.01** |
| PSA density | 0.68±1.71 | 0.19±0.2 | **0.01** |
| Serum 25 (OH) D3, ng/mL | 15.6±7.0 | 16.0±9.2 | 0.38 |
| Prostate volume, mL | 45.7±25.6 | 53.9±26.2 | **0.03** |

BMI: Body mass index, PSA: Prostate-specific antigen, PCa: Prostate cancer

## Statistical Analysis

First, the samples' normal distribution for all variables was checked by the Kolmogorov-Smirnov test. All samples showed a normal distribution. The Student's t-test and ANOVA (for more than two groups) were used to investigate the difference between the continuous variables. Chi-square with Yate's correction test was used for the difference between categorical variables. Correlation analyses were done with Spearman's test. All statistical analyses were performed using the Statistical Package for the Social Sciences v. 22 (SPSS Inc, Illinois, USA). A $p<0.05$ was considered statistically significant.

**Table 2. Subgroup analysis of prostate cancer cases (group 1) according to 25 (OH) D3**

| Characteristic | <20 ng/mL 25 (OH) D3 (n=35) | >20 ng/mL 25 (OH) D3 (n=27) | p-value |
|---|---|---|---|
| Age | 66.7±7.3 | 64.2±8.3 | 0.22 |
| Total Gleason score (median) | 7 | 6 | 0.09 |
| Gleason pattern ≥4 Rate | 54% (19/35) | 44% (12/27) | 0.61 |
| PSA, Ng/mL | 27.1±64.5 | 24.1±57.4 | 0.85 |
| PSA density | 0.8±2.1 | 0.52±0.92 | 0.52 |
| **D'Amico risk classification** | | | |
| Low | 25.7% (9/35) | 29.6% (8/27) | |
| Intermediate | 28.6% (10/35) | 40.8% (11/27) | 0.41 |
| High | 45.7% (16/35) | 29.6% (8/27) | |
| DRE Finding | 46% (16/35) | 26% (7/27) | 0.11 |
| Prostate volume (mL) | 42.3±15.8 | 50.1±34.4 | 0.24 |
| Mean of positive core rate | 43.1±32.5 | 27.8±26.9 | 0.05 |

ISUP: International society of urological pathology, DRE: Digital rectal examination, PSA: Prostate-specific antigen

**Table 3. Comparison of serum 25 (OH) D levels according to ISUP grade groups**

| Characteristic | ISUP 1 | ISUP 2-3 | ISUP 4-5 | p-value |
|---|---|---|---|---|
| Number (n,%) | 30/62 (48.4%) | 23/62 (37.1%) | 9/62 (14.5%) | |
| Serum 25 (OH) D, ng/mL | 17.8±7.4 | 14.8±6.4 | 10.3±4.1 | 0.012 |
| p-value (ISUP 1 vs others) | | 0.023 | | |

ISUP: International society of urological pathology, ISUP: International society of urological pathology

## Results

Forty-two per cent (62/147) of the patients had prostate cancer. Serum 25 (OH) D levels were lower than 20 ng/mL in 84 (57.1%) of 147 patients. There was no difference between serum 25 (OH) D levels of patients with prostate cancer (group 1: 15.6±7.0 ng/mL) and the non-cancer group (group 2: 16.0±9.2 ng/mL) (p=0.38). The prostate cancer detection rate of patients with serum 25 (OH) D less than 20 ng/mL (35/84, 41.7%) was similar to others (27/63, 42.9%) (p=0.98).

There were statistically significant differences between groups 1 and 2 regarding mean age, serum PSA level, PSA density and prostate volume (p=0.007, p=0.01, p=0.01 and p=0.03, respectively). The mean age of the patients in group 1 (65.6±7.8 years) was higher than group 2 (61.9±7.9 years). The patients' serum PSA levels in group 1 (27.8±61 ng/dL) were significantly higher than group 2 (8.5±6.9 ng/dL). Despite this finding, the mean prostate volumes (53.9±26.2 mL) of group 2 were higher than group 1 (45.7±25.6 mL). There was no statistically significant difference between the groups regarding BMI (group 1: 26.1±4.2, group 2: 26.6±3.6, p=0.48) (Table 1).

In addition, we investigated the relationship between clinical and pathological aggressiveness of prostate cancer and vitamin D deficiency in a subgroup analysis (Table 2). The median Gleason score of patients with a prostate cancer diagnosis had a serum 25 (OH) D level of less than 20 ng/mL (Gleason 7) was higher than that of patients with a serum 25 (OH) D level of more than 20 ng/mL (Gleason 6). However, this difference was not statistically significant (p=0.09). Similarly, the proportion of patients with Gleason pattern 4 and above was slightly higher in patients with low serum 25 (OH) D [54% (19/35) vs 44% (12/27), p=0.61]. Patients with low serum 25 (OH) D had higher serum PSA levels, positive core rates, positive digital rectal examination findings, and lower mean prostate volumes (Table 2). However, none of these differences were statistically significant (p=0.85, p=0.11, p=0.05 and p=0.24, respectively).

Serum 25 (OH) D levels of patients with ISUP grade 1 were higher than grade 2-3 patients (17.8±7.4 ng/mL and 14.8±6.4 ng/mL, respectively). Serum 25 (OH) D levels were lowest in patients with ISUP grade 4-5 prostate cancer (10.3±4.1 ng/mL). There was a statistically significant difference between ISUP grade 1, grade 2-3, and grade 4-5 (p=0.012) on analysis of variance. Patients with clinically insignificant prostate cancer (ISUP grade 1) had significantly higher serum 25 (OH) D levels than other prostate cancer patients (p=0.023). (Table 3). There was a weak negative correlation between serum 25 (OH) D levels and ISUP grades (r=–0.319, p=0.01).

## Discussion

Our study's primary outcomes were relationships between prostate cancer biopsy parameters and serum vitamin D status. Although the findings indicated more undifferentiated prostate cancer in vitamin D deficiency, no statistically significant results were obtained from analyses where vitamin D was considered a categorical variable. However, when we considered serum 25 (OH) D levels as a continuous variable, we found that vitamin D levels decreased as the ISUP grade increased (p=0.012). Vitamin D levels of patients with clinically insignificant prostate cancer (ISUP grade 1) were significantly higher than patients with ISUP grade 2 and above prostate cancer (p=0.023).

Published studies show a significant relationship between prediagnostic vitamin D levels and prostate cancer mortality (12,13). Other investigations suggest that high vitamin D levels can improve prostate cancer survival. Nyame et al. (14) showed that serum vitamin D levels were significantly lower in patients with a cancer pathology of Gleason 4 and above after radical prostatectomy.

On the other hand, studies report negative results about the vitamin D-prostate cancer relationship. Stephan et al. (15) found no association between prostate cancer aggressiveness and vitamin D status. Also, 25 (OH) D was not different between men with prostate cancer vs no evidence of malignancy. In another study, researchers found increased odds of a prostate cancer diagnosis on prostate biopsy in patients with serum 25 (OH) D <20 ng/mL (16). The results of this study were obtained from the data of African American patients. African American men are a risky group for vitamin D deficiency and aggressive prostate cancer (17). However, studies have shown that these men develop prostate tissue responses against vitamin D deficiency (18).

There are many measurable forms of vitamin D in the serum. In our study, the 25 (OH) D form, shown to reflect the body's vitamin D status best, was used (8). However, we may need to change our perspective on the relationship between prostate cancer and vitamin D. The 1.25 (OH) 2 D/25 (OH) D molar ratio has been shown to reflect prostate cancer aggressiveness better in a recent study (19). Murphy et al. (16) used 12 ng/mL as the cut-off value for 25 (OH) D deficiency. According to this study's results, there was a relationship between Gleason 8 and above prostate cancer and vitamin D deficiency.

The overall rate in the male population is approximately 90%, according to the population-based TURDEP-II study, which investigated vitamin D deficiency in our country [the deficiency was defined as 25 (OH) D concentration ≤20 ng/mL] (20). According to age groups, the highest prevalence (91.9%) was over 65 years in the subgroup analysis. Prostate cancer risk increases significantly in this age group. Vitamin D deficiency was found in 57% of our cohort. This difference was because our cohort was a selected group of patients that did not fully reflect the population.

The relationship between vitamin D and the prostate may not be limited to malignant processes. A study conducted in 2017 showed that prostate volume was inversely correlated with vitamin D (as a continuous and categorical variable) (21). A significant relationship was found between serum 25 (OH) D less than 30 ng/ml and the risk of prostate volume above 40 grammes in this study. Similar results have been reported in a study conducted in China (22). Our study showed that the prostate volumes of the vitamin D deficient group were higher than. However, the difference was not statistically significant (p=0.24).

In summary, the most remarkable result of our study is that the patients who have clinically insignificant prostate cancer have significantly higher vitamin D levels. With studies conducted

with more extensive series and this theoretical framework, vitamin D cut-off value as an active surveillance criterion can be determined. The effect of vitamin D supplementation on active surveillance results can be investigated.

### Study Limitations

There were many internal and external limitations in our study. First, we are aware that we look at the relationship between vitamin D and prostate cancer indirectly. Clinically proven prostate cancer is the result of a long process of carcinogenesis. Also, patients' final prostatectomy pathology results could not be included in the study. Serum vitamin D levels at the time of diagnosis cannot be considered as a direct indicator of vitamin D status in an entire process. Controversial issues that are mainly related to vitamin D caused some external limitations. Uncertainties regarding the body's vitamin D status remain, including its optimal molecular form, best cut-off value, deficiency or inadequacy (23). On the other hand, discussions suggesting a protective role of vitamin D levels in prostate cancer should be investigated independently.

## Conclusion

There was no correlation between prostate cancer diagnosis and vitamin D deficiency. However, promising results have been obtained in favour of prostate cancer aggressiveness in vitamin D deficiency. Serum 25 (OH) D levels were significantly lower in patients with high ISUP grade prostate cancer on prostate biopsy. Patients with clinically insignificant prostate cancer have lower 25 (OH) D levels.

### Acknowledgements

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

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

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

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

### Ethics

**Ethics Committee Approval:** Ethical approval (İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, number: 83045809/604.01/02-107680).

**Informed Consent:** Patient consent was obtained.

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

### Authorship Contributions

Concept: F.A.T., U.A., Ç.D., Design: F.A.T., U.A., Ç.D., Data Collection or Processing: O.Ö., F.A.T., Analysis or Interpretation: O.Ö., Literature Search: O.Ö., M.F.Ş., U.A., Writing: F.A.T.

## References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Garland C, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? Int J Epidemiol 1980;9:227-231.
3. Grant WB. Review of recent advances in understanding the role of vitamin D in reducing cancer risk: breast, colorectal, prostate, and overall cancer. Anticancer Res 2020;40:491-499.
4. Blajszczak CC, Nonn L. Vitamin D regulates prostate cell metabolism via genomic and non-genomic mitochondrial redox-dependent mechanisms. J Steroid Biochem Mol Biol 2019;195:105484. doi: 10.1016/j.jsbmb.2019.105484.
5. Smith KW, Thompson PD, Rodriguez EP, et al. Effects of vitamin D as a regulator of androgen intracrinology in LNCAP prostate cancer cells. Biochem Biophys Res Commun 2019;519:579-584.
6. Alpdemir M, Alpdemir MF. Vitamin D deficiency status in Turkey: a meta-analysis. Int J Med Biochem 2019;2:118-131.
7. Obek C, Ozkan B, Tunc B, et al. Comparison of 3 different methods of anesthesia before transrectal prostate biopsy: a prospective randomized trial. J Urol 2004;172:502-505.
8. Bouillon R, Carmeliet G. Vitamin D insufficiency: definition, diagnosis and management. Best Pract Res Clin Endocrinol Metab 2018;32:669-684.
9. Shin SY, Kwon MJ, Song J, et al. Measurement of serum total vitamin D (25-OH) using automated ımmunoassay in comparison [corrected] with liquid chromatography tandem-mass spectrometry. J Clin Lab Anal 2013;27:284-289.
10. World Health Organization Scientific Group on the Prevention and Management of Osteoporosis 2003. Prevention and management of osteoporosis: report of a WHO scientific group. Geneva: World Health Organization.
11. Atkinson SA. [The new dietary reference intakes from the Institute of Medicine for calcium and vitamin D]. Perspect Infirm 2011;8:5. [Article in French]
12. Fang F, Kasperzyk JL, Shui I, et al. Prediagnostic plasma vitamin D metabolites and mortality among patients with prostate cancer. PLoS One 2011;6:e18625. doi: 10.1371/journal.pone.0018625.
13. Brändstedt J, Almquist M, Manjer J, Malm J. Vitamin D, PTH, and calcium in relation to survival following prostate cancer. Cancer Causes Control 2016;27:669-677.
14. Nyame YA, Murphy AB, Bowen DK, et al. Associations between serum vitamin D and adverse pathology in men undergoing radical prostatectomy. J Clin Oncol 2016;34:1345-1349.
15. Stephan C, Lein M, Matalon J, et al. Serum vitamin D is not helpful for predicting prostate cancer aggressiveness compared with the prostate health ındex. J Urol 2016;196:709-714.
16. Murphy AB, Nyame Y, Martin IK, et al. Vitamin D deficiency predicts prostate biopsy outcomes. Clin Cancer Res 2014;20:2289-2299.
17. Ginde AA, Liu MC, Cmarago Jr CA. Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. Arch Intern Med 2009;169:626-632.
18. Richards Z, Batai K, Farhat R, et al. Prostatic compensation of the vitamin D axis in African American men. JCI Insight 2017;2:e91054. doi: 10.1172/jci.insight.91054.
19. Ramakrishnan S, Steck SE, Arab L, et al. Association among plasma 1,25(OH)2 D, ratio of 1,25(OH)2 D to 25(OH)D, and prostate cancer aggressiveness. Prostate 2019;79:1117-1124.
20. Satman I, Ozbey N, Boztepe H, et al. Prevalence and correlates of vitamin D deficiency in Turkish adults. Endocrine Abstracts 2013;32:135.
21. Murphy AB, Nyame YA, Batai K, et al. Does prostate volume correlate with vitamin D deficiency among men undergoing prostate biopsy? Prostate Cancer Prostatic Dis 2017;20:55-60.
22. Zhang W, Zheng X, Wang Y, Xiao H. Vitamin D deficiency as a potential marker of benign prostatic hyperplasia. Urology 2016;97:212-218.
23. Manson JE, Brannon PM, Rosen CJ, Taylor CL. Vitamin D deficiency - ıs there really a pandemic? N Engl J Med 2016;375:1817-1820.

*Original Article*

DOI: 10.4274/uob.galenos.2020.1936

*Bull Urooncol 2021;20(2):87-91*

# *Comparison of Cognitive-targeted Biopsy and Systematic Prostate Biopsy for Predicting Radical Prostatectomy Pathology: Upgrading-downgrading and Concordance Rates*

Eriz Özden[1], Arif İbiş[2], Çağrı Akpınar[1], Eralp Kubilay[1], Duygu Kankaya[3], Sümer Baltacı[1], Çağatay Göğüs[1]

[1]*Ankara University Faculty of Medicine, Department of Urology, Ankara, Turkey*
[2]*University of Health Sciences Turkey, Keçiören Training and Research Hospital, Clinic of Urology, Ankara, Turkey*
[3]*Ankara University Faculty of Medicine, Department of Pathology, Ankara, Turkey*

## Abstract

**Objective:** This purpose of this study is to compare the concordance, upgrading and downgrading rates of multiparametric magnetic resonance imaging cognitive-targeted prostate biopsy [COG-targeted biopsy (TB)] and a 12-core systematic prostate biopsy (SB) in order to assess the value of COG-TB in predicting final surgical pathology.

**Materials and Methods:** In this retrospective study, the medical records of 152 consecutive patients who had undergone 12-core SB (n=105) or 12-core SB and COG-TB of suspicious lesions (n=47) and corresponding radical prostatectomy (RP) at our institution were evaluated. Biopsy and RP pathologies of the two methods were compared for downgrading, upgrading and concordance rates based on the 2014 International Society of Urological Pathology grade groups (GG).

**Results:** For COG-TB and SB cohorts, total upgrading rates were 21.3% and 26.7%, total downgrading 10.6% and 21.9% and concordance 68.1% and 51.4%, respectively, but the differences were not statistically significant. For GG 1, 2, 3, 4 and 5, the concordance rates at COG-TB and SB were 69.6% versus 52.8%, 68.7% versus 83.1%, 75% versus 30.8%, 50% versus 9.1% and 50% versus 62.5%, respectively. There was no statistically significant difference in concordance rates regarding GG between COG-TB and SB groups. According to GG, there was also no significant difference in the rates of upgrading and downgrading of COG-TB and SB.

**Conclusion:** Although COG-TB outperforms SB in terms of pathological upgrading, downgrading and concordance rates, COG-TB has no statistically significant advantage over SB in terms of predicting final RP pathology.

**Keywords:** Prostate biopsy, prostate cancer, radical prostatectomy, upgrading

## Introduction

The pathologic grading of prostate cancer (PCa) is based on the Gleason scoring system, and accurate determination of the Gleason score (GS) improves risk prediction, decision-making on treatment alternatives and selection of candidates for active surveillance (AS) (1,2,3,4). The most commonly used method for diagnosing PCs is transrectal ultrasonography (TRUS)-guided systematic biopsy (SB) of the prostate, but nearly one-third of patients are known to have GS upgrading between SB and radical prostatectomy (RP) pathology (5,6,7). Some authors reported that the SB method underestimated the final surgical pathology in 30-43% of cases (7,8). Multiparametric magnetic resonance imaging (mpMRI) is a valuable modality for detecting PCa, and this ability has resulted in the development of various MRI-guided targeted biopsy (TB) methods (1). Furthermore, the most commonly used TB methods are fusion-TB (FUS-TB) and cognitive-targeted biopsy (COG-TB). Previous studies found that TB methods resulted in significantly lower pathologic upgrading or downgrading rates than SB methods (9,10). However, the majority of these studies compared the rates of upgrading and downgrading of SB with FUS-TB (1,10,11). Moreover, the purpose of this study was to compare the concordance, upgrading and downgrading rates of COG-TB and SB in order to assess the value of COG-TB in predicting the final surgical pathology.

## Materials and Methods

Before the mpMRI examination and TRUS-guided biopsies, all patients provided written informed consent. All procedures were carried out in accordance with the 1964 Helsinki Declaration

**Cite this article as:** Özden E, İbiş A, Akpınar Ç, Kubilay E, Kankaya D, Baltacı S, Göğüs Ç. Comparison of Cognitive-targeted Biopsy and Systematic Prostate Biopsy for Predicting Radical Prostatectomy Pathology: Upgrading-downgrading and Concordance Rates. Bull Urooncol 2021;20(2):87-91

**Address for Correspondence:** Arif İbiş, University of Health Sciences Turkey, Keçiören Training and Research Hospital, Clinic of Urology, Ankara, Turkey
**Phone:** +90 541 624 04 50 **E-mail:** m.arifibis@hotmail.com **ORCID-ID:** orcid.org/0000-0001-8581-2101
**Received:** 10.11.2020 **Accepted:** 28.12.2020

and its subsequent amendments. In addition, the study was approved by our Institutional Ethics Committee. The registration number for the local ethics committee is I4-219-20.

### Patients and Study Design

In this retrospective study, the medical records of 181 consecutive patients who had a prostate biopsy and a corresponding RP at our institution between 2015 and 2019 were evaluated. All of the patients were diagnosed with clinically significant PCa following a prostate biopsy and underwent RP surgery within 3 months of the biopsy procedure. Patients who had prostate mpMRI at other hospitals or who had previously been diagnosed with PCa were excluded from the study. Thus, the study population included 152 patients. They were divided into two groups: those who had only 12-core SB (n=105) and those who had 12-core SB and COG-TBs of suspicious lesions (n=47). All of the patients in the COG-TB group were scanned using a 3T MRI scanner at our institution. The prostate lesions in each patient's mpMRI were described by using a standardised method known as the Prostate Imaging Reporting and Data System (PIRADSv2) (12,13). Patients in the SB group either did not have mpMRI examinations or had only PIRADSv2 score 1 or 2 lesions in mpMRI.

### Histopathology

Biopsy and RP pathology specimens were examined at our institution's Department of Pathology by an experienced uropathologist. Biopsy specimens were evaluated using the modified Gleason system developed by the 2014 International Society of Urological Pathology (ISUP) (14). GS and grade groups (GG) were reported separately for each biopsy site. For downgrading, upgrading and concordance rates, the highest GG of biopsy and RP were compared. As a reference standard, histopathological GG from RP sections was used. The patients were divided into five groups labelled GG 1-5 according to the biopsy results. Upgrading and downgrading were defined as an increase or decrease in prognostic GG from one to another.

### Multiparametric MRI

Multiparametric MR images were obtained using a 3.0 Tesla system (MAGNETOM Verio; Siemens Medical Solutions, Erlangen, Germany). For signal reception from the patients' prostate, a standard body matrix coil was used. The sequences used in the study were T2-weighted, diffusion-weighted and dynamic contrast-enhanced imaging. Before the biopsy, all patients had mpMRI, and no endorectal coils were used.

### Prostate Biopsy

TRUS was performed with a GE P5 ultrasound scanner (GE Healthcare, Tokyo, Japan) and a biplanar convex/convex transrectal probe (BE9CS). The biopsies were performed transrectally, using a full automatic core biopsy device with an 18-gauge, 25-cm Tru-Cut-type needle and the same operator (E.O) with 20 years of TRUS-SB experience. For SB, all of the patients underwent the same 12-core systematic prostate biopsy procedure. For COG-TB procedure, prior to biopsy, the operator (E.O) reviewed each patient's mpMRI and the locations of suspicious lesions. Following a 12-core SB, the regions of lesions with PIRADS 3, 4 or 5 scores were cognitively sampled by taking three extra cores from each lesion location. All biopsy specimens were placed in separate containers labelled with the location of the prostate biopsied and sent for histopathologic evaluation.

## Statistical Analysis

For statistical analysis, IBM SPSS® Statistics version 25 was used. Moreover, the Kolmogorov-Smirnov test was used to determine whether variables were suitable for normal distribution. For non-normally distributed variables, descriptive statistics were expressed as median + interquartile range. The chi-square test of independence for categorical variables and Mann-Whitney U test for continuous variables were used to compare cohort demographics and characteristics. As appropriate, the chi-square test was used to determine the significance of differences. In the 95% confidence interval, p-values of $<0.05$ were considered statistically significant.

## Results

Table 1 shows the preoperative clinical and pathological characteristics of the patients, which were similar in both groups. According to biopsy results, GG 1 was the most commonly observed pathology in both the SB and COG-TB groups (52.4%, 48.9%). According to RP, the most common pathology observed was GG 2 for both groups (48.6%, 40.4%). In COG-TB group, total upgrading and downgrading rates were 21.3% and 10.6%, while in the SB group, total upgrading and downgrading rates were 26.7% and 21.9%, respectively. There was no statistically significant difference between the two groups in terms of total upgrading and downgrading rates

**Table 1. Clinical and pathological information of the two patients' cohorts**

| **Characteristics** | **SB (105) COG-TB (47) p-value* (n=105) (n=47)** |
|---|---|
| Median age (yr) (IQR) | 67 (59-71) 65 (58-9) 0.490 |
| Median PSA (ng/mL) (IQR) | 6.10 (5.10-10.20) 5.90 (4.90-8.60) 0.116 |
| Median TRUS Volume mL (IQR) | 42 (35-58.5) 45 (33-65) 0.774 |
| Median MRI volume (IQR) | -50 (37-73) |
| Biopsy ISUP Grade | 0.114 |
| Grade 1<br>Grade 2<br>Grade 3<br>Grade 4<br>Grade 5 | 55 (52.4%) 23 (48.9%)<br>18 (17.1%) 16 (33.9%)<br>13 (12,4%) 4 (8.6%)<br>11 (10,4%) 2 (4.3%)<br>8 (7.7%) 2 (4.3%) |
| Pathologic ISUP Grade | 0.330 |
| Grade 1<br>Grade 2<br>Grade 3<br>Grade 4<br>Grade 5 | 31 (29.5%) 18 (38.3%)<br>51 (48.5%) 19 (40.4%)<br>13 (12.4%) 7 (14.9%)<br>3 (2.9%) 2 (4.3%)<br>7 (6.7%) 1 (2.1%) |

SB: Systematic prostate biopsy, COG-TB: Cognitive-targeted prostate biopsy, IQR: Interquartile range, PSA: Prostate specific antigen, TRUS: Transrectal ultrasound, MRI: Magnetic resonance imaging, ISUP: International society of urological pathology, *Mann-Whitney U test and chi-square test

(p=0.478, p=0.098) (Table 2). For the COG-TB and SB groups, the overall concordance rates between biopsy and RP pathology were 68.1% and 51.4%, respectively. There was no statistically significant difference between the two groups (p=0.056).

When the results were analysed by GG, the highest concordance was observed in the GG 2 (83.1%) for SB and the GG 3 (75%) for COG-TB groups. The lowest concordance was found in the GG 4 (9.1%) for SB and the GG 4 and 5 (50% for both) for COG-TB groups. Table 2 shows the concordance rates according to GG. Moreover, concordance rates did not differ significantly between the SB and COG-TB groups. SB was upgraded at a higher rate than COG-TB in GG 1 and GG 3 (47.2% versus 30.4% and 7.7% versus 0%, respectively) but at a lower rate in GG 2 (5.8% versus 18.8%). In both groups, no upgrading was noted in GG 4. In terms of different GG, no significant difference in upgrading rates of COG-TB and SB was observed (Table 2). SB has a higher downgrading rate than COG-TB in GG 3, GG 4 and GG 5 but a lower rate than COG-TB in GG 2 (Table 2). In terms of different GG, no significant difference in downgrading rates of COG-TB and SB was observed (Table 2).

**Table 2. Upgrading, downgrading and concordance rates according to grade groups**

| | N (152) | Upgrading p-value* rate | Downgrading p-value* rate | Concordance p-value* rate |
|---|---|---|---|---|
| ISUP grade 1 | | 0.081 | - | 0/084 |
| Systematic biopsy<br>COG-TB | 55<br>23 | 6 (47.2%)<br>7 (30.4%) | -<br>- | 29 (52.8%)<br>16 (69.6%) |
| ISUP grade 2 | | 0.231 | 0.772 | 0.089 |
| Systematic biopsy<br>COG-TB | 18<br>16 | 1 (5.8%)<br>3 (18.8%) | 2 (11.1%)<br>2 (12.5%) | 15 (83.1%)<br>11 (68.7%) |
| ISUP grade 3 | | 0.567 | 0.134 | 0.115 |
| Systematic biopsy<br>COG-TB | 13<br>4 | 1 (7.7%) 1<br>- | 8 (61.5%)<br>1 (25%) | 4 (30.8%)<br>3 (75%) |
| ISUP grade 4 | | - | 0.125 | 0.165 |
| Systematic biopsy<br>COG-TB | 11<br>2 | -<br>- | 10 (90.9%)<br>1 (50%) | 1 (9.1%)<br>1 (50%) |
| ISUP grade 5 | | - | 0.647 | 0.567 |
| Systematic biopsy<br>COG-TB | 8<br>2 | -<br>- | 3 (37.5%)<br>1 (50%) | 5 (62.5%)<br>1 (50%) |
| Total | | 0478 | 0098 | 0.056 |
| Systematic biopsy<br>COG-TB | 105<br>47 | 28 (26.7%)<br>10 (21.3%) | 23 (21.9%)<br>5 (10.6%) | 54 (51.4%)<br>32 (68.1%) |

ISUP: International society of urological pathology, COG-TB: Cognitive-targeted prostate biopsy, *According to chi-square and Fisher's Exact test

## Discussion

Classically, GS at RP is regarded as the gold standard and final indicator of cancer severity. On the other hand, preoperative treatment options depend on biopsy GS (3,9). In this regard, biopsy GS is one of the most important criteria for selecting therapeutic approaches such as AS, focal therapy, androgen deprivation therapy, radiotherapy or RP (9,10,15). One of the most important inclusion criteria in AS is GS determined at biopsy, that is, GS less than 7 which equals to ISUP GG 1 (16). On the other hand, definitive treatment is required for patients with clinically localised PCa with GG >1, and these patients generally are typically excluded from AS protocols (16). However, biopsy GS is frequently incongruent with RP GS. Many researchers examined the concordance between biopsy GS to RP GS, and it has been reported that when SB was used, 25-30% of low-grade cancers were upgraded to high-grade cancers at RP (5,6,7,8).

In the relevant literature, some authors evaluated the performance of saturation biopsies, considering that increased sampling would improve the GS concordance, but even saturation biopsy protocols still misclassified GS in 27% to one-third of cases (17,18). This highlights the significance of sampling error in the correlation of biopsy and RP pathology (18). Inaccurate grading is reported to be caused by the sampling error of untargeted SB (19,20). Fortunately, mpMRI allows for the detection and localisation of suspicious prostate lesions, and it has been reported that mpMRI TB predicts the final pathology at RP better than SB (1,9,10,21,22). It was indicated by the PRECISION Trial that TB better detects clinically significant GG 2 and higher PCa than SB (23). The suggested explanation for the lower level of upgrading with TB is that TB may contain a higher percentage of cancer per core due to preferential tumour sampling (11,24,25). TB can be performed using direct MR guidance, with COG-TB or FUS-TB methods (26). Technically, COG-TB is an appealing option because it is not time-consuming and is inexpensive; thus, many centres around the world continue to perform mpMRI-targeted biopsies using the cognitive method (27). However, COG-TB lacks the inherent advantage of FUS-TB in terms of visualising suspicious lesions on the monitor during biopsy. Many studies comparing SB and FUS-TB for upgrading biopsy pathology found that FUS-TB has lower rates of upgrading than SB (1,10,11). However, the purpose of this study was to compare pathology upgrading and downgrading rates of SB and COG-TB, as well as to assess the impact of COG-TB on predicting the final pathology following RP.

In our study group, the rate of total upgrading was 26.7% for SB and 21.3% for COG-TB, but the difference was not statistically significant (p=0.478). Porpiglia et al. (10) reported that the rate of pathological upgrading with SB was significantly higher than with FUS-TB (7.8% for FUS-TB and 39.3% for SB). In a meta-analysis, Goel et al. (9) determined a 23.3% upgrading rate for TB versus 42.7% for SB (p=0.001). The significantly lower upgrading rate of FUS-TB than SB reported in previous studies and the lower but not statistically significant upgrading rate of COG-TB than SB noted in our study can be explained as follows: inaccurate grading is reported to be caused by the sampling error of untargeted biopsy, FUS-TB has the advantage of visualising suspicious lesions on the ultrasound monitor during biopsy, but during COG-TB, the operator is unable to visualise the lesions directly and can only take samples from the suspicious regions (9,10,26). Our results may imply that COG-TB does not have the advantage of FUS-TB when it comes to precise sampling of suspicious lesions.

According to Porpiglia et al. (10), FUS-TB reduced the risk of upgrading at RP for all histopathological categories. In a report

by Epstein et al. (18), a number of SB series were analysed for the incidence of upgrading from biopsy GS 6 to RP GS ≥7, and it was discovered that the mean upgrading was 35%. When we analysed our results by GG, the upgrading rates in GG 1 were 47.2% and 30.4% (p=0.081) for SB and COG-TB, respectively. Here it is important to note that higher upgrading rates from GG 1 to GG 2 will have a significant negative impact on the selection of AS patients. For GG 2, upgrading rate of COG-TB was higher than SB (18.8% versus 5.8%), though the difference was not statistically significant (p=0.231). Within the COG-TB group, no patient was upgraded from GG 3, and only ones (7.7%) was upgraded by SB. Moreover, there were no upgradings noted in both biopsy methods for GG 4 pathology. These findings suggest that, despite not being statistically different, COG-TB may be more valuable than SB for upgrading from GG 1 to GG 2 with lower upgrading rates, thus allowing for more precise selection of patients for AS.

In our study group, the rate of total downgrading was 21.9% for SB and 10.6% for COG-TB, but the difference was not significant (p=0.098). In our cohort, 11.1% of SB and 12.5% of COG-TB pathology were downgraded from GG 2 to GG 1. According to Moussa et al. (28), there is a 7.3% chance of downgrading from GS 3 + 4 to GS 6 for SB. In Epstein's study, 12% of cases diagnosed with GS 3+4 on SB biopsy also had GS 6 at RP (18). Our results support these findings, as we have determined that 12.5% of COG-TB and 11.1% of SB were downgraded from ISUP GG 2 to GG 1. Porpiglia et al. (10) reported that one-third of SB patients with GS 8 in their study group were downgraded to a lesser disease, whereas none were downgraded in the FUS-TB group, and downgrading was significantly higher in SB than in FUS-TB. According to a recent study, it was found that 49% of patients with biopsy GG 4 were downgraded at RP pathology (29). Epstein et al. (18) also reported a similar rate of downgrade from GS 8 as. Another study reported a higher (80.4%) downgrading for single-core GS 8 biopsy pathology (30). According to our results, downgrading of GG 4 was noted at 50% of COG-TB and 90.9% of SB patients (p=0.125). According to Altok et al. (30), the high downgrading rates for biopsy GS 8 may be explained by the ease of finding additional areas of pattern 3 in the predominant foci to downgrade it to GS 4+3 or 3+4 biopsy during histopathological evaluation. They have also proposed that GS 8 patients may have that finding in isolation, with other positive cores showing lower grade (30). Downgrading rate of COG-TB GG 4 pathology in our study group is generally consistent with the literature, but the downgrading of SB GG 4 pathology we have determined is higher than the rates reported in previous studies (10,29,30). This could be due to the relatively lower number of patients with GG 4 biopsy pathology in our study group, which would have an impact on statistical analysis.

According to our findings for the two biopsy methods shows that the overall concordance rate of biopsy and RP pathology was 68.1% for COG-TB and 51.4% for SB (p=0.056). Although COG-TB performed better than SB for concordance with final pathology in all GGs except GG 2, the differences were not statistically significant (Table 2). By using the highest Gleason pattern, Le et al. (11) reported a concordance rate of 54% for SB and 81% for FUS-TB pattern. Our results support the advantage of TB over SB regarding biopsy and RP pathology concordance. However, the overall concordance rate of COG-TB (68.1%) observed in our study is lower than the rate of 81% reported by Le at al. (11) reported using FUS-TB method (17). As previously stated, the reported higher concordance rate of FUS-TB is possibly due to the visualisation of suspicious lesions on the monitor during FUS-TB, as mentioned earlier.

### Study Limitations

It is critical to note that our study has some limitations. This is a retrospective study conducted at a single institution. Because the study is focused on GG concordance, upgrading and downgrading of two different biopsy methods, core length or percentage of cancer-positive cores were not included in the definitions. The population size of COG-TB group may be relatively small to show a difference between COG-TB and SB techniques. Because of the limited number of patients in the COG-TB group, no univariate or multivariate analysis for predicting of concordance rates for variables such as prostate volume, prostate specific antigen or prostate specific antigen density. On the other hand, all biopsies in or study group were performed by a single experienced operator, and which is a strength of our study, but the operators with varying levels of experience may achieve different results.

## Conclusion

Despite not being significantly different, COG-TB may be more valuable than SB for upgrading from GG 1 to GG 2 with lower upgrading rates, thus allowing more precise selection of patients for AS. Although COG-TB outperforms SB in terms of overall pathological upgrading, downgrading and concordance rates, our results indicate that COG-TB has no statistically significant advantage over SB for predicting the final RP pathology.

### Acknowledgements

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

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

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

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

### Ethics

**Ethics Committee Approval:** All procedures were carried out in accordance with the 1964 Helsinki Declaration and its subsequent amendments. In addition, the study was approved by our Institutional Ethics Committee. The registration number for the local ethics committee is I4-219-20.

**Informed Consent:** Before the mpMRI examination and TRUS-guided biopsies, all patients provided written informed consent.

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

### Authorship Contributions

Concept: E.Ö., Design: E.Ö., A.İ., Data Collection or Processing: A.İ., Ç.A., E.K., Analysis or Interpretation: Ç.A., E.K., Ç.G., Literature Search: Ç.G., S.B., D.K., Writing: Ç.G., S.B.

## References


1. Siddiqui MM, Rais-Bahrami S, Truong H, et al. Magnetic resonance imaging/ultrasound–fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. Eur Urol 2013;64:713-719.
2. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969-974.
3. Kattan MW, Wheeler TM, Scardino PT. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. J Clin Oncol 1999;17:1499-1507.
4. Dall'Era MA, Cooperberg MR, Chan JM, et al. Active surveillance for early-stage prostate cancer: review of the current literature. Cancer 2008;112:1650-1659.
5. Chun FK-H, Steuber T, Erbersdobler A, et al. Development and internal validation of a nomogram predicting the probability of prostate cancer Gleason sum upgrading between biopsy and radical prostatectomy pathology. Eur Urol 2006;49:820-826.
6. Shapiro RH, Johnstone PA. Risk of Gleason grade inaccuracies in prostate cancer patients eligible for active surveillance. Urology 2012;80:661-666.
7. Cohen MS, Hanley RS, Kurteva T, et al. Comparing the Gleason prostate biopsy and Gleason prostatectomy grading system: the Lahey Clinic Medical Center experience and an international meta-analysis. Eur Urol 2008;54:371-381.
8. King CR, Long JP. Prostate biopsy grading errors: a sampling problem? Int J Cancer 2000;90:326-330.
9. Goel S, Shoag JE, Gross MD, et al. Concordance between biopsy and radical prostatectomy pathology in the era of targeted biopsy: a systematic review and meta-analysis. Eur Urol Oncol 2020;3:10-20.
10. Porpiglia F, De Luca S, Passera R, et al. Multiparametric-magnetic resonance/ultrasound fusion targeted prostate biopsy improves agreement between biopsy and radical prostatectomy Gleason score. Anticancer Res 2016;36:4833-4839.
11. Le JD, Stephenson S, Brugger M, et al. Magnetic resonance imaging-ultrasound fusion biopsy for prediction of final prostate pathology. J Urol 2014;192:1367-1373.
12. Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS prostate imaging–reporting and data system: 2015, version 2. Eur Urol 2016;69:16-40.
13. Vargas H, Hötker A, Goldman D, et al. Updated prostate imaging reporting and data system (PIRADS v2) recommendations for the detection of clinically significant prostate cancer using multiparametric MRI: critical evaluation using whole-mount pathology as standard of reference. Eur Radiol 2016;26:1606-1612.
14. Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) consensus conference on gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 2016;40:244-252.
15. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA Guideline. J Urol 2013;190:419-426.
16. Mohler JL, Antonarakis ES, Armstrong AJ, et al. Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2019;17:479-505.
17. Numao N, Kawakami S, Yokoyama M, et al. Improved accuracy in predicting the presence of Gleason pattern 4/5 prostate cancer by three-dimensional 26-core systematic biopsy. Eur Urol 2007;52:1663-1669.
18. Epstein JI, Feng Z, Trock BJ, Pierorazio PM. Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified Gleason grading system and factoring in tertiary grades. Eur Urol 2012;61:1019-1024.
19. McKenney JK, Simko J, Bonham M, et al. The potential impact of reproducibility of Gleason grading in men with early stage prostate cancer managed by active surveillance: a multi-institutional study. J Urol 2011;186:465-469.
20. Hu Y, Ahmed HU, Carter T, et al. A biopsy simulation study to assess the accuracy of several transrectal ultrasonography (TRUS)-biopsy strategies compared with template prostate mapping biopsies in patients who have undergone radical prostatectomy. BJU Int 2012;110:812-820.
21. Rosenkrantz AB, Verma S, Choyke P, et al. Prostate magnetic resonance imaging and magnetic resonance imaging targeted biopsy in patients with a prior negative biopsy: a consensus statement by AUA and SAR. J Urol 2016;196:1613-1618.
22. Ahmed HU, Bosaily AE-S, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815-822.
23. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Eng J Med 2018;378:1767-1777.
24. Quentin M, Blondin D, Arsov C, et al. Prospective evaluation of magnetic resonance imaging guided in-bore prostate biopsy versus systematic transrectal ultrasound guided prostate biopsy in biopsy naïve men with elevated prostate specific antigen. J Urol 2014;192:1374-1379.
25. Haffner J, Lemaitre L, Puech P, et al. Role of magnetic resonance imaging before initial biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection. BJU Int 2011;108: E171-E178. doi: 10.1111/j.1464-410X.2011.10112.x.
26. Wegelin O, van Melick HH, Hooft L, et al. Comparing three different techniques for magnetic resonance imaging-targeted prostate biopsies: a systematic review of in-bore versus magnetic resonance imaging-transrectal ultrasound fusion versus cognitive registration. Is there a preferred technique? Eur Urol 2017;71:517-531.
27. Marra G, Ploussard G, Futterer J, Valerio M. Controversies in MR targeted biopsy: alone or combined, cognitive versus software-based fusion, transrectal versus transperineal approach? World J Urol 2019;37:277-287.
28. Moussa AS, Kattan MW, Berglund R, et al. A nomogram for predicting upgrading in patients with low-and intermediate-grade prostate cancer in the era of extended prostate sampling. BJU Int 2010;105:352-358.
29. Ranasinghe W, Reichard CA, Nyame YA, et al. Downgrading from biopsy grade group 4 prostate cancer in patients undergoing radical prostatectomy for high or very high risk prostate cancer. J Urol 2020;204:748-753.
30. Altok M, Troncoso P, Achim MF, et al. Prostate cancer upgrading or downgrading of biopsy Gleason scores at radical prostatectomy: prediction of "regression to the mean" using routine clinical features with correlating biochemical relapse rates. Asian J Androl 2019;21:598-604.

*Original Article*

DOI: 10.4274/uob.galenos.2020.1721

*Bull Urooncol 2021;20(2):92-95*

# *Relationship Between Biopsy Core α-Methylacyl-CoA Racemase Positivity and Five-Year Biochemical Recurrence in D'Amico Low- and Intermediate-Risk Prostate Cancer*

Ersin Gökmen, Oktay Özman, Murat Kars, Serkan Gönültaş, Burak Arslan

*University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Urology, İstanbul, Turkey*

## Abstract

**Objective:** This study aims to explore the association between alpha methylacyl A coenzyme racemase (AMACR)/P504S staining intensity of prostate biopsy cores and five-year biochemical recurrence after radical prostatectomy in patients diagnosed with localised prostate cancer.

**Materials and Methods:** Patients who underwent radical prostatectomy for organ-limited prostate cancer were retrospectively examined. Twenty-five patients without recurrence after definitive treatment and 25 patients with prostate-specific antigen (PSA) recurrence at postoperative follow-up were classified as group 1 and group 2. Positive prostate biopsy cores of patients were stained with AMACR/P504S, prospectively. Staining intensities were scored as negative (score=0), weak (score=1), moderate (score=2) and strong (score=3). Groups were compared regarding AMACR/P504S staining intensities of biopsy cores.

**Results:** The mean AMACR/P504S staining scores of positive biopsy cores were 1.88±0.85 and 1.27±1.22 for group 1 and group 2. There was a statistically significant relationship between mean AMACR/P504S staining scores and PSA recurrence (p=0.002). AMACR score groups were not separated concerning biochemical recurrence endpoints in the Kaplan-Meier analysis (p=0.43).

**Conclusion:** There is a significant relationship between increased AMACR/P504S expression in cancerous prostate tissue and PSA recurrence after radical prostatectomy.

**Keywords:** AMACR/P504S, PSA, prostate cancer

## Introduction

Prostate cancer is the second most common cancer in men worldwide, according to current data of the GLOBOCAN study (1). It is the fifth most common cause of cancer-related death. Relatively low mortality compared with incidence rates of prostate cancer has been attributed to the widespread use of prostate-specific antigen (PSA) as a screening tool, early diagnosis of patients, and cured at the localised early stage. Especially since the mid-1980s, substantial improvements have been made in the diagnosis and treatment of prostate cancer.

α-Methylacyl-CoA Racemase/P504S (AMACR/P504S) is a cytoplasmic immune marker protein found by Xu and colleagues in 2000 (2). It was obtained by high throughput microarray imaging and cDNA library subtraction analysis from prostate tissue. AMACR is mainly localised in peroxisomes in prostate cancer cells. However, its up-regulation causes cancer to start and progress in some cells due to DNA oxidative damage and other unknown causes (3).

Serum PSA levels after radical prostatectomy should be too low to be measured. An increase in serum PSA levels after primary local treatment, or biochemical recurrence, was defined as an early and the first indicator of inadequate treatment. After curative treatment, 20% to 40% of patients develop biochemical recurrence within 10 years (4). Forty-five per cent of biochemical recurrences occur within two years, 77% occur within the first five years, and only 23% occur after five years.

AMACR's effectiveness has been the subject of research in many disciplines, from point-of-care prostate cancer diagnosis to molecular imaging of cancer (5,6). Also, AMACR is a promising molecule to predict biochemical recurrence (7). This study aims to explore the association between AMACR/P504S staining intensity of prostate biopsy cores and the five-year biochemical recurrence after radical prostatectomy in patients diagnosed with localised prostate cancer.

**Cite this article as:** Gökmen E, Özman O, Kars M, Gönültaş S, Arslan B. Relationship Between Biopsy Core α-Methylacyl-CoA Racemase Positivity and Five-Year Biochemical Recurrence in D'Amico Low- and Intermediate-Risk Prostate Cancer. Bull Urooncol 2021;20(2):92-95

**Address for Correspondence:** Ersin Gökmen, University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Urology, İstanbul, Turkey
**Phone:** +90 212 945 30 00 **E-mail:** drersingokmen@gmail.com **ORCID-ID:** orcid.org/0000-0002-9845-163X
**Received:** 25.04.2020 **Accepted:** 04.06.2020

## Materials and Methods

Patients who underwent radical prostatectomy for D'Amico low- and intermediate-risk prostate cancer were retrospectively examined. Patients who have preoperative PSA >20 ng/mL, clinical or pathological stage T2c and above, positive lymph node metastasis and biopsy Gleason score >7 [International Society of Urological Pathology (ISUP) grade group 4-5] were excluded from the study. Fifty patients who had no surgical margin and lymph node positivity were included in the study. Twenty-five patients who did not develop a biochemical recurrence within at least five years of postoperative follow-up and 25 patients with PSA recurrence were classified as group 1 and group 2, respectively. PSA values ≥0.2 ng/mL at postoperative follow-up were considered biochemical recurrences.

Patients' positive prostate biopsy cores were stained with AMACR/P504S, prospectively. The immunohistochemical staining technique was performed as in the similar study we conducted earlier (8). Staining intensities were scored as negative (score=0), weak (score=1), moderate (score=2) and strong (score=3) (Table 1 and Figure 1) (9). Among the same patient's positive cores, the most intensely stained core's score was determined as the relevant patient's AMACR staining score. The biopsy Gleason score of four patients reported as 5 (3+2) was changed to 6 (3+3) according to the updated scoring system.

**Table 1. Staining classification of prostate biopsy cores**

| Score | AMACR/P504S Staining |
|---|---|
| 0 | Negative staining |
| 1 | Weak focal staining |
| 2 | Moderate cytoplasmic staining |
| 3 | Diffuse cytoplasmic staining |

AMACR: Alpha methylacyl A coenzyme racemase

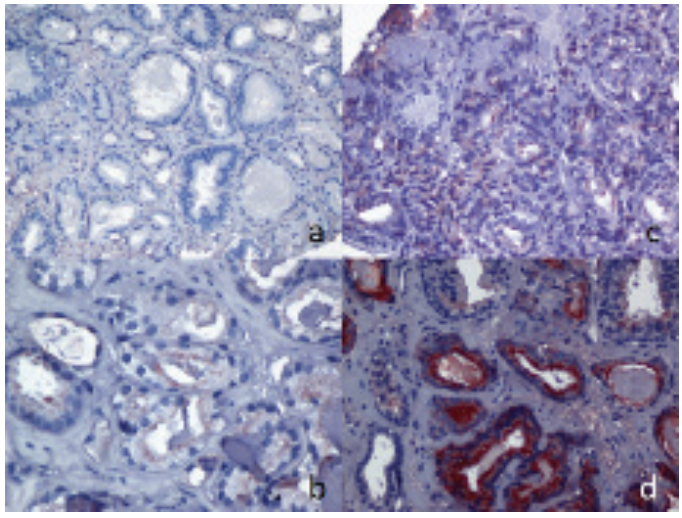


**Figure 1.** (a) Negative staining (AMACR/P504S X 200). (b) Weak, focal apical granular staining (AMACR/P504S X 600). (c) Moderate, disseminated cytoplasmic staining (AMACR/P504S X 400). (d) Diffuse, strong cytoplasmic staining (AMACR/P504S X 400)

AMACR: Alpha methylacyl A coenzyme racemase

## Statistical Analysis

The variables' normality was checked by the Kolmogorov-Smirnov test. Groups were compared regarding AMACR/P504S staining intensities of biopsy cores, positive core number (Mann-Whitney U test), age, preoperative prostate volume and PSA value, tumour volume percentage (Student t-test), biopsy and radical prostatectomy Gleason scores/ISUP grades, up and down-grading rates (chi-square test). In addition, patients were divided into three subgroups according to AMACR staining intensity scores, and the Kaplan-Meier test was applied to each subgroup. A $p<0.05$ value was considered statistically significant.

## Results

The mean follow-up time was 40.48 (12-63) months when recurrent patients were included in the study. The patients' mean age in the PSA recurrence group was slightly higher than the other group (66.1±6.2 vs 63.5±7.9 years, respectively). However, the difference between ages was not statistically significant (p=0.25). There was a statistically significant difference between the two groups regarding preoperative PSA values (9.4±5.5 vs 14.7±7.1 ng/dL, p=0.004). There was no statistically significant difference between the groups' preoperative prostate volumes (47.2±17.9 vs 54.6±20.3 mL, p=0.36). The distribution of the patients' biopsy Gleason/ISUP grade group is shown in Table 2. No statistically significant difference was found between the grade distributions (p=0.55). The positive core median was three in both groups (p=0.65). The mean AMACR/P504S staining scores of positive biopsy cores were 1.88±0.85 and 1.27±1.22 for group 1 and group 2, respectively. The AMACR/P504S staining score of positive cores were significantly higher in patients with PSA recurrence than non-recurrent patients (p=0.002).

**Table 2. Comparison of the groups according to baseline characteristics and AMACR staining**

| | PSA recurrence + Group 1 | PSA recurrence - Group 2 | p-value |
|---|---|---|---|
| Patient number | 25 | 25 | |
| Age (year, mean) | 66.1±6.2 | 63.5±7.9 | 0.25* |
| (median, range) | 67 (54-76) | 65.5 (44-75) | |
| Preop. PSA (ng/mL, mean) | 14.7±7.1 | 9.4±5.5 | **0.004*** |
| **Biospy Gleason scores/ISUP grades** | | | |
| Gleason 3+3/ISUP 1 | 21/25 (84%) | 18/25 (72%) | |
| Gleason 3+4/ISUP 2 | 4/25 (16%) | 4/25 (16%) | 0.55$^{\alpha}$ |
| Gleason 4+3/ISUP 3 | 0/25 (0%) | 3/25 (12%) | |
| Positive core number (median) | 3 (1-6) | 3 (1-8) | 0.65$^{\beta}$ |
| TRUS prostate volume (mL, mean) | 47.2±17.9 | 54.6±20.3 | 0.36* |
| Mean AMACR/P504S staining score of positive cores | 1.88±0.85 | 1.27±1.22 | **0.002**$^{\beta}$ |

*Student t-test, $^{\alpha}$chi-square test, $^{\beta}$Mann-Whitney U test, TRUS: Transrectal ultrasound, AMACR: Alpha methylacyl A coenzyme racemase, ISUP: International Society of Urological Pathology,

**Table 3. Comparison of the groups according to RP pathologic outcomes**

| | PSA Recurrence + Group 1 | PSA Recurrence - Group 2 | p-value |
|---|---|---|---|
| Patient number | 25 | 25 | |
| RP Gleason scores/ISUP grades | | | |
| Gleason 3+3/ISUP 1 | 17/25 (68%) | 18/25 (72%) | |
| Gleason 3+4/ISUP 2 | 5/25 (20%) | 2/25 (8%) | 0.37[α] |
| Gleason 4+3/ISUP 3 | 3/25 (12%) | 5/25 (20%) | |
| Up-grading rate | 8/25 (32%) | 5/25 (20%) | 0.52[α] |
| Down-grading rate | 1/25 (4%) | 3/25 (12%) | 0.61[α] |
| Tumor volume percentage (mean) | 32.1±23.8 | 25.4±15.1 | 0.67* |

[α]chi-square test, *Student t-test, RP: Radical prostatectomy, PSA: Prostate-specific antigen, ISUP: International Society of Urological Pathology

The distribution of the patients' radical prostatectomy Gleason/ISUP grade group is shown in Table 3. No statistically significant difference was found between the grade distributions (p=0.37). Gleason/ISUP up-grading was detected in 32% (8/25) of patients in group 1 and in 20% (5/25) of patients in group 2 (p=0.52). Gleason/ISUP down-grading was detected in 4% (1/25) of patients in group 1 and in 12% (3/25) of patients in group 2 (p=0.61). There was no difference in the tumour volume percentage between the groups (32.1±23.8 vs 25.4±15.1, p=0.67).

The patients were divided into three subgroups according to their biopsy AMACR scores. A Kaplan-Meier test was performed according to the biochemical recurrence outcome (Graphic 1). A test of equality of recurrence distributions for the different AMACR scores did not show statistical significance (p=0.43).

## Discussion

Our study's main finding showed a significant relationship between the increased biopsy core AMACR staining intensity and biochemical recurrence after radical prostatectomy. This clinical finding provides indirect evidence of a possible relationship between prostate cancer aggressiveness and increased AMACR cancer cell expression. However, the AMACR score groups were not separated regarding biochemical recurrence endpoints in the Kaplan-Meier analysis.

Box and colleagues (10) described the relationship between AMACR and biochemical recurrence as marginal in a study of 218 patients who underwent radical prostatectomy for localised prostate cancer. On the other hand, an early study investigating the relationship between AMACR-prostate cancer and lower AMACR tissue expression has been associated with an increased rate of biochemical recurrence (7). Inconsistent results regarding the relationship between AMACR and worse prostate cancer outcomes can be explained by varying AMACR expression during prostate cancer's natural course. Studies show that AMACR expression increases in cancerous cells compared with benign prostate cells but decreases as cancer cells' differentiation decreases. Luo et al. (11) demonstrated in 2002 that the AMACR gene is up-regulated in prostate cancer.

A growing body of literature suggests that the gene groups' predictive value may be more effective than clinical and pathological parameters, such as PSA and Gleason score. Overexpression of four genes, including AMACR, was shown to have a significant relationship with aggressive disease characteristics, such as extracapsular extension, tumour stage, and seminal vesicle invasion in a study conducted in 2019 (12). This statistically significant relationship showed better overall clinical performance than PSA and Gleason score. The AMACR score showed a better diagnostic value than serum PSA in another recent study (13). In that study, AMACR and PSA messenger RNA (mRNAs) obtained by urine sediment analysis were evaluated by quantitative real-time polymerase chain reaction. In our study, the PSA and biopsy core AMACR staining intensity differences between the groups regarding biochemical recurrence after radical prostatectomy were statistically significant.

Since AMACR expression is directly related to carcinogenesis, it makes the AMACR molecule a parameter that offers different clinical benefits than PSA. It is known that PSA synthesis in the prostate cell does not increase significantly even in neoplastic processes (14). The increase in serum PSA is an indirect indicator of the increase in the cancerous cell number, deterioration of the intercellular connections and the basement membrane (15). AMACR's presence in serum has been demonstrated, but no statistically significant difference was found between serum AMACR levels in patients with and without prostate cancer (16). Moreover, AMACR is not a prostate-specific molecule (17). The above-mentioned disadvantages of the molecule in the systemic circulation overshadow its superiority against PSA in the cancer microenvironment. This causes the molecule to be a parameter dependent on tissue diagnosis and limits its clinical use as a candidate for prostate cancer marker. In this context, seminal fluid studies are far from providing the expected results (18).

### Study Limitations

Our study has some limitations. Retrospective patient data and material collection, excluding patients with insufficient data, has affected the groups' random distribution. In addition, the number of patients included in the study was below the number obtained by power analysis due to the lack of staining kits. The categorical evaluation of AMACR staining intensity restricted the statistical efficiency of the parameter. Further scoring can be developed, like the Gleason score, which considers the overall biopsy core specimen. In addition, high up-grading rates (group 1: 32% vs group 2: 20%) in both groups weakened the relationship between the biopsy findings and the clinical course of patients after radical prostatectomy.

## Conclusion

There is a significant relationship between increased AMACR/P504S expression in cancerous prostate tissue and PSA recurrence after radical prostatectomy. Prospective clinical studies are needed to demonstrate AMACR's predictive value of biochemical recurrence with a high level of evidence.

### Acknowledgements

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

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

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

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

### Ethics

**Ethics Committee Approval:** Retrospective study.

**Informed Consent:** Retrospective study.

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

### Authorship Contributions

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

## References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Xu J, Stolk JA, Zhang X, et al. Identification of differentially expressed genes in human prostate cancer using subtraction and microarray. Cancer Res 2000;60:1677-1682.
3. Zheng SL, Chang B, Faith DA, et al. Sequence variants of alpha - methylacyl-CoA racemase are associated with prostate cancer risk. Cancer Res 2002;62:6485-6488.
4. Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 2005;294:433-439.
5. Shapovalova M, Davydova J, Henzler C, et al. Exploiting the Transcriptional specificity of the alpha-methylacyl-CoA racemase AMACR promoter for the molecular ımaging of prostate cancer. Oncotarget 2018;9:36693-36704.
6. Ying Z, Feng L, Dongqing Ji, et al. Phase-regulated sensing mechanism of mos 2 based nanohybrids toward point-of-care prostate cancer diagnosis. Small 2020;16:e2000307. doi: 10.1002/smll.202000307.
7. Rubin MA, Bismar TA, Andrén O, et al. Decreased α – Methylacyl CoA racemace expression in localized prostate cancer is associated with an increased rate of biochemical recurrence and cancer-spesific death. Cancer Epidemiol Biomarkers Prev 2005;14:1424-1432.
8. Kars M, Gökmen E, Özman O, et al. Relationship between AMACR staining density of radical prostatectomy specimen and biochemical recurrence in patients with pathological stage T2a-b. Bull Urooncol 2020;19:38-41.
9. Rubin MA, Whittington R, Malkowicz SB, et al. Alpha-Methylacyl coenzyme A racemase as a tissue biomarker for prostate cancer. JAMA 1998;280:969-974.
10. Box A, Alshalalfa M, Hegazy SA, et al. High alpha-methylacyl-CoA Racemase (AMACR) is associated with ERG expression and with adverse clinical outcome in patients with localized prostate cancer. Tumour Biol 2016;37:12287-12299. doi: 10.1007/s13277-016-5075-1.
11. Luo J, Zha S, Gage RW, et al. Alpha-methylacyl-CoA racemase: a new molecular marker for prostate cancer. Cancer Res 2002;62:2220-2226.
12. de Souza MF, Kuasne H, Barros-Filho MC, et al. Circulating mRNA signature as a marker for high-risk prostate cancer. Carcinogenesis 2020;41:139-145.
13. Ji J, Chen X, Xu Y, et al. Prostate cancer diagnosis using urine sediment analysis-based α-methylacyl-coa racemase score: a single-center experience. Cancer Control 2019;26:1073274819887697. doi: 10.1177/1073274819887697.
14. Henttu P, Liao SS, Vihko P. Androgens up-regulate the human prostate-specific antigen messenger ribonucleic acid (mRNA), but down-regulate the prostatic acid phosphatase mRNA in the LNCaP cell line. Endocrinology 1992;130:766-772.
15. Robles MJ, de Torres Mateos JA, and Soler-Rosello A. [Analysis of the serum concentration of prostate-specific antigen as a biological marker in the evolution of disseminated prostatic cancer]. Actas Urol Esp 1988;12:152-157.
16. Čapoun O, Soukup V, Kalousová M, et al. Diagnostic importance of selected protein serum markers in the primary diagnostics of prostate cancer. Urol Int 2015;95:429-435.
17. Yu YP, Tsung A, Liu S, et al. Detection of fusion transcripts in the serum samples of patients with hepatocellular carcinoma. Oncotarget 2019;10:3352-3360.
18. Etheridge T, Straus J, Ritter MA, et al. Semen AMACR protein as a novel method for detecting prostate cancer. Urol Oncol 2018;36:532.e1-532.e7. doi: 10.1016/j.urolonc.2018.09.010.

*Original Article*

DOI: 10.4274/uob.galenos.2020.1378

*Bull Urooncol 2021;20(2):96-106*

# *Clinicopathological Characteristics and Oncological Outcomes of Non-urothelial Bladder Carcinomas: A Multicenter Study*

İsmail Selvi[1], Eşref Oğuz Güven[2], Mehmet Umut Kütükoğlu[3], Yüksel Ürün[4], İlker Tinay[3]

[1]*University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Urology, İstanbul, Turkey*
[2]*University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Onkology Training and Research Hospital, Clinic of Urology, Ankara, Turkey*
[3]*Marmara University Faculty of Medicine, Department of Urology, İstanbul, Turkey*
[4]*Ankara University Faculty of Medicine, Department of Medical Oncology, Ankara, Turkey*

## Abstract

**Objective:** The incidence of non-urothelial bladder cancers is very low, so our knowledge about their treatment protocols and prognosis is limited. We evaluated the clinicopathological characteristics of 26 patients in three different clinics and aimed to determine the prognostic factors affecting oncological outcomes.
**Materials and Methods:** Between January 2012 and October 2019, we retrospectively analyzed the data of twenty-six patients aged between 44-75 years who were diagnosed and treated due to non-urothelial bladder carcinomas in three clinics.
**Results:** Among twenty-six cases, nineteen (73.1%) were male and seven (26.9%) were female. The mean age at diagnosis was 60.77±8.52. The most common presenting complaint was gross hematuria (84.6%). It was followed by lower urinary tract symptoms (38.4%). Histological types of tumors were squamous cell carcinoma (9 cases, 34.8%), adenocarcinoma (eight cases carrying different histopathologic subtypes: Mucinous, signet ring cell, plasmacytoid/signet ring cell mixed variant and signet ring cell containing osteoclast-like giant cell, 30.8%), small cell carcinoma (3 cases, 11.5%), large cell neuroendocrine carcinoma (2 cases, 7.7%), extra-gastrointestinal stromal tumor (1 case, 3.8%) and malignant undifferentiated mesenchymal tumor (1 case, 3.8%) and leiomyosarcoma (2 cases, 7.6%). At a median follow-up of 13 (2-42) months, the progression-free survival rate was 61.5%, while the overall survival rate was 46.1%. In Kaplan-Meier analysis, the median survival of all cases was found to be 16 (9-33) months. Overall survival times were lower in the presence of advanced (3-4) pathological stages (p=0.006) and higher (≥2) ECOG scores (p=0.005).
**Conclusion:** In our cases, we observed that overall survival rates increased in patients undergoing multimodal treatments involving radical cystectomy compared to the bladder-sparing approach. The survival rates were higher in squamous cell carcinomas, while the rate of metastasis was higher in adenocarcinoma and neuroendocrine tumors. Up-staging rates after cystectomy were higher in adenocarcinomas, sarcomas and squamous cell carcinomas.
**Keywords:** Adjuvant chemotherapy, non-urothelial bladder carcinomas, oncological outcomes, radical cystectomy

## Introduction

Bladder cancer constitutes 7% of cancers in men and 3% of cancers in women all over the world. The male/female incidence rate is 3-4/1, and it is generally detected in the fifth-sixth decade (1). Of bladder cancers, 90-95% are urothelial (transitional cell) carcinoma and 5-10% are non-urothelial (epithelial and/or mesenchymal origin) carcinoma (2). Non-urothelial carcinomas have a worse prognosis than urothelial carcinomas, and they are usually diagnosed at an advanced stage. Its diagnosis, staging, and treatment are generally similar to urothelial carcinomas (3). The largest series on non-urothelial carcinomas in the literature was performed by Cohen et al. (4) in 2.201 patients.

Due to the low incidence rates, our knowledge about the treatment protocols and prognosis of non-urothelial bladder carcinomas is based on retrospective case series and very few prospective studies (3,5). The basic treatment approach is adjuvant chemotherapy (CT)/radiotherapy (RT) applied after radical surgical resection, especially in the locally advanced stage. However, due to the scarcity of randomized studies, adjuvant treatment protocols are still not standardized (3). Since our knowledge about non-urothelial carcinoma was limited, in this study, we aimed to evaluate the clinical and pathological characteristics and oncological results of patients diagnosed in three different centers in our country.

**Cite this article as:** Selvi İ, Güven EO, Kütükoğlu MU, Ürün Y, Tinay İ. Clinicopathological Characteristics and Oncological Outcomes of Non-urothelial Bladder Carcinomas: A Multicenter Study. Bull Urooncol 2021;20(2):96-106

**Address for Correspondence:** İsmail Selvi, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Urology, İstanbul, Turkey
**Phone:** +90 212 909 60 00 **E-mail:** ismselvi33@hotmail.com **ORCID-ID:** orcid.org/0000-0003-3578-0732
**Received:** 08.09.2019 **Accepted:** 03.05.2020

## Materials and Methods

The clinical and pathological data and postoperative follow-up findings of 26 patients aged 44-75 years, who were treated and followed up in three different centers between January 2012 and October 2019, and diagnosed as having non-urothelial carcinoma, were retrospectively analyzed. Demographic data of the patients, complaint at presentation, location of the tumor in the bladder, tumor size, cystoscopy findings, transurethral tumor resection of bladder tumor (TUR-BT) pathology, clinical tumor stage, radical cystectomy status, adjuvant treatments applied during the postoperative follow-up period, postoperative follow-up period, local recurrence, progression and survival conditions were recorded. Eastern Cooperative Oncology Group (ECOG) score and Charlson Comorbidity index, which were used to evaluate the morbidity status of the patients during the preoperative period, were found from the patient data and recorded. Radical cystectomy and bilateral expanded pelvic lymph node dissection (LND) were routinely performed in patients undergoing radical surgery. Colonoscopy was performed in all patients with TUR-BT pathology of adenocarcinoma to investigate the primary focus in the colorectal system. American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system was used for staging of tumors (6). In addition, every increase observed in the pathological staging performed after radical cystectomy compared to the clinical TNM stage after TUR-BT was defined as up-staging.

### Statistical Analysis

Kaplan-Meier method was used for survival analysis, while differences between patient groups were evaluated using the log rank test. This study was not suitable for the multivariate model due to its small sample size. Analyzes were performed using IBM SPSS Statistics 21 (IBM, Armonk, NY USA) software. Values of $p<0.05$ were considered statistically significant.

## Results

Nineteen (73.1%) of the 26 patients we included in the study were male and 7 (26.9%) were female, and the mean age at diagnosis was 60.77±8.52. The most common presenting complaint was macroscopic hematuria (22 patients, 84.6%), followed by lower urinary tract complaints (irritative voiding symptoms, difficulty urinating) (10 patients, 38.4%). More rarely, abdominal distension (1 patient, 3.8%), abdominal pain (1 patient, 3.8%) and obstructive uropathy (1 patient, 3.8%) were observed.

Tumor types in histopathological examination were as follows: Squamous cell carcinoma (9 patients, 38.4%), adenocarcinoma (8 patients with different histopathological subtypes, including mucinous, signet ring cell, plasmacytoid/signet ring cell mixed variant, and signet ring cell containing osteoclast-like giant cells, 30.8%), small cell carcinoma (3 patients, 11.5%), large cell neuroendocrine carcinoma (2 patients, 7.7%), extra-gastrointestinal stromal tumor (1 patient, 3.8%) and malignant undifferentiated mesenchymal tumor (1 patient, 3.8%) and leiomyosarcoma (2 patients, 7.6%).

In the median 13-month (2-42) follow-up of the 26 patients included in our study, the progression-free survival rate was 61.5%, and the overall survival rate was 46.1%. While radical cystectomy was applied to 14 of 18 patients, whose clinical stage was determined as T2-T4a N0M0, 9 of them underwent adjuvant CT, 1 of them adjuvant RT, 1 of them neoadjuvant CT, and 1of them adjuvant CT + RT. Of these 18 patients, adjuvant CT was applied following complete TUR-BT in 3 patients who did not want radical surgery, while partial cystectomy was performed in the patient with extra-gastrointestinal stromal tumor pathology because the tumor was limited to the bladder dome. In the patient with signet ring cell adenocarcinoma with osteoclast-like giant cells without muscle invasion, only complete TUR-BT was performed surgically. These last 2 patients, who did not have a clear treatment scheme, were followed up without adjuvant treatment because the tumor characteristic was not aggressive. Seven patients who were in the metastatic stage at the time of diagnosis were included in the CT program, while palliative RT was applied in 4 patients who developed pain due to bone metastasis during follow-up.

Fourteen patients who underwent radical cystectomy + bilateral expanded pelvic LND and/or neoadjuvant/adjuvant therapy had a median follow-up of 13 (2-42) months, while progression was observed in 4 (28.5%) cancer-related death was observed in 6 (42.8%). In the median 15-month (10-17) follow-up of 3 patients who underwent adjuvant CT and complete TUR-BT, progression and cancer-related death were observed in 2 (66.6%) of them. While no recurrence or progression was observed in the 22-month follow-up of a single patient who underwent partial cystectomy, despite the CT program of 7 patients who were metastatic at the time of diagnosis, 4 (57.1%) had progression and 6 (85.7%) died at a median 9-month (7-22) follow-up. According to the cystectomy pathologies, 9 (60%) of 15 patients had up-staging, while the patient with small cell carcinoma who underwent radical cystectomy after neoadjuvant CT had down-staging.

When we divided the patients into four classes according to histopathological subtype as squamous cell carcinoma, adenocarcinoma, neuroendocrine tumors and sarcomas, the overall survival rates after multimodal treatments were 77.8%, 25%, 20% and 50%, respectively. Metastasis was seen only in patients with adenocarcinoma (62.5%) or neuroendocrine tumors (40%) at the time of diagnosis. Up-staging after cystectomy was observed in 37.5% of patients with squamous cell carcinomas and in all patients with adenocarcinomas or sarcomas. The characteristics of the patients are shown in Table 1. Demographic and clinical characteristics of patients with and without mortality are shown in Table 2.

In the Kaplan-Meier analysis; while the median survival time of all patients was found to be 16 (9-33) months (Figure 1), in the presence of advanced pathological stage (3-4, $p=0.006$) and higher ECOG score ($\geq 2$, $p=0.005$), it was observed that overall survival times were shorter (Figure 2,3).

## Discussion

Non-urothelial bladder carcinomas constitute approximately 5-10% of all bladder carcinomas. The most common

**Table 1. Demographic, clinical, pathological data and oncological results of the patients**

| Patient no | Age | Gender | Complaint at admission | Risk factor and comorbidity status | Localization of the tumor in the bladder | Pathological diagnosis | Treatment | Postoperative follow up period | Recurrence/ progression status |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 54 | Male | Painless, clotted hematuria | Paraplegic patient due to a traffic accident,<br><br>Applying CIC<br><br>ECOG score: 2<br><br>Charlson comorbidity index: 3 | Widespread, multiple solid-based masses in the anterior bladder wall | TUR-BT: Squamous cell carcinoma,<br>There was muscle invasion<br>Clinical stage 2<br><br>Radical cystoprostatectomy: Squamous cell carcinoma, pT4aN2M0 | Radical cystoprostatectomy bilateral pelvic LND + ileal conduit<br><br>Adjuvant 3 cures of cisplatin + gemcitabine | 9 months | Liver and bone metastasis in the 4th month<br><br>Palliative RT for bone metastasis was given.<br>Ex in the 9th month |
| **2** | 47 | Male | Clotted hematuria, irritative voiding symptoms | Smoking history<br><br>ECOG score: 3<br><br>Charlson comorbidity index: 5 | Papillary-looking mass with a diameter of 5 cm in the posterior wall of the bladder | TUR-BT: Mucinous adenocarcinoma, muscle invasion was present<br>Clinical stage 2<br><br>Radical cystoprostatectomy: Mucinous adenocarcinoma, pT4bN1M0 | Radical cystoprostatectomy bilateral pelvic LND + ileal conduit<br><br>Adjuvant 4 cures of 5-Fluorouracil + Doxorubicin + Cisplatin | 16 months | Lung metastasis in the 8th month<br>Ex in the 16th month |
| **3** | 48 | Male | Non-clotted hematuria<br>Increase in KFT, Bilateral grade 3 hydronephrosis | Smoking history<br><br>ECOG score: 3<br><br>Charlson comorbidity index: 5 | 7.5 cm diameter solid-based mass at the bladder floor | TUR-BT: Signet ring cell adenocarcinoma, muscle invasion was present<br>Clinical stage 2<br><br>Radical cystoprostatectomy: Signet ring cell adenocarcinoma, pT3bN1M0 | Radical cystoprostatectomy + bilateral pelvic LND + ureterocutaneostomy<br><br>Adjuvant 4 cures of 5-Fluorouracil + Doxorubicin + Cisplatin | 4 months | Postoperative impairment of general condition, bilateral deep vein thrombosis, acute renal failure, Respiratory Failure<br><br>Ex in the 4th month |
| **4** | 53 | Female | Non-clotted hematuria, irritative voiding symptoms | Applying CIC due to neurogenic bladder,<br><br>ECOG score: 1<br><br>Charlson comorbidity index: 2 | 3 cm diameter solid-based mass at the bladder floor | TUR-BT: Squamous cell carcinoma,<br>There was muscle invasion<br>Clinical stage 2<br><br>Radical cystectomy: Squamous cell carcinoma, pT2N0M0 | Radical cystectomy + urethrectomy + bilateral pelvic LND + ileal conduit +<br><br>Adjuvant 4 cures of MVAC | 42 months | No recurrence,<br><br>Alive |
| **5** | 74 | Male | Difficulty urinating | Smoking history<br><br>ECOG score: 3<br><br>Charlson comorbidity index: 3 | On the bladder floor and right sidewall, multiple, solid mass with 9 cm diameter, invazing the prostate | TUR-BT: Small cell carcinoma<br>There was muscle invasion<br><br>CT: clinical stage T4N2M1 (prostate invasion, bone metastasis, bilateral Grade 2 hydronephrosis) | The patient did not want radical surgical treatment,<br><br>Adjuvant 6 cures of carboplatin + etoposide +<br>RT (because of pain due to bone metastasis) | 9 months | Progression of bone metastases in the 6th month<br><br>Ex in the 9th month |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 6 | 57 | Male | Painless, clotted hematuria | Smoking history<br><br>ECOG score: 3<br><br>Charlson comorbidity index: 4 | 4 cm diameter solid-based mass in the right lateral wall of the bladder | TUR-BT: Large cell neuroendocrine carcinoma<br>There was muscle invasion<br><br>CT: Clinical stage T3bN0M0<br>(invasion in perivesical adipose tissue) | The patient did not want radical surgical treatment,<br><br>Adjuvant 6 cures of cisplatin + etoposide | 15 months | Involvement of right internal iliac lymph nodes in the 8th month<br><br>Ex in the 15th month |
| 7 | 49 | Male | Abdominal pain, bloating, weakness, hemauria | Smoking history<br><br>ECOG score: 3<br><br>Charlson comorbidity index: 4 | Widespread, multiple, polypoid lesions on the left lateral wall of the bladder | TUR-BT: adenocarcinoma with high grade plasmacytoid / signet ring cell mixed variant<br>There was muscle invasion<br><br>CT: Left pleural effusion, bilateral iliac, pararectal, and widespread LN with a large diameter of 2 cm in the right parailiac area. LN biopsy result for adenocarcinoma metastasis<br>Clinical stage: T3bN2M0 | The patient's general condition was not appropriate for radical surgery,<br><br>Adjuvant 5 cures of gemcitabine + carboplatin | 7 months | The patient whose general condition deteriorated further in the 7th month |
| 8 | 66 | Male | Painless, clotted hematuria, difficulty urinating | None<br><br>ECOG score: 1<br><br>Charlson comorbidity index: 1 | Two solid-based masses on the right lateral wall of the bladder with a diameter of 2 cm. | TUR-BT: Signet ring cell adenocarcinoma with osteoclast-like giant cells<br>Lamina propria invasion was present<br><br>Clinical stage: T1N0M0 | In this subtype, which did not have a clear treatment scheme, the patient did not want additional treatment after complete TUR-BT, and was followed up. | 14 months | No recurrence,<br><br>Alive |
| 9 | 67 | Male | Painless, clotted hematuria | Paraplastic patient due to CVA,<br><br>Applying CIC<br><br>ECOG score: 2<br><br>Charlson comorbidity index: 2 | Widespread solid-based mass at the bladder floor, 2 bladder stones with a diameter of 2 cm. | TUR-BT: Squamous cell carcinoma,<br>There was muscle invasion<br><br>Clinical stage: T2N0M0 | The patient did not want radical surgical treatment,<br><br>Following complete TUR-BT + endoscopic cystolithotripsy,<br><br>Adjuvant 4 cures of Cisplatin + gemcitabine were administered. | 17 months | No recurrence in 17 months of follow-up,<br><br>After that, the patient was out of follow-up. |
| 10 | 61 | Female | Non-clotted hematuria, abdominal distension | None<br><br>ECOG score: 1<br><br>Charlson comorbidity index: 2 | A solid mass with a diameter of 8 cm and a necrotic appearance originating from the bladder dome | TUR-BT: Extra-gastrointestinal stromal tumor,<br>There was muscle invasion<br><br>CT: A solid mass of 20 cm in diameter in the right adnexal area pushing the intestinal segments, invading the ileum, and suppressing the vena cava.<br><br>Partial cystectomy: pT4N0M0 | Partial cystectomy + ileal resection + partial omentectomy<br><br>In this subtype, which didi not have a clear treatment scheme,<br>the patient was followed up. | 22 months | No recurrence,<br><br>Alive |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 11 | 63 | Male | Non-clotted hematuria | Smoking history<br><br>ECOG score: 3<br><br>Charlson comorbidity index: 4 | Multiple solid masses on the bladder floor, right sidewall and dome | TUR-BT: Large cell neuroendocrine carcinoma<br>There was muscle invasion<br><br>PSA: 33, TRUS-biopsy: prostate adenocarcinoma Gleason 5 + 5<br>Clinical stage of the mass in the bladder: T2N2M0 | The patient did not want radical surgical treatment,<br><br>For bladder carcinoma<br>6 cures of cisplatin + etaposide following complete TUR-BT<br><br>RT + HT for prostate adenocarcinoma | 10 months | Liver metastasis in the 6th month<br><br>Ex in the 10th month |
| **12** | 55 | Male | Painless, clotted hematuria | None<br><br>ECOG score: 3<br><br>Charlson comorbidity index: 5 | Multiple solid masses on the bladder floor, both sidewalls and domes | TUR-BT: Malignant undifferentiated mesenchymal tumor<br>There was muscle invasion<br>Clinical stage 2<br><br>Radical cystoprostatectomy: malignant undifferentiated mesenchymal tumor, pT3bN0M0 | Radical cystoprostatectomy + bilateral pelvic LND + ileal conduit<br><br>Adjuvant 3 cures of doxorubicin, cyclophosphamide, cisplatin | 8 months | Lung metastasis in the 3rd month<br><br>Ex in the 8th month |
| 13 | 74 | Female | Painless, clotted hematuria | Performing CIC<br><br>ECOG score: 2<br><br>Charlson comorbidity index: 5 | Multiple solid masses 3x2 cm in size in the bladder dome | TUR-BT: Squamous cell carcinoma,<br>There was muscle invasion<br>Clinical stage: T2N0M0<br>Radical cystectomy: Squamous cell carcinoma, T3aN0M0 | Radical cystectomy bilateral pelvic LND + ileal conduit<br>Adjuvant RT | 18 months | No recurrence,<br><br>Alive |
| 14 | 44 | Female | Non-clotted hematuria | None<br><br>ECOG score: 0<br><br>Charlson comorbidity index: 2 | Multiple solid masses on the bladder floor, both sidewalls and domes | TUR-BT: small cell carcinoma showing neuroendocrine differentiation<br>There was muscle invasion<br>Clinical stage: T2N0M0<br>Radical cystectomy: No residual tumor was observed<br>T0N0M0 | Neo-adjuvant 3 cycles of cisplatin + etoposide<br>Radical cystectomy bilateral pelvic LND + ileal conduit | 6 months | No recurrence,<br><br>Alive |
| 15 | 61 | Female | Painless, clotted hematuria | None<br><br>ECOG score: 0<br><br>Charlson comorbidity index: 4 | Multiple solid masses 3x3 cm in size on the right side wall of the bladder | TUR-BT: Squamous cell carcinoma,<br><br>There was muscle invasion<br>Clinical stage: T2N0M0<br>Radical cystectomy: Squamous cell carcinoma, T2N0M0 | Radical cystectomy bilateral pelvic LND + ileal conduit | 26 months | No recurrence,<br><br>Alive |
| 16 | 67 | Male | Lower urinary tract complaint | Smoking history<br><br>ECOG score: 1<br><br>Charlson comorbidity index: 9 | Multiple solid-based mass of 7x7 cm in the right lateral wall of the bladder | TUR-BT: Leiomyosarcoma High grade<br><br>Clinical stage: T2N0M0<br>Radical cystectomy: Leiomyosarcoma with a component of small cell neuroendocrine carcinoma.<br>T3bN1M0 | Radical cystoprostatectomy bilateral pelvic LND + ileal conduit | 2 months | General condition disorder in the postoperative period,<br>Ex in the 2nd month |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 17 | 59 | Female | Painless, clotted hematuria | Smoking history<br><br>ECOG score: 0<br><br>Charlson comorbidity index: 3 | Multiple solid-based mass of 6x5 cm in the left lateral wall of the bladder | TUR-BT: Leiomyosarcoma High grade<br><br>Clinical stage: T2N0M0<br>Radical cystectomy: Leiomyosarcoma T3bN1M0 | Radical cystectomy bilateral pelvic LND + ileal conduit<br>Adjuvant RT + 3 cures of ifosfamide/ mesna and doxorubicin | 13 months | No recurrence,<br><br>Alive |
| **18** | 72 | Male | Painless, clotted hematuria, lower urinary tract symptoms | Smoking history<br><br>ECOG score: 1<br><br>Charlson comorbidity index: 3 | Multiple solid-based mass 7x5 cm in size at the bladder floor | TUR-BT: Signet ring cell adenocarcinoma<br>There was muscle invasion<br><br>Clinical stage: T2N1M1 | Since there was bone metastasis at the time of diagnosis<br>3 cures of gemcitabine monotherapy were performed | 8 months | No recurrence or metastasis was observed.<br>Ex in the 8th month due to poor general condition |
| 19 | 60 | Male | Non-clotted hematuria | Smoking history<br><br>ECOG score: 2<br><br>Charlson comorbidity index: 5 | Multiple solid-based masses of 5x4 cm in size in the bladder dome and base | TUR-BT: Mucinous adenocarcinoma, Muscle invasion was present<br><br>Clinical stage: T2N0M1 | Since there was liver metastasis at the time of diagnosis<br>6 cures of gemcitabine + carboplatin were performed | 7 months | No recurrence or metastasis was observed.<br>Ex in the 7th month due to poor general condition |
| 20 | 75 | Male | Non-clotted hematuria | Smoking history<br><br>ECOG score: 2<br><br>Charlson comorbidity index: 5 | Multiple solid-based masses, 3x3 cm in size, on the left sidewall and base of the bladder | TUR-BT: Signet ring cell<br>There was muscle invasion<br><br>Clinical stage: T2N2M1 | Since there was lung metastasis at the time of diagnosis<br>6 cures of gemcitabine + cisplatin were performed. | 16 months | Atezolizumab was added due to the progression in the 5th month.<br>Ex in the 16th month |
| 21 | 58 | Male | Non-clotted hematuria | Smoking history<br><br>ECOG score: 1<br><br>Charlson comorbidity index: 4 | Multiple solid-based masses of 4x4 cm in size at the bladder floor | TUR-BT: Mucinous adenocarcinoma, muscle invasion was present<br><br>Clinical stage: T2N1M1 | Since there was liver metastasis at the time of diagnosis<br>6 cures of gemcitabine + cisplatin were performed | 22 months | 6 cycles of atezolizumab were added due to the progression in the 9th month.<br>Stable illness in the 22nd month, alive |
| 22 | 62 | Male | Non-clotted hematuria | Paraplegic patient due to a traffic accident,<br><br>Applying CIC<br><br>ECOG score: 1<br><br>Charlson comorbidity index: 4 | Widespread, multiple solid-based mass in the bladder floor | TUR-BT: Squamous cell carcinoma,<br>There was muscle invasion<br>Clinical stage 2<br><br>Radical cystoprostatectomy: Squamous cell carcinoma, pT3aN1M0 | Radical cystoprostatectomy bilateral pelvic LND + ileal conduit<br><br>Adjuvant 3 cures of cisplatin + gemcitabine | 11 months | Bone metastasis in the 6th month<br><br>Palliative RT for bone metastasis<br><br>Ex in the 11th month |
| 23 | 61 | Female | Irritative voiding symptoms | Applying CIC due to neurogenic bladder,<br><br>ECOG score: 0<br><br>Charlson comorbidity index: 5 | Solid-based multiple masses with a diameter of 3x3 cm on the bladder floor and left sidewall | TUR-BT: Squamous cell carcinoma,<br>There was muscle invasion<br>Clinical stage 2<br><br>Radical cystectomy: Squamous cell carcinoma, pT2N0M0 | Radical cystectomy + urethrectomy + bilateral pelvic LND + ileal conduit +<br><br>Adjuvant 4 cures of MVAC | 17 months | No recurrence,<br><br>Alive |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 24 | 59 | Male | Painless, clotted hematuria, lower urinary tract symptoms | Paraplastic patient due to a traffic accident,<br><br>Applying CIC<br><br>ECOG score: 1<br><br>Charlson comorbidity index: 4 | Diffuse solid-based multiple masses with a diameter of 5x5 cm on the bladder floor | TUR-BT: Squamous cell carcinoma,<br>There was muscle invasion<br><br>Clinical stage 2<br><br>Radical cystectomy: Squamous cell carcinoma, pT2N0M0 | Radical cystoprostatectomy bilateral pelvic LND + ileal conduit<br><br>Adjuvant 4 cures of MVAC | 13 months | No recurrence,<br><br>Alive |
| **25** | 69 | Male | Non-clotted hematuria lower urinary tract symptoms | Smoking history<br><br>ECOG score: 2<br><br>Charlson comorbidity index: 7 | Widespread solid-based multiple masses in all bladder walls | TUR-BT: Small cell carcinoma<br>There was muscle invasion<br><br>CT: Clinical stage T2N2M1 | Since there was bone metastasis at the time of diagnosis Adjuvant 6 cures of carboplatin + etoposide + palliative RT were applied due to pain due to bone metastasis. | 11 months | Progression of bone metastases in the 7th month<br><br>Ex in the 11th month |
| 26 | 65 | Male | Lower urinary tract symptoms | Paraplastic patient,<br><br>Applying CIC<br><br>ECOG score: 1<br><br>Charlson comorbidity index: 3 | Solid-based multiple masses with a diameter of 3x3 cm on the bladder floor | TUR-BT: Squamous cell carcinoma,<br>There was muscle invasion<br><br>Clinical stage 2<br><br>Radical cystectomy: Squamous cell carcinoma, pT2N0M0 | Radical cystoprostatectomy bilateral pelvic LND + ileal conduit<br><br>Adjuvant 4 cures of cisplatin + gemcitabine | 14 months | No recurrence,<br><br>Alive |

CIC: Clean intermittent catheterization, ECOG: Eastern cooperative oncology group, LND: Lymph node dissection, TUR-BT: Transurethral tumor resection, KFT: Kidney function test, MVAC: Methotrexate, Vinblastine, Adriamycin, Cisplatin, CT: Computed tomography, LN: Lymph node, CVA: Cerebrovascular accident, PSA: Prostate specific antigen

histopathological type in Western population is squamous cell carcinoma (3-5%), followed by adenocarcinoma (0.5-2%), and small cell carcinoma (0.35-0.70%). Other histological types such as neuroendocrine carcinoma, sarcomas, and carcinosarcoma are less common and the incidence has been reported as 0.1-0.5% (7). In our study consisting of 26 patients, the most common type was squamous cell carcinoma, in accordance with the literature.

In all types of non-urothelial bladder carcinomas, the most common risk factor observed was smoking (63%) and the most common complaint at presentation was reported as macroscopic hematuria (64%) (8,9). In these tumors with a male/female incidence rate of 3-4.8/1, the presence of muscle invasion at the time of diagnosis is between 72.2-100% in different series (5,10). In our patient group, male/female ratio was 2.71 and macroscopic hematuria and lower urinary tract symptoms, which were the most common complaints at presentation, were observed with a rate of 84.6% and 38.4%, respectively. Muscle invasion was detected in the TUR-BT specimen in all patients (96.1%) except for signet ring cell adenocarcinoma containing osteoclast-like giant cells. While smoking history was a risk factor in half of our patients, 8 (88.8%) of 9 patients with squamous cell carcinoma had a history of clean intermittent catheterization. In 5 patients, no history that could constitute a risk factor was found.

The majority of patients with non-bilharzial squamous cell carcinoma (62.7%) are seen at younger ages compared to transitional cell carcinoma and they are in stage 3-4 at the time of diagnosis, while the rate of distant metastasis is 8-34%. Five-year survival rate is 25.1-57% in patients who have undergone radical cystectomy (5,11,12,13,14). The most recommended chemotherapeutic agents in adjuvant therapy are gemcitabine and cisplatin (4). While radical cystectomy was performed in 8 of our 9 patients with squamous cell carcinoma, who were at the clinically localized stage at the time of diagnosis, 6 of them were given adjuvant CT and 1 adjuvant RT. In one patient who did not want radical surgery, complete TUR-BT + CT was applied. It was seen that CT protocols used were gemcitabine + cisplatin in 4 patients and MVAC in 3 patients. In the median 17-month (9-42) follow-up of these 9 patients, the overall survival rate was found to be 77.7%.

While patients with adenocarcinoma reported in the literature are mostly diagnosed in the sixth decade and the male/female ratio is 4.8/1 (15). If non-urachal adenocarcinoma, which has a worse prognosis and constitutes approximately 90% of bladder adenocarcinomas, is suspected, other primary tumors in the anatomical regions (colon, prostate, endometrium, cervix, breast, lung, etc.) that are likely to develop adenocarcinoma should be excluded (16,17). Standard treatment in primary, localized non-urachal adenocarcinomas is radical cystectomy + bilateral pelvic LND (18). While adjuvant CT/RT is recommended in advanced stage adenocarcinomas, it is known that the prognosis is worse in patients without radical cystectomy (3). In non-urachal adenocarcinomas, approximately 45.7% of the patients are in stage 4, while the rate of distant metastasis is 16.7-25% (5,15). The five-year survival rate was reported as 13-

| Table 2. Demographic and clinical characteristics of patients with and without mortality | | |
|---|---|---|
| **Parameters** | **Surviving patients (n=12, 46.2%)** | **Patients with mortality (n=14, 53.8%)** |
| Age | 60.67±7.47 | 60.86±9.61 |
| **Gender (n, %)** | | |
| -Male | 5 (41.7) | 14 (100.0) |
| -Female | 7 (58.3) | 0 (0.0) |
| **Histopathological tumor types (n, %)** | | |
| Squamous cell carcinoma | 7 (58.3) | 2 (14.3) |
| Adenocarcinoma | 2 (16.7) | 6 (42.9) |
| Neuroendocrine tumors | 1 (8.3) | 4 (28.6) |
| Sarcomas | 2 (16.7) | 2 (14.3) |
| **Pathological tumor stage (n, %)** | | |
| -1 | 1 (8.3) | 0 (0.0) |
| -2 | 7 (58.3) | 0 (0.0) |
| -3 | 1 (8.3) | 2 (14.3) |
| -4 | 3 (25.0) | 12 (85.7) |
| **Status of undergoing cystectomy (n, %)** | | |
| -Yes | 9 (75.0) | 6 (42.9) |
| -No | 3 (25.0) | 8 (57.1) |
| **Charlson comorbidity index (n, %)** | | |
| ≤2 | 5 (41.7) | 0 (0.0) |
| 3-4 | 5 (41.7) | 7 (50.0) |
| ≥5 | 2 (16.6) | 7 (50.0) |
| **ECOG score (n, %)** | | |
| ≤1 | 11 (91.7) | 3 (21.4) |
| ≥2 | 1 (8.3) | 11 (78.6) |
| **Presence of up-staging in patients undergoing cystectomy (n, %)** | | |
| -Yes | 3 (33.3) | 6 (100.0) |
| -No | 6 (66.7) | 0 (0.0) |
| ECOG: Eastern cooperative oncology group | | |

35% in patients who underwent radical cystectomy (5,8,14). In the median 11-month (4-22 months) follow-up of 8 patients with adenocarcinoma including different histological variants in our study, the progression rate was 37.5% and the overall survival rate was 25%. Although one patient was detected in clinical stage 1 and 2 patients were in clinical stage 2 at the time of diagnosis, up-staging to stage 4 was observed in both patients who underwent cystectomy. Intravesical treatments have no role in the treatment of bladder adenocarcinomas (19). As a matter of fact, no recurrence or progression was detected in the 14-month follow-up of our patient of singlet ring cell adenocarcinoma with osteoclast-like giant cells at T1 stage who underwent only complete TUR-BT.

Ploeg et al. (10) reported that the survival time was significantly lower in squamous cell carcinoma than adenocarcinoma (10 months vs 31.6 months), while Arslan et al. (20) could not find a significant difference (21 months vs 22 months) between the two histological types. On the other hand, in our limited

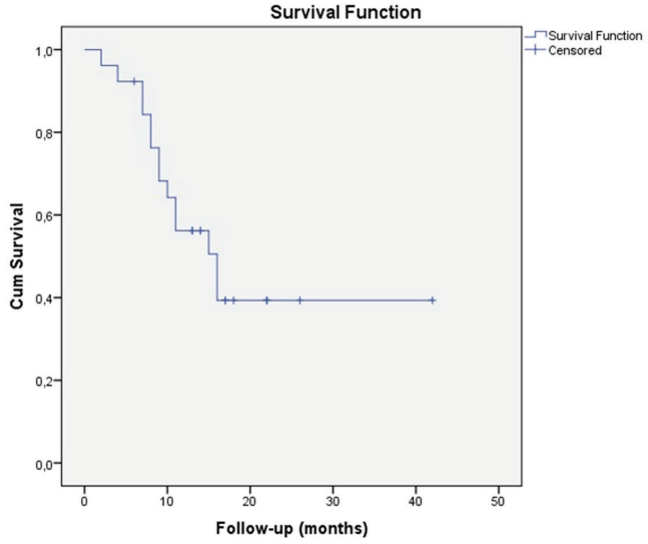


**Figure 1.** Overall survival plot of all patients

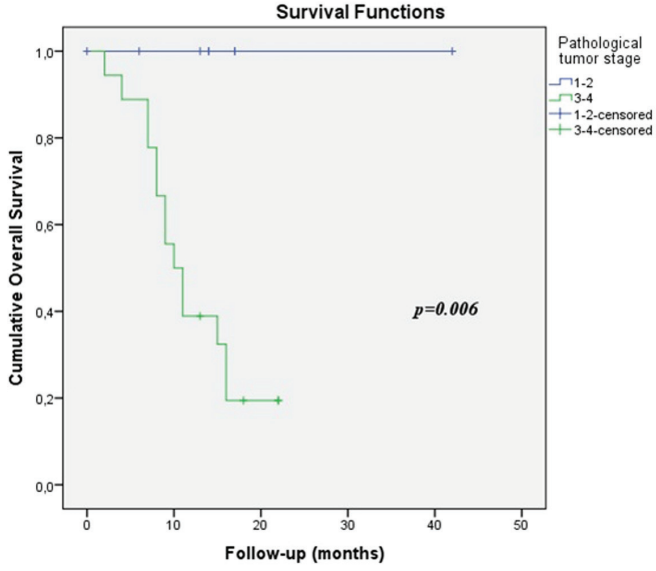


**Figure 2.** Overall survival plot according to pathological tumor stage

number of patients, we could not find a significant difference between the two groups in terms of overall survival (17 months vs 11.5 months, p=0.149).

Neuroendocrine bladder carcinomas generally constitute 0.45-1.2% of all bladder tumors. In this group, small cell carcinomas, which are the more common subtypes, often have muscle invasion, distant organ metastasis and paraneoplastic syndromes at the time of diagnosis (21). Of the patients, 53% are at pT3-4 stage at the time of diagnosis (22). It is necessary to differentiate bladder urothelial carcinoma from small cell carcinoma of prostate origin, and primary small cell carcinoma of the lung, and screening for another primary focus is important (23). Although there is no agreed clear treatment strategy, since micrometastatic involvement may occur at the time of diagnosis, following radical cystectomy/RT and adjuvant CT (cisplatin +

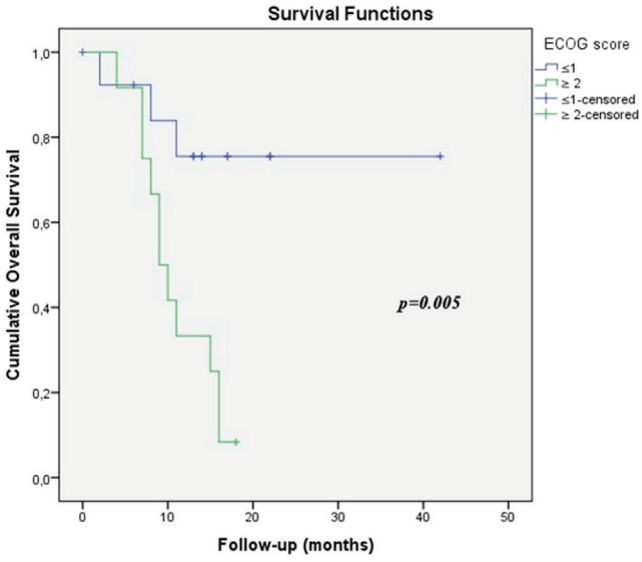


**Figure 3.** Overall survival plot according to ECOG score
ECOG: Eastern cooperative oncology group

etoposide)/RT is the most recommended scheme (3,4). Despite these combinations of therapy, the five-year survival rate has been reported as 10% (24). In patients in whom radical cystectomy cannot be performed, adjuvant CT+RT combination is required in addition to TUR-BT (25,26). Our patient, who was diagnosed at clinical stage 2 and underwent radical cystectomy following neoadjuvant cisplatin + etoposide in accordance with the information in the literature, was still alive at the 6-month follow-up, and death was observed in a median 10-month (9-11 months) follow-up in 2 patients who were found in the metastatic stage and underwent CT.

Large cell carcinomas of the bladder are another less common subtype of neuroendocrine carcinoma (3). As in small cell carcinoma, it is recommended to investigate the presence of another primary focus for differential diagnosis (27). The most common treatment approach reported for this carcinoma with poor prognosis, which is usually detected at an advanced stage, is the combination of adjuvant cisplatin/carboplatin and etoposide following radical cystectomy. Adjuvant cisplatin and etoposide were administered following TUR-BT in 2 patients who were evaluated as having clinical stage 3 disease at the time of diagnosis and did not want radical cystectomy; however, at a median 12.5-month (10-15 months) follow-up, death due to cancer was observed following progression.

Extra-gastrointestinal stromal tumors originating from the bladder are extremely rare mesenchymal tumors (28). Clinical presentation symptoms are generally non-specific, but patients presenting with macroscopic hematuria have also been reported. There is no specific tumor marker and radiological appearance (29). Complete surgical resection is the most curative treatment approach in this tumor, which is resistant to CT and RT. In our patient, who presented with macroscopic hematuria and abdominal distention without clot, partial cystectomy + ileal resection + partial omentectomy was applied to the mass that originated from the bladder dome and spread to the right adnexal area adjacent to the bladder and invaded the ileum. Our patient, who did not receive any additional treatment other than surgery, was in remission during a follow-up of 22 months.

Sarcomas of the bladder and malignant undifferentiated mesenchymal tumors constitute less than 0.5% of all bladder carcinomas. The most common histopathological type among non-epithelial malignant bladder tumors is leiomyosarcoma (3). In these patients, who mostly present with macroscopic hematuria, the tumor is large and often in advanced stage at the time of diagnosis. While radical cystectomy is recommended in the localized stage, adjuvant CT/RT should be combined in advanced stages. The most commonly used CT protocol is doxorubicin and ifosfamide. Nevertheless, since the number of patients reported in the literature is very low, standardization of treatment has not been achieved and mortality rates are quite high (3,30). Although radical cystectomy + adjuvant CT was applied in our patient with malignant undifferentiated mesenchymal tumor diagnosed at clinical stage 2, mortality was observed within 8 months. While one of our two patients with leiomyosarcoma who underwent radical cystectomy died in the second month postoperatively, in our other patient, no recurrence or progression was observed in the 13-month follow-up after adjuvant RT+CT.

Cohen et al. (4) found that the rate of up-staging was higher in non-urothelial carcinomas compared to urothelial carcinomas after radical cystectomy + bilateral expanded pelvic LND. They also stated that in patients with non-urothelial carcinoma with up-staging, overall survival was lower (32.4% vs 46%), and the highest up-staging rate was observed in patients with squamous cell carcinoma (61.8%). On the other hand, unlike the results of the study by Cohen et al. (4), we observed that the rate of up-staging in adenocarcinomas and sarcomas was higher than in squamous cell carcinomas.

When all non-urothelial carcinomas were evaluated, advanced tumor stage, lymph node involvement, advanced age (>70), poor ECOG score, histological types other than squamous cell carcinoma, presence of positive surgical margins, detection of local recurrence during follow-up were found to be significant factors in predicting overall survival (5,12,13,20). We could not evaluate the effects of these factors on survival, since the number of patients was not sufficient to perform multivariate regression analysis. On the other hand, according to Kaplan-Meier analysis; we observed that overall survival times were shorter as expected in the presence of advanced (stages 3-4) pathological stage and high (≥2) ECOG score.

### Study Limitations

Although we shared the results of 3 centers in our study, the retrospective design of our study, the limited number of patients, not being able to make randomization, not being able to perform multivariate regression analysis due to the inadequate number of patients, short follow-up periods, and non-standard CT regimens were the main limiting factors.

## Conclusion

When multimodal treatments including radical cystectomy were applied to non-urothelial carcinomas of the bladder, which

were rare and had very heterogeneous subtypes, as observed in our patients, overall survival rates increased compared to the bladder-sparing approach. According to our results, while survival rates were higher in squamous cell carcinomas, the rate of metastasis at the time of diagnosis was higher in adenocarcinoma and neuroendocrine tumors. We found higher up-staging rates in adenocarcinomas, sarcomas and squamous cell carcinomas after cystectomy. However, since neoadjuvant or adjuvant treatment protocols standardized according to tumor subtype are still not established; there is a need for better determination of prognostic factors that have an impact on survival. Prospective, randomized, controlled and multi-center studies with a large number of patients and longer follow-up periods are needed.

### Acknowledgements

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

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

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

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

### Ethics

**Ethics Committee Approval:** All procedures in our study were conducted in accordance with the ethical standards of the institutional and national research committee including human participants and the principles of the Helsinki Declaration, and since it was a retrospective study, no ethics committee approval was made.

**Informed Consent:** Each patient was informed before the surgery that oncological follow-up information such as recurrence, metastasis development, and survival analysis can be used in various oncological studies to be performed in the clinic without specifying the patient names and identity information, and the data of patients who did not consent were not used.

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

### Authorship Contributions

Concept: E.O.G., Design: İ.S., Data Collection or Processing: İ.S., M.U.K., Y.Ü., Analysis or Interpretation: İ.S., E.O.G., Y.Ü., İ.T., Literature Search: İ.S., Writing: İ.S.

## References

1. Kaur S, Gupta A, Gulwani HV. A clinicopathological and immunohistochemical study of non-urothelial bladder tumours. Indian J Cancer 2019;56:254-260.
2. Citgez S, Erözenci A, Yörükoğlu K. Non-ürotelyal mesane kanserleri. Bull Urooncol 2007;4:9-14.
3. Alanee S, Alvarado-Cabrero I, Murugan P, et al. Update of the International Consultation on Urological Diseases on bladder cancer 2018: non-urothelial cancers of the urinary bladder. World J Urol 2019;37:107-114.
4. Cohen AJ, Packiam V, Nottingham C, et al. Upstaging of nonurothelial histology in bladder cancer at the time of surgical treatment in the National Cancer Data Base. Urol Oncol 2017;35:34.e1-34.e8. doi: 10.1016/j.urolonc.2016.08.002.
5. Erdem GU, Dogan M, Sakin A, et al. Non-urothelial bladder cancer: comparison of clinicopathological and prognostic characteristics in pure adenocarcinoma and non-bilharzial squamous cell carcinoma of the bladder. Oncol Res Treat 2018;41:220-225.
6. AJCC Cancer Staging Manual. 7th edition. 2010. p. 497-502.
7. Ravi K, Kumar T, Bakshi H, et al. Non urothelial bladder cancers: a case series. Indian J Surg Oncol 2013;4:2-8.
8. Abdollah F, Sun M, Jeldres C, et al. Survival after radical cystectomy of non-bilharzial squamous cell carcinoma vs urothelial carcinoma: a competing-risks analysis. BJU Int 2012;109:564-569.
9. Manunta A, Vincendeau S, Kiriakou G, et al. Non-transitional cell bladder carcinomas. BJU Int 2005;95:497-502.
10. Ploeg M, Aben KK, Hulsbergen-van de Kaa CA, et al. Clinical epidemiology of nonurothelial bladder cancer: analysis of the Netherlands Cancer Registry. J Urol 2010;183:915-920.
11. Dahm P, Gschwend JE. Malignant non-urothelial neoplasms of the urinary bladder: a review. Eur Urol 2003;44:672-681.
12. Izard JP, Siemens DR, Mackillop WJ, et al. Outcomes of squamous histology in bladder cancer: a populationbased study. Urol Oncol 2015;33:425.e7-13. doi: 10.1016/j.urolonc.2015.06.011.
13. Lagwinski N, Thomas A, Stephenson AJ, et al. Squamous cell carcinoma of the bladder: a clinicopathologic analysis of 45 cases. Am J Surg Pathol 2007;31:1777-1787.
14. Rogers CG, Palapattu GS, Shariat SF, et al. Clinical outcomes following radical cystectomy for primary nontransitional cell carcinoma of the bladder compared to transitional cell carcinoma of the bladder. J Urol 2006;175:2048-2053; discussion 2053.
15. Zaghloul MS, Nouh A, Nazmy M, et al. Long-term results of primary adenocarcinoma of the urinary bladder: a report on 192 patients. Urol Oncol 2006;24:13-20.
16. Grignon DJ, Ro JY, Ayala AG, et al. Primary adenocarcinoma of the urinary bladder. A clinicopathologic analysis of 72 cases. Cancer 1991;67:2165-2172.
17. Wright JL, Porter MP, Li CI, et al. Differences in survival among patients with urachal and nonurachal adenocarcinomas of the bladder. Cancer 2006;107:721-728.
18. Zafuto E, Gazdovich S, Leyh-Bannurah SR, et al. Contemporary rates of pathological features and mortality for adenocarcinoma of the urinary bladder in the USA. Int J Urol 2017;24:117-123.
19. Roy S, Pradhan D, Ernst WL, et al. Next-generation sequencing-based molecular characterization of primary urinary bladder adenocarcinoma. Mod Pathol 2017;30:1133-1143.
20. Arslan B, Bozkurt IH, Yonguc T, et al. Clinical features and outcomes of nontransitional cell carcinomas of the urinary bladder: analysis of 125 cases. Urol Ann 2015;7:177-182.
21. Vincendeau S, de Lajarte-Thirouard AS, Bensalah K, et al. Neuroendocrine differentiation of bladder tumors. Prog Urol 2003;13:375-384.
22. Williams HA, Punjani N, Khan O, Power NE. The oncological outcomes of small cell carcinoma of the bladder. Can Urol Assoc J 2018;13:260-265.
23. Ou WT, Liang QL, Huang X, et al. Small cell carcinoma of the urinary bladder: a case report and review of the literature. Oncol Lett 2015;9:488-490.
24. Quek ML, Nichols PW, Yamzon J, et al. Radical cystectomy for primary neuroendocrine tumors of the bladder: the university of southern california experience. J Urol 2005;174:93-96.
25. Church DN, Bahl A. Clinical review - small cell carcinoma of the bladder. Cancer Treat Rev 2006;32:588-593.

26. Lohrisch C, Murray N, Pickles T, Sullivan L. Small cell carcinoma of the bladder: long term outcome with integrated chemoradiation. Cancer 1999;86:2346-2352.
27. Coelho HM, Pereira BA, Caetano PA. Large cell neuroen docrine carcinoma of the urinary bladder: case report and review. Curr Urol 2013;7:155-159.
28. Ayık E, Elpek Ö. Extragastrointestinal stromal tumors: localization and clinicopathological features. Turkiye Klinikleri J Med Pathol-Special Topics 2017;2:173-183.
29. He F, Fang Z, Zhu P, et al. Bladder extragastrointestinal stromal tumor in an adolescent patient: A case-based review. Mol Clin Oncol 2014;2:960-962.
30. Lee TK, Miyamoto H, Osunkoya AO, et al. Smooth muscle neoplasms of the urinary bladder: a clinicopathologic study of 51 cases. Am J Surg Pathol 2010;34:502-509.

*Original Article*

DOI: 10.4274/uob.galenos.2020.1734

*Bull Urooncol 2021;20(2):107-110*

# *The Investigation of Treatment Effects on Serum Biochemical Parameters in Bladder Cancer Diseases*

Oktay Üçer[1], Funda Kosova[2], Gökhan Temeltaş[1], Sedat Abuşoğlu[3], Ali Ünlü[3], Aylin Sepici Dinçel[4], Zeki Arı[2]

[1]*Celal Bayar University Faculty of Medicine, Department of Urology, Manisa, Turkey*
[2]*Celal Bayar University Faculty of Medicine, Department of Medical Biochemistry, Manisa, Turkey*
[3]*Selçuk University Faculty of Medicine, Department of Medical Biochemistry, Konya, Turkey*
[4]*Gazi University Faculty of Medicine, Department of Medical Biochemistry, Ankara, Turkey*

## Abstract

**Objective:** The most common cancer in smokers is bladder cancer (BC). Intravesical chemo immunotherapies are used to lower the risk of progression in patients who are at risk. Bacillus Calmette-Guérin immunotherapy is the most effective adjuvant therapy discovered. We aimed to evaluate the levels of arginine, citrulline, ornithine, symmetrically dimethylated arginine (SDMA), N-monomethyl-Larginine. (L-NMMA) or asymmetrically dimethylated arginine (ADMA) in patients with BC, as well as their relationship with methylarginine.

**Materials and Methods:** Blood samples were collected from all patients (n=30) and controls (group 1) prior to transurethral resection of bladder tumour (TURBT) (group 2), 20 days after TURBT (group 3) and at the end of intravesical immunotherapy 74 (group 4). The levels of serum methylated arginine were measured using ABSCIEX API 3200 tandem mass spectrometry system in positive ESI mode.

**Results:** In comparison to group 2, group 1's ADMA and arginine/total methylated arginine levels were 98 significantly lower (p=0.035 and p=0.049, respectively), while SDMA/ADMA, L-NMMA and arginine/ADMA levels (p=0.001, p=0.008 and p=0.017) increased, and no statistical difference was found for other parameters (p>0.05). When compared to group 3, ADMA, arginine, citrulline, methylated arginines and L-NMMA levels in group 2 (p=0.035, p=0.001, p=0.015, p=0.032, p=0.032) increased, while SDMA/ADMA levels (p=0.041) decreased.

**Conclusion:** The decrease in arginine and ADMA levels in non-muscle invasive BC patients is thought to be promising, and these markers may be useful in monitoring the diagnosis and treatment of patients.

**Keywords:** Bladder cancer, ADMA, arginine, citrulline, SDMA, L-NMMA

## Introduction

Bladder cancer (BC) is one of the most common cancers worldwide (1). The diagnosis of BC, the most common urinary tract tumour, is based on urinary cytology and white-light cystoscopy in patients suspected of having a bladder mass and haematuria (2). As a result, despite the fact that many drugs for BC have been developed, we need new agents for therapeutic and diagnostic purposes due to the toxicity and resistance caused by these drugs. Protein arginine methyltransferases (PRMTs) are enzymes that play a key role in important cellular events such as signal transduction and transcriptional activation and inhibition, by catalysing methylene residues (3,4) and by transferring methyl groups from S-adenosyl-1-methionine to terminal guanidino nitrogen atoms (5). Arginine methylation can generate asymmetric NG, NG-dimethylarginine as well as type I (PRMT5 and PRMT7) symmetrical NG and NkenG-, while S-adenosylmethionine (PRMT 1, 2, 3, 4, 6 and 8), used as a methyl donor, is a posttranslational modification catalysed by PRMTs (6), which are the functions of dimethylarginine. Through signal transduction, transcription and mRNA splicing, arginine methylation facilitates protein-protein interactions and protein localisation (7,8). There are three types of methylated arginine: monomethylated arginine (MMA), asymmetrically dimethylated arginine (ADMA) and symmetrically dimethylated arginine (SDMA) (9).

In general, histone ADMA is associated with active transcription, whereas histone SDMA is correlated with transcriptional repression (10). While histones are true PRMT substrates, the majority of nuclear arginine methylation is found in heterogeneous nuclear ribonucleoproteins, implying that PRMTs can also regulate gene expression post-transcriptionally (11).

**Cite this article as:** Üçer O, Kosova F, Temeltaş G, Abuşoğlu S, Ünlü A, Sepici Dinçel A, Arı Z. The Investigation of Treatment Effects on Serum Biochemical Parameters in Bladder Cancer Diseases. Bull Urooncol 2021;20(2):107-110

**Address for Correspondence:** Funda Kosova, Celal Bayar University Faculty of Medicine, Department of Medical Biochemistry, Manisa, Turkey
**Phone:** +90 533 557 36 29 **E-mail:** fundakosova@gmail.com **ORCID-ID:** orcid.org/0000-0001-8070-5067
**Received:** 06.05.2020 **Accepted:** 01.07.2020

After being converted to L-citrulline and dimethylarginine by hydrolysis (12), ADMA is obtained by arginine methylation in intracellular proteins by N-methyltransferases (13) of Type I protein arginine.

As a result, arginine methylation and PRMT structural defects are linked to carcinogenesis, metastasis and drug resistance (14,15). In light of this information, we believe PRMTs hold promise for cancer diagnosis and treatment. We aimed to evaluate the levels of arginine, citrulline, ornithine, SDMA, N-monomethyl-Larginine (L-NMMA) or ADMA in patients with BC, as well as their relationship with methylarginine.

## Materials and Methods

### Participants and Study Design

The study included 30 non-muscle invasive bladder cancer (NMIBC) patients and 30 control subjects (group 1) who applied to Manisa Celal Bayar University Faculty of Medicine, Department of Urology, and also patients without malignancy, chronic disease or infection as inclusion criteria. Furthermore, the study involved NMIBC patients with pTa (low grade) and ≥ pT2 UCB with transurethral resection of bladder tumour (TURBT) and only intravesical treatment. Blood samples were taken from all patients (n=30) before TURBT (group 2), 20 days after TURBT (group 3) and at the end of intravesical immunotherapy (group 4). All patients and controls who took part in the study provided informed consent, and the study protocol was approved by the Local Ethics Committee.

## Methods

Shimadzu LC-20AD system was used to analyse serum ADMA, SDMA, L-NMMA, arginine and citrulline (16). A total of 200 µL of 100 microliters (µL) internal standard serum in methanol was added and centrifuged before the supernatant was collected and dried under nitrogen gas. This dried extract was then dissolved in 200 µL of a freshly prepared butanol solution containing 5% (v/v) acetyl chloride for 20 minutes at 60°C. This solution was evaporated at 600°C using nitrogen gas, then dissolved in 100 µL of water-methanol (90:10, v/v) containing 0.1% (v/v) formic acid and loaded onto an ultra-performance liquid chromatography analytical column. A total of 40 µL was injected. Verieler is built with optimal cone and collision energy values, and the intraday and inter-day coefficients of variation are 8.6% and 10.1%, respectively.

### Statistical Analysis

When appropriate, data are expressed as the mean ± standard deviation or means with 95% confidence interval. The Mann-Whitney U test was used to examine differences in outcome measures among the groups, and $p<0.05$ was considered statistically significant. Moreover, statistical analysis was done using SPSS software package (15.0; SPSS, Chicago, IL).

## Result

The mean age in the patient group was found to be 67.27±8.44, while it was 65.74±7.22 in the control group. The difference in mean ages was not statistically significant (p=0.54). In comparison to group 2, ADMA and arginine/total methylated arginine levels in group 1 were significantly lower (p=0.035 and p=0.049, respectively), while SDMA/ADMA, L-NMMA and arginine/ADMA levels (p=0.001, p=0.008 and p=0.017) increased, and no statistical difference was found for other parameters ($p>0.05$). When compared to group 3, ADMA, arginine, citrulline, methylated arginines and L-NMMA levels in group 2 (p=0.035, p=0.001, p=0.015, p=0.032, p=0.032) increased, while SDMA/ADMA levels (p=0.041) decreased. Furthermore, ADMA and SDMA levels were higher in group 3, but arginine/ADMA ADMA/total methylarginine were lower than in group 4. Tables 1 and 2 summarise the mean ADMA, SDMA, L-NMMA, arginine, citrulline, arginine/ADMA, SDMA/ADMA, total methylated arginines and ADMA/methylated arginine levels in each group.

**Table 1. ADMA, SDMA, L-NMMA, arginine and citrulline levels in bladder cancer patients**

| | ADMA (uMol/L) | SDMA (uMol/L) | L-NMMA (uMol/L) | Arginine (uMol/L) | Citrulline (uMol/L) |
|---|---|---|---|---|---|
| Control | 0.196 | 0.211 | 0.26 | 118.57 | 44.55 |
| Before TURBT | 0.148 | 0.214 | 0.291 | 103.16 | 34.66 |
| After TURBT-1 | 0.188 | 0.206 | 0.423 | 192.64 | 47.53 |
| After TURBT-2 | 0.257 | 0.282 | 0.408 | 161 | 50.38 |

ADMA: Asymmetrically dimethylated arginine, SDMA: Symmetrically dimethylated arginine, L-NMMA: N-monomethyl-Larginine, TURBT: Transurethral resection of bladder tumour

**Table 2. Arginine/ADMA ratio, SDMA/ADMA ratio, total methylated arginines, ADMA/total methylated arginine levels in bladder cancer patients**

| | Arginine/ ADMA ratio | SDMA/ ADMA RATIO | Total methylated arginines | ADMA/ total methylated arginines |
|---|---|---|---|---|
| Control | 618.47 | 1.04 | 0.67 | 191.5 |
| Before TURBT | 791.5 | 1.57 | 0.65 | 165.78 |
| After TURBT-1 | 1262.39 | 1.2 | 0.82 | 249.81 |
| After TURBT-2 | 800.98 | 1.27 | 0.95 | 185.37 |

ADMA: Asymmetrically dimethylated arginine, SDMA: Symmetrically dimethylated arginine, TURBT: Transurethral resection of bladder tumour

## Discussion

BC is one of the most common types of cancers in men. Over 80% of bladder tumours are (NMIBC, i.e. Tis, Ta or T1), with the remaining 20% being muscle invasive BC or metastatic BC (17). Most BC are limited to the urothelium and lamina propria, and local treatment has been shown to be effective in many cases. In high-risk patients, an effect is achieved by inducing an immune response through tumour resection and Bacillus Calmette-Guérin to reduce the risk of recurrence (18). Cancer is one of the most common causes of death in the world, with a

rapidly increasing mechanism due to environmental and genetic factors, the mechanism of which has not been fully disclosed (17).

Today, research is being conducted on signal mechanisms, angiogenesis, apoptosis, metastasis and a variety of other mechanisms in order to gain a better understanding of cancer (19,20). Given the need to improve patient outcomes, it has recently become evident that experimental approaches (including novel chemotherapeutic regimens, biologic agents, immunotherapy and vaccines) are being studied. Arginine modification has been shown to affect DNA repair pathways associated with metastasis and genomic instability (8), while arginine methylation has been shown to be effective in RNA, signal transduction and transcription (21). We aimed to evaluate the levels of arginine, citrulline, ornithine, SDMA, L-NMMA or ADMA in BC patients, as well as their correlation with methylarginine.

Skeletal muscle plasticity has been identified as the regulator (PRMTs), and *in vitro* studies have shown that these are activated by the methyltransferase pathway, reshaping the muscle remodelling in this way (22). PRMT is an enzyme family that catalyses the addition of one or two methyl groups to the guanidine nitrogen atoms of arginine residues, altering the stability, localisation and/or activity of the labelled molecules (23). Recent research has found that arginine residues in proteins are important for methylation, as well as phosphate groups as control elements in protein functions of methyl groups in mammalian cells (21,24). The protein-DNA complex contains five donors of hydrogen bonds in the arginine structure, which also contains hydrogen bonds with arginine residues.

PRMTs are classified as Type I (PRMT1, 3, 4, 6 and 8) and Type II (PRMT5, 7 and FBXO11) based on their specific catalytic activities (12). S-adenosyl-L-methionine (SAM) is a PRMT family member that is produced by the methionine adenosyltransferase enzyme using methionine and adenosine triphosphate substrates. Moreover, SAM and L-arginine are used by all PRMTs to form the S-adenosylhomocysteine product (22).

As a result of PRMT activity, three types of methylarginines are formed: MMA, SDMA and ADMA (4), where non-specific PRMT produces MMA, type I PRMT generates ADMA, and type II PRMT forms SDMA, all of which are known as PRMT activity indicators (21,25).

PRMT1 and PRMT5 catalyse the reactions that produce ADMA and SDMA, demonstrating enzyme activities (25). The nitric oxide synthase (NOS) family, which includes endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS), is responsible for vasodilation and platelet aggregation in response to l-homoarginine (l-hArg). It catalyses the formation of nitric oxide (NO), which is one of its inhibitors, and is inhibited by MMA, ADMA and SDMAs in formed NOs (26). ADMA (13), which is formed by the methylation of arginine in intracellular proteins by type I protein arginine N-methyltransferases, turns into L-citrulline and dimethylarginine when hydrolysed by dimethylaminohydrolase (12). Yoshimatsu et al. (12) discovered that PRMT1, PRMT6 and serum-free ADMA levels increased in various types of cancer. It has been suggested that altering overexpressed PRMT activity in breast, prostate, lung, colon and BCs, as well as leukaemia, may be related to the treatment of these diseases (27). Neault et al. (28) showed that PRMT6 was suppressed indirectly by p21 expression by decreasing *p53* gene expression through methylation of PR3T6 in mouse embryonic fibroblasts. Yongchul et al. (8) demonstrated that PRMT6 in the nucleus was stained immunohistochemically positive in colorectal cancers. During the progression of muscle differentiation, Nicole et al. (4) observed an increase in ADMA levels alongside unchanged amounts of MMA and SDMA methylarginine species. The significant up-regulation in ADMA content was consistent with the rise in PRMT1 protein content (4). Despite the fact that Yoshimatsu et al. (12) demonstrated that Type I PRMT expressions increased ADMA serum levels in cancer patients, no studies on BC have been conducted. Any PRMT1 or PRMT6 expression reduction is likely to be beneficial for cancer treatment because it inhibits cancer cell growth (13). We discovered that the mean levels of ADMA and arginine/total methylated arginines in group 2 were significantly lower than those in group 1, while SDMA/ADMA, L-NMMA and arginine/ADMA levels were higher. Other parameters revealed no statistically significant differences. Moreover, group 2 has higher levels of ADMA, arginine, citrulline, methylated arginines and L-NMMAbut lower levels of SDMA/ADMA than group 3.

### Study Limitation

Our study has some limitations. The first one is that we do not know the long-term outcomes of patients, such as recurrence or progression. Further studies should be conducted to determine the relationship between these parameters and recurrence or progression. The second limitation is that the number of patients was relatively small. The results of our study should be confirmed in future studies involving more patients with BC.

## Conclusion

It is thought that decreases in arginine and ADMA levels in NMIBC patients and these markers can be promising in monitoring patient diagnosis and treatment. Moreover, methylated arginine levels may be useful fin predicting prognosis.

### Acknowledgements

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

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

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

**Financial Disclosure:** This work was supported by Research Fund of Manisa Celal Bayar University.

### Ethics

**Ethics Committee Approval:** The study protocol was approved by the Local Ethics Committee.

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

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

### Authorship Contributions

Supervision: G.T., Critical Review: G.T., Concept: G.T., F.K., Design: F.K., Data Collection or Processing: G.T., F.K., O.Ü., Analysis or Interpretation: G.T., F.K., S.A., A.Ü., A.S.D., Literature Search: G.T., F.K., Writing: G.T., F.K., Z.A.

## References


1. Luo K-W, Lung W-Y, Xie C, et al. EGCG inhibited bladder cancer T24 and 5637 cell proliferation and migration via PI3K/AKT pathway. Oncotarget 2018;9:12261-12272.
2. Drăgoescu PO, Tudorache Ş, Drocaş AI, et al. Improved diagnosis and long-term recurrence rate reduction for non-muscle-invasive bladder cancer patients undergoing fluorescent hexylaminolevulinate photodynamic diagnosis. Rom J Morphol Embryol 2017;58:1279-1283.
3. Kim SJ, Yoo BC, Uhm CS, Lee SW. Posttranslational arginine methylation of lamin A/C during myoblast fusion. Biochim Biophys Acta 2011;1814:308-317.
4. Nicole YS, Sean YN, Stephen LT, Vladimir L. Protein arginine methyltransferase expression and activity during myogenesis, Biosci Rep 2018;38:BSR20171533. doi: 10.1042/BSR20171533.
5. Stouth DW, van Lieshout TL, Shen NY, Ljubicic V. Regulation of skeletal muscle plasticity by protein arginine methyltransferases and their potential roles in neuromuscular disorders. Front Physiol 2017;8:870.
6. Paik WK, Paik DC, Kim S. Historical review: the field of protein methylation. Trends Biochem Sci 2007;32:146-152.
7. Bedford MT, Richard S. Arginine methylation an emerging regulator of protein function. Mol Cell 2005;18:263-272.
8. Yongchul L, Suyeun Y, Jung-A Y, et al. The prognostic significance of protein arginine methyltransferase 6 expression in colon cancer. Oncotarget 2018;9:9010-9020.
9. McCabe MT, Mohammad HP, Barbash O, Kruger RG. Targeting histone methylation in cancer. Cancer J 2017;23:292-301.
10. Wysocka J, Allis CD, Coonrod S. Histone arginine methylation and its dynamic regulation. Front Biosci 2006;11:344-355.
11. Di Lorenzo A, Bedford MT. Histone arginine methylation. FEBS Lett 2011;585:2024-2031.
12. Yoshimatsu M, Toyokawa G, Hayami S, et al, Dysregulation of PRMT1 and PRMT6, Type I arginine methyltransferases, is involved in various types of human cancers. Int J Cancer 2011;128:562-573.
13. Kielstein JT, Cooke JP. Should we measure asymmetric dimethylarginine in patients with coronary artery disease? Clin Chem 2007;53:161-163.
14. Yang Y, Bedford MT. Protein arginine methyltransferases and cancer. Nat Rev Cancer 2013;13:37-50.
15. Li T, Kong AN, Ma Z, et al. Protein arginine methyltransferase 1 may be involved in pregnane x receptor-activated overexpression of multidrug resistance 1 gene during acquired multidrug resistant. Oncotarget 2016;7:20236-20248. doi: 10.18632/oncotarget.7752.
16. Di Gangi IM, Chiandetti L, Gucciardi A, et al. Simultaneous quantitative determination of N(G), N(G)-dimethyl-L-arginine or asymmetric dimethylarginine and related pathway's metabolites in biological fluids by ultrahigh-performance liquid chromatography/electrospray ionization-tandem mass spectrometry. Anal Chim Acta 2010;677:140-148.
17. Zhang G, Gomes-Giacoia E, Dai Y, et al, Validation and clinicopathologic associations of a urine-based bladder cancer biomarker signature. Diagn Pathol 2014;9:200.
18. Teply BA, Kim JJ. Systemic therapy for bladder cancer - a medical oncologist's perspective, J Solid Tumors 2014;4:25 35.
19. Chen Q, Zhou Z, Shan L, et al. Association of the vascular endothelial growth factor -2578c/a polymorphism with cancer risk: a meta-analysis update. Biomed Rep 2014;2:823-830.
20. Temeltas G, Kosova F, Ucer O, et al. Effects of treatment on angiogenic (vascular endothelial growth factor-2 and matrix metalloproteinase-2) and antiangiogenic (endostatin and thrombospondin-1) factors in non-muscle invasive bladder carcinoma. J Uro Surg 2017;4:71-75.
21. Bedford MT, Clarke SG. Protein arginine methylation in mammals: who, what, and why. Mol Cell 2009;33:1-13.
22. Derek W. Stouth, Tiffany L. vanLieshout, Nicole Y. Shen and Vladimir Ljubicic, Regulation of Skeletal Muscle Plasticity by Protein Arginine Methyltransferases and Their Potential Roles in Neuromuscular Disorders, Front Physiol, 2017 Nov 1;8:870.
23. Paik WK, Kim S. Protein methylase I purification and properties of the enzyme. J Biol Chem 1968;243:2108-2114.
24. Najbauer J, Johnson BA, Young AL, Aswad DW. Peptides with sequences similar to glycine, arginine-rich motifs in proteins interacting with RNA are efficiently recognized by methyltransferase(s) modifying arginine in numerous proteins. J Biol Chem 1993;268:10501-10509.
25. Dhar S, Vemulapalli V, Patananan AN, et al. Loss of the major type I arginine methyltransferase PRMT1 causes substrate scavenging by other PRMTs. Sci Rep 2013;3:1311.
26. Tsikas D, Bollenbach A, Hanff E, Kayacelebi AA. Asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA) and homoarginine (hArg): the ADMA, SDMA and hArg paradoxes. Cardiovasc Diabetol 2018,4;17:1.
27. Baldwin RM, Morettin A, Côté J. Role of PRMTs in cancer: could minor isoforms be leaving a mark? World J Biol Chem 2014;5.115-129.
28. Neault M, Mallette FA, Vogel G, et al. Ablation of PRMT6 reveals a role as a negative transcriptional regulator of the p53 tumor suppressor. Nucleic Acids Res 2012;40:9513-9521.

*Original Article*

DOI: 10.4274/uob.galenos.2020.1885

*Bull Urooncol 2021;20(2):111-116*

# *Predictive Factors of Perioperative Significant Complications Following Partial Nephrectomy for Renal Cell Cancer*

Mehmet Çağlar Çakıcı[1], Nihat Karakoyunlu[2], Alihan Kokurcan[2], Görkem Özenç[2], Sercan Sarı[3], Emre Hepşen[4], Fatih Yalçınkaya[2]

[1]*İstanbul Medeniyet University, Göztepe Training and Research Hospital, Clinic of Urology, İstanbul, Turkey*
[2]*University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Clinic of Urology, Ankara, Turkey*
[3]*Bozok University Faculty of Medicine Hospital, Clinic of Urology, Yozgat, Turkey*
[4]*Yıldırım Beyazıt University, Yenimahalle Training and Research Hospital, Clinic of Urology, Ankara, Turkey*

## Abstract

**Objective:** Estimating surgical complications is crucial to assess the benefit-harm balance of partial nephrectomy (PN), a complex surgical option compared to radical nephrectomy. This study aimed to assess the factors affecting the occurrence of modified Clavien-Dindo grade 2 or higher complications after PN.
**Materials and Methods:** Data of patients who underwent PN due to renal cancer from January 2015 to June 2018 were prospectively collected. Database was analysed retrospectively by dividing into two groups with Clavien-Dindo grade 0-1 complications (group 1) and with grade 2 or higher complications (group 2). The resection technique was classified by the surgeon as enucleation, enucleo-resection or resection according to the Surface-Intermediate-Base (SIB) margin scores of 0, 1 and 2, respectively. Factors affecting the occurrence of grade 2 or higher complications were evaluated by univariate and multivariate regression analysis.
**Results:** A total of 161 patients were included in the study. The overall rate of perioperative complications was 18.6%. Twenty-four patients (14.9%) had grade 2 or higher complications and 11 patients (6.8%) had serious complications (grade 3 or higher). SIB-score was 0 in 103 (63.9%) patients, 1 in 36 (22.4%) patients and 2 in 22 (13.7%) patients. Multivariate binary logistic regression analysis revealed that the C-index [odds ratio (OR): 0.224, 95% confidence interval (CI): 0.092-0.493, p=0.001], laparoscopic surgical technique (OR: 12.668, 95% CI: 2.825-59.326, p=0.001), and SIB-score 1-2 (OR: 2.852, 95% CI: 1.416-9.826, p=0.002) are independent factors in predicting complications of Clavien-Dindo grade 2 or higher.
**Conclusion:** C-index, laparoscopic approach and resection techniques (SIB-score 1-2) are independent factors in predicting perioperative complications of Clavien-Dindo grade 2 or higher following PN.
**Keywords:** Complication, partial nephrectomy, predictors, renal cell cancer, resection technique

## Introduction

The incidence of renal cell cancer (RCC) is the 6th most common type of cancer in men and the 10th most common type of cancer in women. Its rate among all cancers is 5% in men and 3% in women (1). Radical nephrectomy was the only treatment option for these tumours in the past; however, the frequency of partial nephrectomy (PN) has been increasing gradually, as studies reported in recent years demonstrated better renal function and similar oncological results (2). A study even reported that PN had better survival outcomes (3).

However, complications are not uncommon in these challenging cases. Complication rates after PN have been reported up to 30% (4,5), and major life-threatening complications have been reported with a rate of 3%-6% (6). Numerous renal scoring systems have been identified to predict complications. However, results of these scoring systems also vary. Thus, revealing the benefit-harm balance of PN is thoroughly necessary. Evaluating complications plays an important role in reducing perioperative deficiencies and improving patient care. Complications that require additional medical or surgical treatment or require intensive care can have devastating effects on the patient.

**Cite this article as:** Çakıcı MÇ, Karakoyunlu N, Kokurcan A, Özenç G, Sarı S, Hepşen E, Yalçınkaya F. Predictive Factors of Perioperative Significant Complications Following Partial Nephrectomy for Renal Cell Cancer. Bull Urooncol 2021;20(2):111-116

**Address for Correspondence:** Mehmet Çağlar Çakıcı, İstanbul Medeniyet University, Göztepe Training and Research Hospital, Clinic of Urology, İstanbul, Turkey
**Phone:** +90 216 566 40 00 **E-mail:** mcaglarcakici@hotmail.com **ORCID-ID:** orcid.org/0000-0002-0176-5887
**Received:** 06.10.2020 **Accepted:** 14.12.2020

Therefore, this study aimed to determine the factors affecting significant complications.

## Materials and Methods

Data of patients who underwent PN for RCC from January 2015 to June 2018 were prospectively collected. Demographic data, radiological features, perioperative characteristics, histopathological and follow-up outcomes of patients were recorded. Computed tomography and/or magnetic resonance imaging were used for preoperative kidney and tumour imaging, and thoracic X-ray or computed tomography data were recorded. The size of the tumour, its location in the kidney, clinical stage, surgical technique and characteristics were recorded using the patient follow-up cards. Tumour size was calculated as the longest diameter of the tumour. Renal scoring systems such as tumour centrality index (C-index), Radius exophytic-endophytic nearness anterior-posterior location (RENAL) nephrometry score and preoperative aspects and dimensions used for anatomic (PADUA) classification were calculated by the same urologists in a team of two. Surgeries were undertaken by a team of 4 experienced urologists with at least 10 years of urooncological experience. Histopathological evaluations were performed by a pathologist with 18 years of experience.

The resection technique was divided into 3 categories by the surgeon according to the Surface-Intermediate-Base (SIB) margin scores. The SIB margin score of these categories, defined as enucleation, enucleo-resection or resection, was recorded as 0, 1 or 2, respectively. Perioperative complications were assessed according to the modified Clavien-Dindo classification (7). Grade 2 or higher complications were defined as significant complications. Factors affecting the occurrence of significant complications were evaluated by univariate and multivariate regression analysis. Impact of SIB-score on significant complications of PN was also assessed. This database was reviewed retrospectively by dividing into two groups with Clavien-Dindo grade 0-1complications (group 1) and with grade 2 or higher complications (group 2). Masses with benign pathology (n=12), non-RCC malignant masses (n=9), and patients with missing data or who have not been evaluated for complications (n=24) were excluded from the current study. This study was approved by the institutional research ethics committee of our tertiary health care provider hospital (İnstitutional review board decision number IRB-97/11, dated 05.10.2020).

### Statistical Analysis

One-sample Kolmogorov-Smirnov test was used to control the distribution of data for numerical variables. These quantitative variables were compared with Student's t-test when parametric test criteria were found. In the absence of these criteria, Mann-Whitney U test was used. Pearson chi-square test and Fisher's exact test were used to determine whether a difference between percentages of categorical variables is present. Binary logistic regression analysis was used to obtain independent risk factors affecting major complications after PN. The probability of first type error was $\alpha$=0.05 for all tests. Statistical analysis of the study was performed using the International Business Machines Statistical Package for the Social Sciences 22.0 package programme.

## Results

Out of 206 patients who underwent PN in our clinic, data of 161 patients were analysed in the study (Figure 1). The overall rate of perioperative complications was 18.6%. A total of 24 patients (14.9%) had grade 2 or higher complications and 11 patients (6.8%) had serious complications (grade 3 or higher) (Table 1). The mean age was 59.2±12.4 years in group 1 and 57.1±13.1 years in group 2. Interestingly, female gender is dominant in

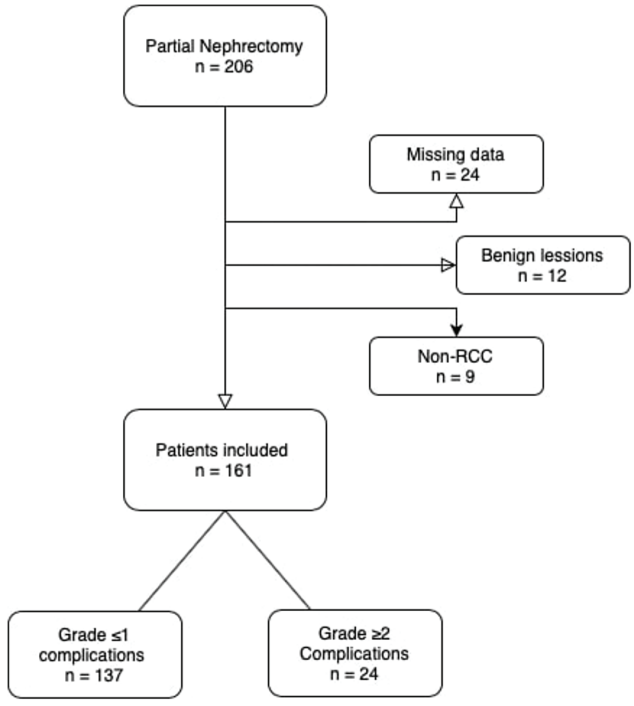


**Figure 1.** Flow chart of patients who met study inclusion and exclusion criteria
RCC: Renal cell cancer

**Table 1. Clavien-Dindo classification of surgical complications**

| Grade | Number of patients, n (%) | Definition |
|---|---|---|
| Grade 1 | 6 (3.7) | Any deviation from the normal postoperative course without the need for pharmacological treatment other than antiemetics, antipyretics, analgesics, diuretics, electrolytes or physiotherapy. Wound infections opened at the bedside. |
| Grade 2 | 13 (8.1) | Requiring pharmacological treatment with drugs other than which were allowed for grade I complications.<br>Blood transfusions and total parenteral nutrition. |
| Grade 3 | 6 (3.7) | Requiring surgical, endoscopic or radiological intervention. |
| Grade 4 | 4 (2.5) | Life-threatening complication requiring intensive care unit management. |
| Grade 5 | 1 (0.6) | Death of the patient. |

group 2, but not statistically significant (p=0.097). Among the renal nephrometry systems, only the C-index was statistically different. The C-index was higher in group 1 compared to group 2 (2.7±1.1 vs 1.8±0.8, respectively, p=0.006) (Table 2). A laparoscopic procedure was performed in 33.3% of patients in group 1 and 62.5% of patients in group 2 (p=0.016). SIB-score was 0 in 103 (63.9%) patients, 1 in 36 (22.4%) patients and 2 in 22 (13.7%) patients. Tumour excision was performed in 45 patients (32.8%) in group 1 and in 13 patients (54.2%) in group 2 by resection or enucleo-resection method (p=0.045). Histopathological outcomes were similar in both groups. Intraoperative blood transfusion was administered to 5 patients (3.1%), whereas 7 patients (4.3%) received a postoperative blood transfusion. Intraoperative blood transfusion was performed in 2 patients (1.5%) in group 1, which was not required during the postoperative period, whereas blood transfusion was given to 10 patients (41.7%) in group 2 during the perioperative period. The volume of intraoperative bleeding was higher in group 2 than in group 1 (p=0.002). Similarly, haemoglobin drop was more pronounced in group 2 (p=0.048). In addition, hospitalisation in group 2 was longer as expected (p<0.001) (Table 3). Multivariate binary logistic regression analysis revealed that the C-index [odds ratio (OR): 0.224, 95% confidence interval (CI): 0.092-0.493, p=0.001], laparoscopic surgical technique (OR: 12.668, 95% CI: 2.825-59.326, p=0.001) and SIB-score of 1-2 (OR: 2.852, 95% CI: 1.416-9.826, p=0.002) are independent factors in predicting complications of Clavien-Dindo grade 2 or higher (Table 4).

**Table 2. Demographic characteristics of patients and radiological assessments of renal masses**

| | Group 1 (n=137) | Group 2 (n=24) | p-value |
|---|---|---|---|
| Age, years | 59.2±12.4 | 57.1±13.1 | 0.372 |
| Gender (male/female) | 82/55 | 10/14 | 0.097 |
| Body mass index, kg/m² | 27.1±4.4 | 28.9±6.3 | 0.104 |
| Charlson Comorbidity index | 3.4±2.1 | 2.8±2.2 | 0.275 |
| **ECOG performance score** | | | |
| 0 | 50 (36.5) | 8 (33.3) | 0.876 |
| 1 | 53 (38.7) | 11 (45.8) | |
| 2 | 30 (21.9) | 4 (16.7) | |
| 3 | 4 (2.9) | 1 (4.2) | |
| Tumour size, mm | 36.2±15.2 | 41.6±16.8 | 0.208 |
| PADUA score | 8.5±1.9 | 9.2±1.6 | 0.194 |
| RENAL nephrometry score | 7.0±1.8 | 7.8±2.2 | 0.096 |
| C-index | 2.7±1.1 | 1.8±0.8 | 0.006 |

ECOG: Eastern cooperative oncology group, PADUA: Preoperative aspects and dimensions used for anatomic classification, RENAL: Radius exophytic-endophytic nearness anterior-posterior location nephrometry score, C-index: Centrality index

## Discussion

Estimating surgical complications is crucial to assess the benefit-harm balance of PN, a complex surgical option compared to radical nephrectomy. In the current study, the overall perioperative surgical complication rate was 18.6%, and the major complication (grade 3 or higher) rate was 6.8%. Perioperative complication rates of PN have been reported in the literature up to 30% (4,5). Mari et al. (8) reported the total and major complication rates as 10.2% and 2.5%, respectively. In the perioperative outcomes of the Italian RECORd 1 study

**Table 3. Perioperative characteristics, resection techniques and histopathological outcomes of patients**

| | Group 1 (n=137) | Group 2 (n=24) | p-value |
|---|---|---|---|
| **Surgical technique, n (%)** | | | **0.016** |
| Open | 87 (66.7) | 9 (37.5) | |
| Laparoscopic | 50 (33.3) | 15 (62.5) | |
| **Surgical approach, n (%)** | | | **0.720** |
| TP/RP | 21/116 | 3/21 | |
| Presence of ischaemia, n (%) | 93 (67.9) | 15 (62.5) | 0.102 |
| Ischaemia time, min (± SD) | 23.0±5.6 | 25.8±7.6 | 0.193 |
| **SIB-score, n (%)** | | | **0.039** |
| 0 (Enucleation) | 92 (67.2) | 11 (45.8) | |
| 1 (Enucleo-resection) | 30 (21.9) | 6 (25) | |
| 2 (Resection) | 15 (10.9) | 7 (29.2) | |
| **SIB-score subgroup, n (%)** | | | **0.045** |
| Enucleation | 92 (67.2) | 11 (45.8) | |
| Resection | 45 (32.8) | 13 (54.2) | |
| Operative time, min | 112.6±32.4 | 126.9±31.1 | 0.069 |
| Bleeding volume, mL | 319.2±139.2 | 541.3±401.2 | **0.002** |
| Haematocrit drop, % | 7.4±3.3 | 9.7±6.3 | 0.097 |
| Haemoglobin drop, g/dL | 2.4±1.0 | 3.3±2.1 | **0.048** |
| Serum creatinine elevation, mg/dL | 0.2±0.2 | 0.3±0.4 | 0.246 |
| eGFR decrease, mL/min/1.73 m² | 4.3±16.7 | 9.1±20.2 | 0.268 |
| Hospitalisation, day | 3.8±1.4 | 6.9±4.5 | **<0.001** |
| **pT stage, n (%)** | | | 0.178 |
| pT1 | 132 (96.4) | 21 (87.5) | |
| pT2 | 3 (2.2) | 2 (8.3) | |
| pT3 | 2 (1.4) | 1 (4.2) | |
| **Subtype of RCC, n (%)** | | | 0.884 |
| Clear cell | 110 (80.3) | 20 (83.3) | |
| Papillary | 16 (11.7) | 2 (8.3) | |
| Chromophobe | 8 (5.8) | 1 (4.2) | |
| Other | 3 (2.2) | 1 (4.2) | |
| **Nuclear grade, n (%)** | | | 0.070 |
| Low grade (I-II) | 104 (75.9) | 13 (54.2) | |
| High grade (III-IV) | 21 (15.3) | 8 (33.3) | |
| Not available | 12 (8.8) | 3 (12.5) | |

TP: Transperitoneal, RP: Retroperitoneal, SIB: Surface-intermediate-base margin scores, eGFR: Estimated glomerular filtration rate, pT: Pathological T-stage, RCC: Renal cell cancer, SD: Standard deviation

| Table 4. Univariate and multivariate binary logistic regression analysis of factors affecting complications after partial nephrectomy | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Univariate model | | | | | Multivariate model | | | | |
| | OR (95% CI) | | | | p | OR (95% CI) | | | | p |
| Age, years | 0.987 | 0.958 | - | 1.028 | 0.364 | - | - | - | - | - |
| Female gender | 2.137 | 0.984 | - | 6.911 | 0.066 | - | - | - | - | - |
| Body mass index, kg/m² | 1.132 | 0.914 | - | 1.451 | 0.098 | - | - | - | - | - |
| Charlson Comorbidity index | 0.903 | 0.719 | - | 1.168 | 0.274 | - | - | - | - | - |
| ASA score | | | | | | | | | | |
| 1-2 | 1.014 | 0.988 | - | 1.042 | 0.340 | - | - | - | - | - |
| 3-4 | 1.420 | 0.780 | - | 2.18 | 0.180 | | | | | |
| Tumour size, mm | 1.014 | 0.996 | - | 1.034 | 0.221 | - | - | - | - | - |
| PADUA score | 1.256 | 0.728 | - | 1.812 | 0.283 | - | - | - | - | - |
| RENAL nephrometry score | 1.318 | 0.886 | - | 1.827 | 0.102 | - | - | - | - | - |
| C-index | 0.368 | 0.182 | - | 0.724 | 0.011 | 0.224 | 0.092 | - | 0.493 | **0.001** |
| Surgery technique, Laparoscopy | 3.210 | 1.097 | - | 9.112 | 0.022 | 12.668 | 2.825 | - | 59.326 | **0.001** |
| Retroperitoneal approach | 1.820 | 0.382 | - | 8.410 | 0.428 | - | - | - | - | - |
| SIB-score (1-2), Enucleo-resection Resection | 1.984 | 1.030 | - | 5.260 | 0.034 | 2.852 | 1.416 | - | 9.826 | **0.002** |
| Operative time | 1.492 | 0.923 | - | 2.258 | 0.092 | - | - | - | - | - |

*The p-value of the model was <0.001 and the R-square was 0.283.
ASA: American Society of Anaesthesiologists, PADUA: Preoperative aspects and dimensions used for anatomic classification, RENAL: Radius exophytic/endophytic nearness anterior/posterior location nephrometry score, C-index: Centrality index, SIB: Surface-intermediate-base margin scores, CI: Confidence interval, OR: Odds ratio

designed between 2008 and 2012, these rates were reported as 13.1% and 3.5%, respectively (5). Similar to our current study, the overall complication rate was 17.8%, whereas the grade ≥3a complication rate was reported as 5% in the study, including 1,044 patients who underwent PN in 2001-2012 as participated by 10 centres (9). Complication rates were very high in a study participated by approximately 2,000 patients that underwent PN with older and high comorbidity scores, the total complication rate was reported as 37%. The data of this study were obtained from SEER database registry (4).

The relationship between resection techniques and complications has also been examined in many studies (10,11,12,13). Standard or traditional technique resects a width approximately 5-10 mm of paratumour tissue for ensuring a negative surgical margin (14,15). Minervini et al. (10) reported that grade >2 complications more frequently occurred after enucleo-resection than after enucleation (10.7% vs 4.2%, p=0.01) and resection (10.7% vs 3.3%, p=0.04) technique. Similar to our study, Takagi et al. (11) found that enucleation was associated with lower complication rate. Unlikely, the resection technique was reported to not affect the complication (12). Dong et al. (13) stated that the overall complication rates of enucleo-resection and standard technique in laparoscopic PN cases were similar (11.2% vs 16.3%, respectively, p=0.3), and that enucleo-resection technique caused less bleeding.

Moreover, the renal score was reported to be associated with the incidence of complications (16). The complication rate increases as the tumour approaches the centre of the kidney. In our study, tumour centrality determined by C-index was one of the independent risk factors predicting grade >2 complications. In another study, tumour size was reported to be a predictive factor for complication (17,18,19,20). Schiavina et al. (18) noticed that the diameter of clinical tumour was significantly correlated to grade 3-4 complications. The common feature of all these renal scoring systems is the aim to predict the difficulty of surgery and complications that may occur. PADUA and RENAL nephrometry scores were higher in group with grade >2 complications in our current study; however, only the C-index was found to be statistically significant.

In a study participated by 1,308 patients comparing open, laparoscopic and robotic PN, intraoperative complications were found to be statistically significantly higher in laparoscopic technique (p=0.001). In the same study, two groups were not different from each other for grade 3 and higher complications (21). However, only intraoperative complications were evaluated instead of perioperative complications as in our study. In the present study, grade >2 complications were found to be higher in patients who underwent laparoscopic PN. The operation time was not statistically significantly different between two groups; however, it may have played a role in the increase of major complications in laparoscopic cases. The transperitoneal and retroperitoneal approach have been used for PN according to tumour characteristics and/or surgeon's preferences. In addition, the transperitoneal approach offers a greater working area and well-known landmarks but requires bowel mobilisation to demonstrate the kidney. The retroperitoneal approach has positive aspects such as not requiring bowel mobilisation; however, with shorter operative time and direct access to the kidney, disorientation can be seen without enough surgical experience. Moreover, it offers a more convenient access,

especially in posteriorly located tumours (22). The retroperitoneal approach is mostly preferred due to the experience in our clinic. Both approach methods have positive and negative aspects; however, we think that complications will be reduced by using the method with extensive surgical experience.

The traditional resection in PN has been reported to cause more postoperative bleeding and complications than enucleo-resection. In the same study, the rate of total complications was found to be similar (13). However, most studies reported that enucleation technique causes less complication than enucleo-resection or resection (10,11,12,23). The technique of dissecting the renal mass from the renal parenchyma is used in the avascular plane extending along the fibrous pseudo-capsule in enucleation. Therefore, enucleation appears to be more minimally invasive compared to resection techniques as it will cause less disruption in the vascular structure. Similarly, the resection technique in our study was performed more frequently in the group with significant complications. The bleeding volume and haemoglobin drop were also higher in this group, as expected. A statistical difference was observed; however, due to a small number of patients who applied blood transfusion, a definitive conclusion could not be correctly reached. In addition, major complications result in longer hospitalisations to complete treatment. In our study, hospitalisation was longer in group 2.

A multivariable analysis was established to predict the risk of occurrence of perioperative significant complications following PN. Age, gender, body mass index, comorbidity score, tumour size, tumour location, surgical approach and techniques were analysed in this model, which was constructed to predict significant life-threatening complications including blood transfusion. C-index, laparoscopic technique and SIB-score 1-2 were significant predictive factors of perioperative significant complications. We found that as the centrality of the tumour increased, the complication rates increased (OR: 0.224, p=0.001). According to the study results, laparoscopic PN increased the risk of complications by 12,668 times compared to open PN. Additionally, we revealed that the use of enucleo-resection or resection techniques in tumour excision increased the risk of significant complications by 2.852 times (p=0.002).

### Study Limitations

Several limitations of this study warrant mention in addition to the retrospective design and a population of tertiary care patients. The relatively small number of patients with major complications after PN may have affected the results. Additionally, excision techniques selection was dependent upon surgeons. Finally, SIB-score determination inherently shows a certain degree of inter-observer subjectivity. Nonetheless, despite these limitations, renal scoring and SIB-score were determined by the same two urologists. In addition, one of the strengths of our study is that all cases belong to a single centre.

## Conclusion

Major complications that occur after PN may have significant effects on the patient and may be life-threatening. Therefore, it is very important that these complications are detected and treated early. Tumour centrality index, laparoscopic approach and resection techniques (SIB-score 1-2) are independent factors in predicting perioperative complications of Clavien-Dindo grade 2 or higher after PN.

### Acknowledgements

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

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

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

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

### Ethics

**Ethics Committee Approval:** This study was approved by the institutional research ethics committee of our tertiary health care provider hospital (İnstitutional review board decision number IRB-97/11, dated 05.10.2020).

**Informed Consent:** Retrospective study.

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

### Authorship Contributions

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

## References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin.2018;68:7-30.
2. Robson CJ, Churchill BM, Anderson W. The results of radical nephrectomy for renal cell carcinoma. J Urol 1969;101:297-301.
3. Crépel M, Jeldres C, Perrotte P, et al. Nephron-sparing surgery is equally effective to radical nephrectomy for T1BN0M0 renal cell carcinoma: a population-based assessment. Urology 2010;75:271-275.
4. Larcher A, Fossati N, Tian Z, et al. Prediction of complications following partial nephrectomy: implications for ablative techniques candidates. Eur Urol 2016;69:676-682.
5. Mari A, Antonelli A, Bertolo R, et al. Predictive factors of overall and major postoperative complications after partial nephrectomy: results from a multicenter prospective study (The RECORd 1 project). Eur J Surg Oncol 2017;43:823-830.
6. Pierorazio PM, Johnson MH, Patel HD, et al. Management of renal masses and localized renal cancer: systematic review and meta-analysis. J Urol 2016;196:989-999.
7. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-213.
8. Mari A, Campi R, Schiavina R, et al. Nomogram for predicting the likelihood of postoperative surgical complications in patients treated with partial nephrectomy: a prospective multicenter observational study (the RECORd 2 project). BJU Int 2019;124:93-102.
9. Fernando A, Fowler S, O'Brien T. Nephron-sparing surgery across a nation – outcomes from the British Association of Urological Surgeons 2012 national partial nephrectomy audit. BJU Int 2016;117:874-882.
10. Minervini A, Campi R, Lane BR, et al. Impact of resection technique on perioperative outcomes and surgical margins after partial

nephrectomy for localized renal masses: a prospective multicenter study. J Urol 2020;203:496-504.

11. Takagi T, Kondo T, Tachibana H, et al. Comparison of surgical outcomes between resection and enucleation in robot-assisted laparoscopic partial nephrectomy for renal tumors according to the surface-intermediate-base margin score: a propensity score-matched study. J Endourol 2017;31:756-761.
12. Citamak B, Haberal HB, Akdogan B. Assessing the Association of Surface-Intermediate-Base Margin Score with perioperative outcomes and parenchymal volume preserved during partial nephrectomy. Urol Int 2020;104:781-788.
13. Dong W, Lin T, Li F, et al. Laparoscopic partial nephrectomy for t1 renal cell carcinoma: comparison of two resection techniques in a multi-institutional propensity score-matching analysis. Ann Surg Oncol 2016;23:1395-1402.
14. Li QL, Guan HW, Zhang QP, et al. Optimal margin in nephron sparing surgery for renal cell carcinoma 4 cm or less. Eur Urol 2003;44:448-451.
15. Marshall FF. Is nephron-sparing surgery appropriate for a small renal cell carcinoma? Lancet 1996;348:72-73.
16. Shi N, Zu F, Shan Y, et al. The value of renal score in both determining surgical strategies and predicting complications for renal cell carcinoma: A systematic review and meta-analysis. Cancer Med 2020;9:3944-3953.
17. Zhang Z-Y, Tang QI, Li X-S, et al. Clinical analysis of the PADUA and the RENAL scoring systems for renal neoplasms: a retrospective study of 245 patients undergoing laparoscopic partial nephrectomy. Int J Urol 2014;21:40-44.
18. Schiavina R, Novara G, Borghesi M, et al. PADUA and R.E.N.A.L. nephrome- try scores correlate with perioperative outcomes of robot-assisted partial nephrectomy: analysis of the Vattikuti Global Quality Initiative in Robotic Urologic Surgery (GQI-RUS) database. BJU Int 2017;119:456-463.
19. Tanagho YS, Kaouk JH, Allaf ME, et al. Perioperative complica- tions of robot-assisted partial nephrectomy: analysis of 886 pa- tients at 5 United States centers. Urology 2013;81:573-579.
20. Antonelli A, Ficarra V, Bertini R, et al. Elective partial nephrec- tomy is equivalent to radical nephrectomy in patients with clinical T1 renal cell carcinoma: results of a retrospective, comparative, multi-institutional study. BJU Int 2012;109:1013-1018.
21. Chang KD, Abdel Raheem A, Kim KH, et al. Functional and oncological outcomes of open, laparoscopic and robot-assisted partial nephrectomy: a multicentre comparative matched-pair analyses with a median of 5 years' follow-up. BJU Int 2018;122:618-626.
22. Wright JL, Porter JR. Laparoscopic partial nephrectomy: comparison of transperitoneal and retroperitoneal approaches. J Urol 2005;174:841-845.
23. Cao DH, Liu LR, Fang Y, et al. Simple tumor enucleation may not decrease oncologic out- comes for T1 renal cell carcinoma: a systematic review and meta-analysis. Urol Oncol 2017;35:661.

*Original Article*

DOI: 10.4274/uob.galenos.2020.1707

*Bull Urooncol 2021;20(2):117-121*

# *Postoperative and Mid-term Outcomes of Unclassified Renal Cell Carcinoma*

Serdar Çelik[1], Canan Altay[2], Müslim Doğan Değer[3], Ozan Bozkurt[3], Ömer Demir[3], Burçin Tuna[4], Kutsal Yörükoğlu[4], Mustafa Seçil[2], Güven Aslan[3]

[1]*University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital, Clinic of Urology, İzmir, Turkey*
[2]*Dokuz Eylül University Faculty of Medicine, Department of Radiology, İzmir, Turkey*
[3]*Dokuz Eylül University Faculty of Medicine, Department of Urology, İzmir, Turkey*
[4]*Dokuz Eylül University Faculty of Medicine, Department of Pathology, İzmir, Turkey*

## Abstract

**Objective:** To present the postoperative and oncological outcomes of patients diagnosed with unclassified renal cell carcinoma (uRCC).
**Materials and Methods:** Radiological and pathological data of patients who underwent radical nephrectomy for renal tumour diagnosed with uRCC according to histopathologic evaluation were investigated between 2006 and 2013. Follow-up data, such as metastasis-free and overall survivals, were also evaluated. Patients' characteristics and data were compared between localised tumour (T1-T2) and locally invasive tumour (T3-T4) groups and metastasis positive and negative groups during follow-up, separately.
**Results:** A total of 17 patients participated in the study, wherein 7 had adrenalectomy in addition to radical nephrectomy and 3 had lymph node dissection. The mean tumour diameter was 91.9±44 mm (30-200 mm), and seven patients were pathologically T3a, two were T3b and one patient had T4 tumour, whereas eight had Fuhrman grade 4 and five had Fuhrman grade 3 tumours. Pathologically, seven patients had tumours with sarcomatoid features, whereas four had microvascular invasion and seven had renal sinus invasion. T-stage correlated with renal sinus invasion and was identified as an important factor in metastasis progression. The overall survival time was observed to be low in locally invasive and metastasis positive groups. Nevertheless, differences were not statistically significant. In the investigation of factors affecting metastasis development, microvascular invasion and renal sinus invasion were significant.
**Conclusion:** The study revealed more aggressive nature (advanced stage, bigger tumour, more aggressive histopathological features and more metastasis and shorter survival on follow-up) of uRCC tumours, even without obtaining statistically significant differences.
**Keywords:** Renal cell carcinoma, mid-term follow-up, survival, unclassified renal cell carcinoma

## Introduction

Renal cell carcinomas (RCC) contains the most-commonly observed subtypes of conventional (clear cell) RCC (cRCC), chromophile (papillary) RCC and chromophobe RCC. Additionally, apart from these three, collecting duct carcinoma was described. In 1997, the World Health Organization (WHO) classified RCCs not meeting the criteria for these four types as a fifth type called unclassified RCCs (uRCC) (1,2,3,4,5,6,7). The effect of each RCC subtype on prognosis is reported at certain rates, with many studies available for the commonly observed subtypes. However, very few studies assessing the effect of uRCC on prognosis are reported and many have very small series (4,5,6,7,8,9,10,11). This situation is due to the fact that uRCC comprise 3%-5% of all RCC (2,12). Studies about uRCC have generally reported them as heterogeneous, high grade and aggressive tumours with high metastasis rates and low life expectancy (4,5,12).

This study aimed to present the mid-term follow-up outcomes of patients diagnosed with uRCC along with radiologic, pathologic and clinical data because uRCC comprises rarely-observed aggressive tumours of the kidney.

## Materials and Methods

Patients diagnosed with uRCC according to the 2004 WHO criteria after radical nephrectomy treatment at our clinic from 2006 to 2013 were retrospectively evaluated in accordance with the Helsinki Declaration. Demographic data (age and gender), radiologic data (tumour diameter, laterality, location, adrenal

**Cite this article as:** Çelik S, Altay C, Değer MD, Bozkurt O, Demir Ö, Tuna B, Yörükoğlu K, Seçil M, Aslan G. Postoperative and Mid-term Outcomes of Unclassified Renal Cell Carcinoma. Bull Urooncol 2021;20(2):117-121

**Address for Correspondence:** Serdar Çelik, University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital, Clinic of Urology, İzmir, Turkey
**Phone:** +90 505 701 96 31 **E-mail:** serdarcelik84@hotmail.com **ORCID-ID:** orcid.org/0000-0003-0939-9989
**Received:** 08.04.2020 **Accepted:** 03.05.2020

invasion, lymph node metastasis and central necrosis), pathologic data [pathologic T-stage, tumor-node-metastasis (TNM) stage, Fuhrman grade, sarcomatoid features, microvascular invasion, renal vein invasion, perinephric invasion and renal sinus invasion, adrenal invasion and lymph node metastasis], intraoperative data [operation time, need for adrenalectomy and lymph node dissection (LND)], need for adjuvant treatment (interferon-alpha and sunitinib treatments), laboratory data and indexes [neutrophil/lymphocyte ratio (NLR), albumin/globulin ratio (AGR), aspartate aminotransferase/alanine aminotransferase (De-Ritis) ratio (AAR), lactate dehydrogenase (LDH), platelet levels and calcium levels] and postoperative oncological data (occurrence of metastasis, overall survival, metastasis-free survival and mortality) were investigated. LND was performed for only detected positive lymph nodes on radiological imaging and/or during exploration. Patients were divided into two groups as pathologic T1 and T2 (localised tumours) and pathologic T3 and T4 (locally invasive) tumours; then all patients were divided again into two new different groups as those who were metastasis positive or negative in follow-up. Patient data were compared between groups.

### Statistical Analysis

Patients' data were comparatively assessed between groups using the Mann-Whitney U test and Pearson $\chi^2$ test. Significant data were then assessed with the multivariate binary logistic regression analysis. Overall survival and metastasis-free survival were evaluated with the Kaplan-Meier survival analysis. Statistical Package for the Social Sciences (Version 20.0; SPSS, Chicago, Illinois, USA) programme was used for all statistical analyses. Data are given as mean and standard deviation; however, statistical analyses were calculated using median values. For analysis results, a p-value of <0.05 was accepted as significant.

## Results

A total of 17 patients diagnosed with uRCC were evaluated in the study. Characteristics and radiological findings from all patients are given in Table 1. In the examination of radiological data, nine patients had upper pole tumour and one had both adrenal gland invasion and T4 stage tumour findings. In a total of 10 patients who had upper pole tumour including the radiological T4 patient, 7 underwent radical nephrectomy and additional adrenalectomy. Lymph node metastasis on preoperative radiological imaging was observed in three patients who then underwent radical nephrectomy and additional LND.

**Table 1. Patients' characteristics and radiological findings**

| Variables | N=17, Mean ± SD (min-max) |
|---|---|
| Mean age (year) | 62±7.4 (51-75.2) |
| Gender: Male/Female, n (%) | 11 (64.7%)/6 (35.3%) |
| Laterality of tumour: Right/Left, n (%) | 8 (47.1%)/9 (52.9%) |
| Location of tumour: Upper pole/Mid/Lower pole, n (%) | 9 (52.9%)/4 (23.5%)/4 (23.5%) |
| Tumour diameter (mm) | 91.9±44 (30-200) |
| Adrenal invasion in radiologic images, n (%) | 1 (5.9%) |
| T4 stage tumour in radiologic images, n (%) | 1 (5.9%) |
| Lymph node metastasis in radiologic images, n (%) | 3 (17.6%) |
| Central necrosis in radiologic images, n (%) | 7 (41.2%) |

SD: Standard deviation, Min: Minimum, Max: Maximum

When pathologic data are investigated, the mean tumour diameter was 91.9±44 mm (30-200 mm), and seven patients had pathologic T3a, two had T3b and one had T4 stage tumour, eight patients had Fuhrman grade 4 and 5 had Fuhrman grade 3 tumours. Pathologically, 7 tumours contained sarcomatoid features, whereas 4 had microvascular invasion. Additionally, seven patients had renal sinus invasion, five had perinephric invasion, one had adrenal invasion, one had collecting system invasion and three had renal vein invasion. Three patients with LND were identified to have lymph node metastasis. The median follow-up for patients was 22 months [mean was 52.9±29.6 (1-118.5) months], with mean overall survival of 86.7±13.9 months and mean metastasis-free survival of 41.4±13 months.

When all of the preoperative variables were analysed (age, gender, NLR, AGR, AAR, calcium level, LDH level, platelet level and tumour diameter) and compared between groups (localised vs locally invasive tumour groups), any statistical significance was not found (Table 2). The locally invasive group were identified to have higher renal sinus invasion (0% vs 70%, p<0.05), perinephric invasion (0% vs 50%, p<0.05) and metastasis rate (28.6% vs 80%, p<0.05) during the follow-up compared to the localised tumour group (Table 3). Other pathologic data and operation time were similar between groups. T-stage was not observed to affect interferon-alpha treatment and targeted therapy rates. Overall survival and metastasis-free survival in the locally invasive group (38.4±7.3 months and 20.1±5.5 months, respectively) were shorter than the localised tumour group (90.6±24.2 months and 77.8±23.9 months, respectively) but were not statistically significant.

In the investigation of factors affecting the metastasis during follow-up, the adrenalectomy rate (14.3% vs 60%, p=0.05) and operation time (137.8±58.6 min vs 201±47 min, p<0.05) were higher in the metastasis positive group (Table 3). The pathologic data for microvascular invasion (0% vs 40%, p<0.05) and renal sinus invasion (14.3% vs 60%, p=0.05) were significantly higher in the metastasis group. During follow-up, 10 patients in the metastasis group had interferon-alpha treatment, whereas 1 patient was exitus in the early period before treatment. Sunitinib was given to four patients, everolimus was given to a patient as targeted therapy, whereas no targeted therapy was given to six patients. The currently popular data of NLR, AGR and AAR did not have a significant correlation with metastasis (Table 2). No significance was identified between groups in terms of prognostic factors like LDH, calcium and platelet levels. The mean overall survival in the metastasis positive group (23.5±5.1 months) was shorter compared to metastasis negative group (101.7±15.6 months), but did not reach statistical significance.

## Discussion

In 1997, the WHO classified RCCs without the characteristics of the four subtypes of RCC under the name uRCC (1,2,3,4,5,6,7). Accordingly, when the WHO 2004 classification is examined,

**Table 2. Preoperative data and analysis results between localised (T1 and T2) and locally invasive (T3 and T4) according to pathological T-stage and metastasis positive and negative in follow-up, respectively**

| Variables (n=17), mean ± SD | T1 and T2 stage tumours (n=7) | T3 and T4 stage tumours (n=10) | p* | Metastasis negative in follow-up (n=7) | Metastasis positive in follow-up (n=10) | p* |
|---|---|---|---|---|---|---|
| Mean age (year) | 59.5±6.8 | 63.8±7.7 | 0.205 | 61.2±7.3 | 62.6±7.9 | 0.813 |
| Gender, Female/Male, n (%) | 3 (42.9%)/4 (57.1%) | 3 (30%)/7 (70%) | 0.585 | 3 (42.9%)/4 (57.1%) | 3 (30%)/7 (70%) | 0.585 |
| NLR | 1.56±1.25 | 7.3±5.69 | 0.120 | 9.2±3.9 | 5.1±3.4 | 0.120 |
| AGR | 1.1±0.05 | 1.2±0.2 | 0.378 | 1±0.1 | 1.2±0.2 | 0.243 |
| AAR | 1.3±0.4 | 0.8±0.3 | 0.121 | 0.4±0.2 | 1±0.3 | 0.121 |
| Calcium level | 9.2±0.9 | 9.5±0.8 | 0.510 | 9.7±0.9 | 9.2±0.5 | 0.124 |
| LDH level | 182±75.6 | 242.4±84.9 | 0.827 | 135±73 | 249.1±76.4 | 0.127 |
| Platelet level | 272.8±61.8 | 321.3±98.6 | 0.386 | 302±111.7 | 304.8±83.8 | 0.733 |
| Tumour diameter (cm) | 106.1±56.1 | 82±32.8 | 0.494 | 90±41.5 | 93.3±47.9 | 0.883 |

*Mann-Whitney U test vs Pearson $\chi^2$ test, NLR: Neutrophil/lymphocyte ratio, AGR: Albumin/globulin ratio, AAR: Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) (De-Ritis) ratio, SD: Standard deviation, LDH: Lactate dehydrogenase

**Table 3. Pathologic and postoperative findings and analysis results between localised (T1 and T2) and locally invasive (T3 and T4) according to pathological T-stage and metastasis positive and negative in follow-up, respectively**

| Variables (n=17), mean ± SD | | T1 and T2 stage tumours (n=7) | T3 and T4 stage tumours (n=10) | p | Metastasis negative in follow-up (n=7) | Metastasis positive in follow-up (n=10) | p |
|---|---|---|---|---|---|---|---|
| Operation time (s) | | 165.7±53.2 | 181.5±65.7 | 0.553 | 137.8±58.6 | 201±47 | **0.043** |
| Pathological T-stage, n (%) | pT1 and pT2 | - | - | - | 5 (71.4%) | 2 (20%) | **0.034** |
| | pT3 and pT4 | | | | 2 (28.6%) | 8 (80%) | |
| TNM stage, n (%) | Stage 1 | 2 (28.6%) | 0 (0%) | - | 2 (28.6%) | 0 (0%) | **0.048** |
| | Stage 2 | 5 (71.4%) | 0 (0%) | | 3 (42.8%) | 2 (20%) | |
| | Stage 3 | 0 (0%) | 7 (70%) | | 2 (28.6%) | 5 (50%) | |
| | Stage 4 | 0 (0%) | 3 (30%) | | 0 (0%) | 3 (30%) | |
| Fuhrman grade, n (%) | Grade 2 | 2 (28.6%) | 1 (10%) | 0.672 | 2 (28.6%) | 1 (10%) | 0.672 |
| | Grade 3 | 2 (28.6%) | 3 (30%) | | 2 (28.6%) | 3 (30%) | |
| | Grade 4 | 3 (42.8%) | 5 (50%) | | 3 (42.8%) | 5 (50%) | |
| Adrenalectomy-applied, n (%) | | 2 (28.6%) | 5 (50%) | 0.377 | 1 (14.3%) | 6 (60%) | **0.050** |
| LN dissection-applied, n (%) | | 0 (0%) | 3 (30%) | 0.057 | 0 (0%) | 3 (30%) | 0.057 |
| Sarcomatoid features, n (%) | | 3 (42.8%) | 4 (40%) | 0.906 | 2 (28.6%) | 5 (50%) | 0.377 |
| Microvascular invasion, n (%) | | 1 (14.3%) | 3 (30%) | 0.442 | 0 (0%) | 4 (40%) | **0.024** |
| Renal vein invasion, n (%) | | 0 (0%) | 3 (30%) | 0.057 | 1 (14.3%) | 2 (20%) | 0.761 |
| Perinephric invasion, n (%) | | 0 (0%) | 5 (50%) | **0.026** | 2 (28.6%) | 3 (30%) | 0.949 |
| Renal sinus invasion, n (%) | | 0 (0%) | 7 (70%) | **0.004** | 1 (14.3%) | 6 (60%) | **0.050** |
| Interferon-alpha treatment, n (%) | | 3 (42.8%) | 7 (70%) | 0.263 | 1 (14.3%) | 9 (90%) | **0.002** |
| Sunitinib treatment, n (%) | | 1 (14.3%) | 3 (30%) | 0.452 | 0 (0%) | 4 (40%) | **0.024** |
| Metastasis in follow-up, n (%) | | 2 (28.6%) | 8 (80%) | **0.034** | - | - | - |
| Overall survival (months) | | 90.6±24.2 | 38.4±7.3 | 0.514 | 101.7±15.6 | 23.5±5.1 | 0.514 |
| Metastasis-free survival (months) | | 77.8±23.9 | 20.1±5.5 | 0.187 | - | - | - |
| Exitus, n (%) | | 1 (14.3%) | 3 (30%) | 0.452 | 1 (14.3%) | 3 (30%) | 0.452 |

LN: Lymph node, SD: Standard deviation

some pathologic data for distinction of uRCC were found. This data lists pure sarcomatoid morphology without compositions and epithelial elements of four defined RCC subtypes, mucin production, rare involvement of epithelial and stromal elements and unknown cell types (4). Pathologic studies about this topic are limited, stating that the presence of vacuole cytoplasm

and *Wilms' Tumour 1 (WT1)* gene expression are in favour of uRCC unless otherwise stated (13). Additionally, Bruder et al. (8) defined additional morphologic findings. However, in general, the use of current WHO criteria for pathologic assessment is recommended (13).

The diagnosis of uRCC is observed more rarely (3%-5%) compared to other RCC subtypes (2,12,14). When series in the literature are investigated, a variety of studies report a variety of rates (0.7%-5.7%) (4,5,6,7,8,9,10,11). The mean rate in large series was identified as 2.9% in the study by Zisman et al. (12), and uRCC prevalence was identified as 5.2% in the study by Karakiewicz et al. (14). There are many small-series studies on this topic (15,16,17), with three noteworthy basic studies on oncologic outcomes of uRCC. Zisman et al. (12) compared 31 uRCC and 317 cRCC cases and identified that the uRCC group had higher metastatic disease development during follow-up compared to the cRCC group (94% vs 83%). A higher tumour size, 25% adrenal metastasis, 42% direct invasion to neighbouring organs, 52% bone metastasis, 52% regional lymph node metastasis and 41% non-regional lymph node metastasis were observed in uRCC. Additionally, the median survival for uRCC was identified as 4.3 months (12). However, in this study only 19 patients in the uRCC group had nephrectomy (61%, nephrectomy rate in the cRCC group was 90, with the importance of nephrectomy for cancer control not clearly stated. A large series and multicentre study by Karakiewicz et al. (14) compared 85 uRCC with 4322 cRCC and emphasised that uRCC was more aggressive.

Accordingly, the uRCC group in the study had higher Fuhrman grade (grade 3 and 4) and higher distant organ metastasis rates at time of nephrectomy (54.1% vs 16.8%) and lower cancer-specific survival (1 year CSS 48.7% vs 89.9% and 5 year CSS 32.6% vs 74.3%) compared to the cRCC group. Additionally, the cancer-specific mortality in the uRCC group was identified to be 1.7 times higher (14). However, the median survival was identified to be higher compared to the study by Zisman et al. (12) (1.9 years vs 4.3 months). The difference in median survival between the two studies may be explained by the fact that in the study by Karakiewicz et al. (14) the patient rate operated in the early stages was higher and patient performance was better, while the study by Zisman et al. (12) had low nephrectomy rates. Additionally, the immunotherapy administration rates and treatment times may affect survival. In the study examination, our data had better progression compared to the literature; however, bad prognostic findings were observed. In our study 58.8% of patients were in advanced stage and 76.5% had high Fuhrman grade. During follow-up, 58.8% of patients developed metastasis. Mean follow-up time and overall survival were 22±29.6 and 86.7±13.9 months, respectively, and mortality was observed in four patients. Additionally 41.2% had renal sinus invasion. However, as adrenalectomy was performed for seven patients and LND for three patients in our series, only one patient (5.9%) had adrenal metastasis and three patients (17.6%) had lymph node metastasis. These rates may be said to be lower than the rates in literature.

The study by Lopez-Beltran et al. (13) assessed 56 patients with uRCC. A study reported that histologic subtype, tumour grade, TNM stage, presence of necrosis, tumour size and microvascular invasion were independent risk factors for disease-free survival and cancer-specific survival (18,19). Another 38-patient series reported high rates of lymph node metastasis, high Fuhrman grade tumour rates, tumour necrosis and sarcomatoid features in uRCC; they identified overall survival and cancer-specific survival were similar to cRCC (10). In our study, in accordance with these two studies, mean tumour diameter, central necrosis on radiologic imaging, microvascular invasion and sarcomatoid properties were observed to be high at 9.2 cm, 41.2%, 23.5% and 41.2%, respectively.

Generally, small-series studies were reported; however, specific findings of uRCC are unclear in some large studies. The reason for this may be the small number of patients, comparison of uRCC data with other commonly observed histologic subtypes and large proportional difference between the patient numbers in these groups. Additionally, the experience of the pathologist is important for pathologic diagnosis as emphasised in studies. As a result, we presented a 17-patient series with uRCC diagnosed by experienced uropathologists (BT and KY) without making comparisons. In addition to general patient data in our study, we assessed the patient data for locally invasive tumours and metastasis positive tumours in the follow-up. Accordingly, the development of metastasis rate was identified as high and mean metastasis-free survival was low (but insignificant) in the locally invasive group compared to the localised tumour group. Metastasis positivity in the follow-up was found to be correlated with high T-stage, microvascular invasion and renal sinus invasion. Additionally, the operation time and adrenalectomy rates in the metastasis group were identified to be high. However, in spite of the low overall survival time in the metastasis group, no significant difference was identified. The majority of the patient group with adrenalectomy had upper pole tumours; however, no correlation was shown between metastasis development and tumour location. After metastasis development, interferon-alpha treatment was used for 58.8% of patients; sunitinib and everolimus were used for 23.5% and targeted therapy for 5.9% of patients. When prognostic markers are investigated in our study, the NLR, AGR and AAR ratios, popular in recent times, and LDH, calcium and platelet levels were not shown to be related to metastasis development.

### Study Limitations

The most important limitations of our study are the small number of patients and the retrospective data.

## Conclusion

This study revealed a more aggressive nature of uRCC tumours, even without reaching statistically significant differences (such as more frequent adrenal and lymph node involvement, more advanced stage, larger tumour diameter, more aggressive histopathological features and more metastasis and shorter survival during follow-up). Large series studies are necessary to determine the real radiological, pathological and oncological characteristics of this aggressive subtype of RCC tumours although performing it is difficult because of low incidence.

### Acknowledgements

**Publication:** This study was presented in the 13th Urooncology Congress, Antalya, Turkey.

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

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

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

### Ethics

**Ethics Committee Approval:** Patients diagnosed with uRCC at our clinic from 2006 to 2013 were retrospectively evaluated in accordance with the Helsinki Declaration.

**Informed Consent:** Retrospective study.

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

### Authorship Contributions

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

## References

1. Greene FL. American Joint Committee on Cancer. American Cancer Society. AJCC Cancer Staging Manual, 6th ed. New York: Springer, 2002.
2. Kovacs G, Akhtar M, Beckwith BJ, et al. The Heidelberg classification of renal cell tumours. J Pathol 1997;183:131-133.
3. Storkel S, Eble JN, Adlakha K, et al. Classification of renal cell carcinoma: workgroup No. 1. Union Internationale Contrele Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Cancer 1997;80:987-989.
4. Eble JN, Sauter G, Epstein JI, Sesterhenn IA. Pathology and genetics. Tumors of the urinary system and male genital organs. Lyon: IARC Press, 2004.
5. Reuter VE. The pathology of renal epithelial neoplasms. Semin Oncol 2006;33:534-543.
6. Skolarus TA, Serrano MF, Berger DA, et al. The distribution of histological subtypes of renal tumors by decade of life using the 2004 WHO classification. J Urol 2008;179:439-443.
7. Lopez-Beltran A, Scarpelli M, Montironi R, Kirkali Z. 2004 WHO classification of the renal tumors of the adults. Eur Urol 2006;49:798-805.
8. Bruder E, Passera O, Harms D, et al. Morphologic and molecular characterization of renal cell carcinoma in children and young adults. Am J Surg Pathol 2004;28:1117-1132.
9. Lopez-Beltran A, Carrasco JC, Cheng L, et al. 2009 update on the classification of renal epithelial tumors in adults. Int J Urol 2009;16:432-443.
10. Crispen PL, Tabidian MR, Allmer C, et al. Unclassified renal cell carcinoma: impact on survival following nephrectomy. Urology 2010;76:580-586.
11. Ficarra V, Brunelli M, Cheng L, et al. Prognostic and therapeutic impact of the histopathologic definition of parenchymal epithelial renal tumors. Eur Urol 2010;58:655-668.
12. Zisman A, Chao DH, Pantuck AJ, et al. Unclassified renal cell carcinoma: clinical features and prognostic impact of a new histological subtype. J Urol 2002;168:950-955.
13. Lopez-Beltran A, Kirkali Z, Montironi R, et al. Unclassified renal cell carcinoma: a report of 56 cases. BJU Int 2012;110:786-793.
14. Karakiewicz PI, Hutterer GC, Trinh QD, et al. Unclassified renal cell carcinoma: an analysis of 85 cases. BJU Int 2007;100:802-808.
15. Ljungberg B, Alamdari FI, Stenling R, Roos G. Prognostic significance of the Heidelberg classification of renal cell carcinoma. Eur Urol 1999;36:565-569.
16. Amin MB, Amin MB, Tamboli P, et al. Prognostic impact of histologic subtyping of adult renal epithelial neoplasms: an experience of 405 cases. Am J Surg Pathol 2002;26:281-291.
17. Ficarra V, Schips L, Guille F, et al. Multiinstitutional European validation of the 2002 TNM staging system in conventional and papillary localized renal cell carcinoma. Cancer 2005;104:968-974.
18. Sevinc M, Kirkali Z, Yorukoglu K, et al. Prognostic significance of microvascular invasion in localized renal cell carcinoma. Eur Urol 2000;38:728-733.
19. Dall' Oglio MF, Ribeiro-Filho LA, Antunes AA, et al. Microvascular tumor invasion, tumor size and Fuhrman grade: a pathological triad for prognostic evaluation of renal cell carcinoma. J Urol 2007;178:425-428.

Case Report

DOI: 10.4274/uob.galenos.2020.1742

*Bull Urooncol 2021;20(2):122-125*

# *A Case of Unclassified Renal Cell Carcinoma Initially Considered as Translocation RCC and Review of Literature*

Nejdet Karşıyakalı[1], Mahir Bülent Özgen[1], Bora Özveren[2], Işın Doğan Ekici[3], Levent Türkeri[1]

[1]*Acıbadem Mehmet Ali Aydınlar University, Altunizade Hospital, Clinic of Urology, İstanbul, Turkey*
[2]*Acıbadem Mehmet Ali Aydınlar University, School of Medicine, Altunizade Hospital, Clinic of Urology, İstanbul, Turkey*
[3]*Acıbadem Mehmet Ali Aydınlar University, School of Medicine, Clinic of Pathology, İstanbul, Turkey*

## Abstract

This case report aimed to review the literature on translocation renal cell carcinoma (tRCC), which is a rare form of kidney cancer and was the initial diagnosis of a recently treated patient. We report our findings in a 30-year-old female who underwent robot-assisted radical nephrectomy for an incidental right renal mass, which was reported as unclassified RCC at final pathologic evaluation after eliminating tRCC as differential diagnosis, and discuss the main aspects of tRCC based on current literature.

**Keywords:** Chromosome translocation, MiT family carcinomas, renal cell carcinoma, translocation renal cell carcinoma, Xp11 translocation

## Introduction

Unclassified renal cell carcinoma (RCC) as defined by the 2016 World Health Organization (WHO) classification is a diagnostic category for renal tumours that do not fit into any of the well-recognised subtypes (1,2). Xp11 and t(6;11) translocation renal cell carcinomas (tRCC) are rare subtypes of RCC, which share variable morphological features that overlap considerably with other subtypes, including both clear cell (ccRCC) and papillary RCCs (pRCC) (2).

Xp11 and t(6;11) tRCCs have similar clinical, morphological, immunohistochemical and genetic features. Therefore, they are grouped as "MiT family translocation RCC" in the 2016 WHO urogenital tumour classification (1). Diagnosis of MiT family tRCC may pose some difficulties since ccRCC and pRCC must be considered in differential diagnosis as they are more common in the adult age group (3).

t(6;11) tRCC generally has an indolent clinical behaviour, whereas Xp11 tRCC has a variable course. Rapid progressive disease and subsequent deaths have been reported in Xp11 tRCC (4). Nevertheless, the prognosis of the tRCCs remains unclear owing to its extremely low incidence rate, and patient series are limited in the literature often with short follow-up times. Surgery is the main treatment modality of localised disease. However, the most appropriate treatment option remains unclear for metastatic cases.

Thus, we present the details of the clinical, morphological and pathological features of tRCC in a 30-year-old female patient who underwent robot-assisted radical nephrectomy for an incidental right renal mass, which was initially considered as tRCC. Further molecular analysis categorised the tumour as unclassified RCC at the final pathologic evaluation.

## Case Presentation

A 30-year-old female patient who had no chronic disease was referred to the urology outpatient department with a possible diagnosis of renal cancer according to magnetic resonance imaging (MRI) findings. The patient did not describe any history of macroscopic haematuria. She never smoked and had no occupational chemical exposure. Laboratory examination showed normal liver and renal function levels, and coagulation test findings were within normal limits. Complete blood count showed mild microcytic anaemia. No pathological findings were observed on the posteroanterior chest X-ray, which was performed according to the National Comprehensive Cancer Network guidelines. After gadolinium injection, minimal heterogeneous enhancement in arterial phase was detected on MRI (Figure 1). Contrast-enhanced computed tomography (CT) scan revealed a completely endophytic right renal mass at 42×37×40 mm, located in the middle lower pole and displayed increased enhancement in the arterial phase (Figure 2). Although the renal mass was highly endophytic, robot-assisted

**Cite this article as:** Karşıyakalı N, Özgen MB, Özveren B, Ekici ID, Türkeri L. A Case of Unclassified Renal Cell Carcinoma Initially Considered as Translocation RCC and Review of Literature. Bull Urooncol 2021;20(2):122-125

**Address for Correspondence:** Nejdet Karşıyakalı, Acıbadem Mehmet Ali Aydınlar University, Altunizade Hospital, Clinic of Urology, İstanbul, Turkey
**Phone:** +90 505 865 24 63 **E-mail:** nkarsiyakali@hotmail.com **ORCID-ID:** orcid.org/0000-0002-0709-0331
**Received:** 12.05.2020 **Accepted:** 10.06.2020

partial nephrectomy was planned considering the patient's age. During the surgical planning, the patient was informed about the possibility of a radical nephrectomy since the mass was extending to the renal hilum resulting in close contact with the renal pelvis and major vessels.

An intraoperative ultrasound (US) examination via intracorporeal US probe confirmed a completely endophytic renal mass with possible invasion to the renal pelvis and close proximity to the anterior middle and lower branches of the renal artery and the posterior branch. Robot-assisted radical nephrectomy was performed since a partial nephrectomy required resection through the major vessels with a high risk of significant haemorrhage. The postoperative course was uneventful, and the patient was discharged on postoperative day 3 without complications.

Pathological examination revealed a pT1b renal tumour with the widest diameter of 4.3 cm, Fuhrman grades 1-2 and negative surgical margins without coagulation necrosis, calcification, sarcomatoid features and microvascular invasion. Chromophobe RCC, hybrid renal tumours and MiT family RCCs were included in the differential diagnosis owing to the morphological features of the tumour.

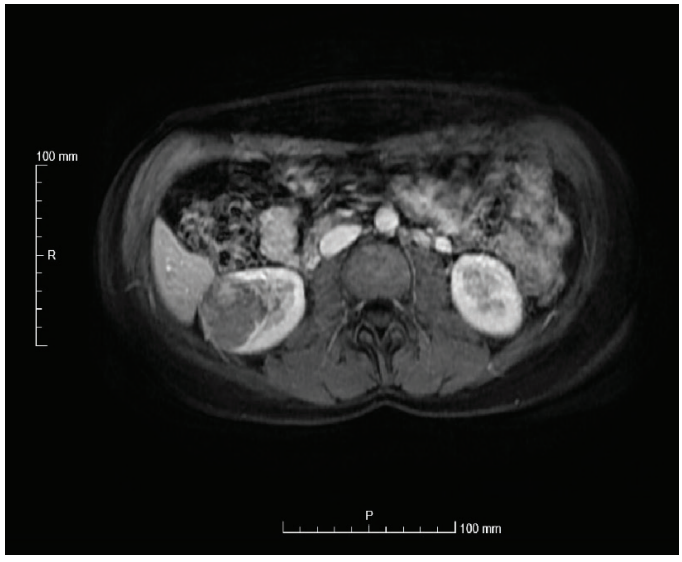


**Figure 1.** Magnetic resonance imaging findings of the right renal mass. Minimal heterogeneous contrast uptake is visualised on axial contrast-enhanced T1-weighted images

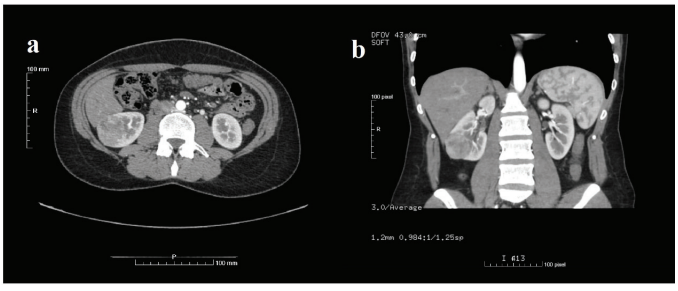


**Figure 2.** Contrast-enhanced computerised tomography findings of the right renal mass on axial (a) and coronal (b) sections. Highly endophytic renal mass without calcification is seen in the middle lower pole

Microscopic evaluation showed clear and eosinophilic cells with papillary features in a wide morphological spectrum (Figure 3a). Immunohistochemically, negative staining was observed for CK7, CD117, S-100, PAX8, Cytokeratin AE1/AE3 and Vimentin. However, mild positive staining was observed for TFE3 (Figure 3b). Based on these findings a preliminary diagnosis of tRCC was considered. However, further molecular characterisation with fluorescent *in situ* hybridisation (FISH) analysis failed to show any translocation, resulting in a final pathological diagnosis of unclassified RCC. The follow-up protocol was planned according to the European Association of Urology Guidelines on RCC recommendations for high-risk patients.

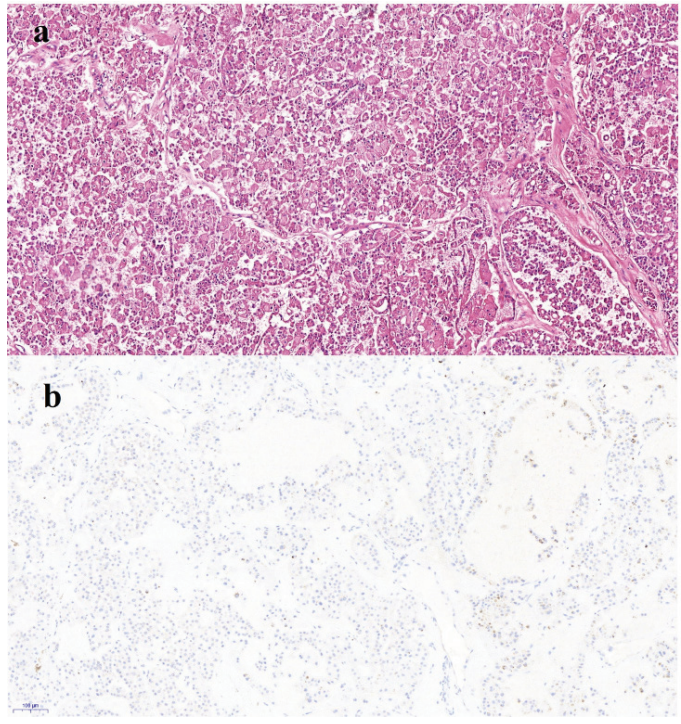


**Figure 3.** Clear and eosinophilic cells with papillary features in a wide morphological spectrum (H&E, ×100) (a). Focal and weak positive brown staining was considered as uncertain (TFE3 immunohistochemistry, ×10) (b)

H&E: Haemotoxylin and eosin

## Discussion

Unclassified RCC comprise a significant proportion of adult renal epithelial tumours, accounting for 2-6% of RCCs (2). Unclassified RCC remains a diagnosis of exclusion, with careful characterisation of recognizable histologic subtypes through immunohistochemistry and molecular analysis if necessary. MiT family tRCC is a subtype that must be considered. Similarly, in the present case, the diagnosis of unclassified RCC had been possible after the elimination of the tRCC by FISH. Estimated tRCC incidence was reported to be approximately 4.2% (5). The rate of diagnosis is arguably low due to the morphological similarities with other more frequent RCC types more commonly seen in adults such as ccRCC and pRCC (6). tRCCs can be diagnosed by pathological evaluation of the excised renal

mass. The renal mass was detected incidentally in our patient by imaging modalities due to symptoms not related to the genitourinary system, and a definitive diagnosis of tRCC was designated after pathological examination.

It has been reported that on CT imaging, both high attenuation areas [>40 Hounsfield Unit (HU)] due to high cellular component and heterogeneous low attenuation areas due to necrosis/haemorrhage can be detected simultaneously (7). Similar to these reports, we observed both high attenuation (up to 80 HU) and low attenuation areas together on CT imaging in the present case.

Urologists must be familiar with tRCC, since they are seen in younger patients and may have aggressive clinical behaviour. Aggressive behaviour defined as metastatic potential was reported to be 46% and 17% in Xp11 and t(6;11) tRCCs, respectively (8). Age, gender and Fuhrman grade had no significant effect on aggressive clinical behaviour. In contrast, high tumour diameter, existence of necrosis and >50% immunohistochemical staining with MET were statistically significantly correlated with aggressive clinical behaviour (8).

Xp11 tRCC and ccRCCs are extremely macroscopically similar, as they are both brown-yellowish in colour and may have necrotic and haemorrhagic areas (9). Microscopically, clear epithelioid cells with papillary structure are the most remarkable features of the tRCCs. Similarly, clear and eosinophilic cells with papillary features were seen in the present case. Both tRCC types may have variable morphological features such as solid, nested, alveolar, tubulocystic and papillary growth as well as pseudocapsules, hyalinisation, necrosis and psammoma bodies (6,8). Therefore, MiT family tRCCs can be confused with ccRCC and pRCC (3).

Immunohistochemical diagnostic methods are important for differential diagnosis. In this context, cathepsin K is a significant immunohistochemical marker, which always stains negative in other RCC subtypes. In contrast, positive staining is observed in approximately 60% of the Xp11 and almost all of the t(6:11) tRCC cases (10). The most sensitive and specific immunohistochemical marker for Xp11 tRCC is strong nuclear TFE3 immunoreactivity (6). Immunohistochemical staining with TFE3 was seen in all of the Xp11 tRCCs although with variable staining intensity (11). Similarly, there was mild positive staining with TFE3 in our case with immunohistochemistry. The use of a narrow immunohistochemical panel when making a differential diagnosis for RCC in daily practice may lead to false results (8). In the immunohistochemical differential diagnosis of these cases, staining negative with CK7 and positive with cathepsin K suggested Xp11 tRCC (3,8). Calio et al. (8) defined a useful immunohistochemical panel that included cathepsin K, CD68, CK7, CA9 and PAX8 and excluded CD10 and AMACR.

Since the MiT family tRCCs may display a highly variable morphology, it is not always possible to diagnose with immunohistochemical examinations. Analysis of genetic changes by FISH is the gold standard technique in these cases and makes it possible to evaluate the *TFE3* and *TFEB* genes (12). In evaluation with FISH, TFE3 fluorescent signal was observed in 45-90% and 61-94% of the cells in Xp11 and t(6;11) tRCC, respectively (8). Moreover, higher fluorescent signal with TFE3 in Xp11 tRCC, higher *TFEB/VEGFA* gene copy number and amplification were reported to be associated with the aggressive behaviour of the tumour (8).

Few studies evaluated VEGFR-targeted agents in metastatic tRCCs and reported objective response rates of up to 30%. Progression-free survival was (PFS) 7.1-8.2 months in these series (13). Reported PFS was four, three and four months in metastatic Xp11 tRCC cases treated with sunitinib, sorafenib and temsirolimus, respectively (11). In a retrospective study of 24 patients treated with immune check-point inhibitors as a second or subsequent line treatment for metastatic tRCC, PFS was 2.5 (1-40) months, and partial response was observed in 4 (16.7%) patients and stable disease in 3 (12.5%) (14). A recent study with cabozantinib, which is a multiple tyrosine kinase inhibitor (VEGFR, MET and AXL), was found to be effective and associated with downregulation of cathepsin K in tRCC (15).

## Conclusion

Although, tRCCs are rare RCC subtypes, they may present a diagnostic problem. Definitive diagnosis is possible after surgical resection of the tumour by immunohistochemical analysis. If the diagnosis remains unclear after immunohistochemical examinations, genetic analyses can be performed with FISH.

### Acknowledgements

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

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

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

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

### Ethics

**Informed Consent:** The patient was informed about the possibility of a radical nephrectomy since the mass was extending to the renal hilum resulting in close contact with the renal pelvis and major vessels.

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

### Authorship Contributions

Concept: B.Ö., L.T., Design: B.Ö., L.T., Data Collection or Processing: N.K., I.D.E., Analysis or Interpretation: N.K., M.B.Ö., I.D.E., Literature Search: N.K., Writing: N.K.,

## References

1. Moch H, Cubilla AL, Humphrey PA, et al. The 2016 WHO classification of tumours of the urinary system and male genital organs-part a: renal, penile, and testicular tumours. Eur Urol 2016;70:93-105.
2. Sirohi D, Smith SC, Agarwal N, et al. Unclassified renal cell carcinoma: diagnostic difficulties and treatment modalities. Res Rep Urol 2018;10:205-217.
3. Ross H, Martignoni G, Argani P. Renal cell carcinoma with clear cell and papillary features. Arch Pathol Lab Med 2012;136:391-399.
4. Calio A, Segala D, Munari E, et al. MiT family translocation renal cell carcinoma: from the early descriptions to the current knowledge. Cancers (Basel) 2019;11:1110.

5. Zhong M, De Angelo P, Osborne L, et al. Dual-color, break-apart FISH assay on paraffin-embedded tissues as an adjunct to diagnosis of Xp11 translocation renal cell carcinoma and alveolar soft part sarcoma. Am J Surg Pathol 2010;34:757-766.
6. Argani P. MiT family translocation renal cell carcinoma. Semin Diagn Pathol 2015;32:103-113.
7. Koo HJ, Choi HJ, Kim MH, et al. Radiologic-pathologic correlation of renal cell carcinoma associated with Xp11.2 translocation. Acta Radiol 2013;54:827-834.
8. Calio A, Brunelli M, Segala D, et al. Comprehensive analysis of 34 MiT family translocation renal cell carcinomas and review of the literature: investigating prognostic markers and therapy targets. Pathology 2020;52:297-309.
9. Argani P, Lae M, Ballard ET, et al. Translocation carcinomas of the kidney after chemotherapy in childhood. J Clin Oncol 2006;24:1529-1534.
10. Martignoni G, Gobbo S, Camparo P, et al. Differential expression of cathepsin K in neoplasms harboring TFE3 gene fusions. Mod Pathol 2011;24:1313-1319.
11. Su HH, Sung MT, Chiang PH, et al. The preliminary experiences of translocation renal cell carcinoma and literature review. Kaohsiung J Med Sci 2014;30:402-408.
12. Rao Q, Williamson SR, Zhang S, et al. TFE3 break-apart FISH has a higher sensitivity for Xp11.2 translocation-associated renal cell carcinoma compared with TFE3 or cathepsin K immunohistochemical staining alone: expanding the morphologic spectrum. Am J Surg Pathol 2013;37:804-815.
13. Choueiri TK, Lim ZD, Hirsch MS, et al. Vascular endothelial growth factor-targeted therapy for the treatment of adult metastatic Xp11.2 translocation renal cell carcinoma. Cancer 2010; 116:5219-5225.
14. Boileve A, Carlo MI, Barthelemy P, et al. Immune checkpoint inhibitors in MITF family translocation renal cell carcinomas and genetic correlates of exceptional responders. J Immunother Cancer 2018;6:159.
15. Martinez Chanza N, Xie W, Asim Bilen M, et al. Cabozantinib in advanced non-clear-cell renal cell carcinoma: a multicentre, retrospective, cohort study. Lancet Oncol 2019;20:581-590.

Case Report
DOI: 10.4274/uob.galenos.2020.1950
Bull Urooncol 2021;20(2):126-128

# A Lesion Mimicking Malignancy: Granulomatous Orchitis

Çiğdem Öztürk[1], Esra Paşaoğlu[2], Tuğçe Bölme Şavlı[3]

[1]Recep Tayyip Erdoğan University Training and Research Hospital, Clinic of Pathology, Rize, Turkey
[2]University of Health Sciences Turkey, Bağcılar Training and Research Hospital, Clinic of Pathology, İstanbul, Turkey
[3]Gaziantep Cengiz Gökçek Maternity and Children's Hospital, Clinic of Pathology, Gaziantep, Turkey

## Abstract

Granulomatous orchitis is a rare disease with mixed chronic and granulomatous inflammation. Various factors cause granulomatous inflammation in the testicles, and it may accompany malignancies. Radiologically, granulomatous orchitis can be confused with malignancy. This paper presents the differential diagnoses of granulomatous orchitis. A 52-year-old man with testicular swelling was referred to the urology clinic. A palpable mass was detected by physical examination. Ultrasonography revealed a solid, heterogeneous 2.5 cm mass suspected as a malignancy in the right testes. The patient underwent elective orchiectomy. Microscopically, the testicle showed necrotising granulomatous inflammation accompanied by an inflammatory infiltrate that destroyed the testicular structure and caused rete testis hyperplasia. Radiologically, granulomatous orchitis can be confused with malignancy. Sufficient samples should be taken to exclude malignancy. Idiopathic granulomatous orchitis can be diagnosed after excluding all possible causes of granulomatous orchitis.
**Keywords:** Granulomatous orchitis, malignancy, testicle

## Introduction

Granulomatous orchitis is a rare disease with mixed chronic and granulomatous inflammation. Tuberculosis, brucellosis, actinomycosis, and sarcoidosis are known aetiological factors. Idiopathic granulomatous orchitis (IGO), an inflammatory condition of the testis of unknown aetiology, is rarely encountered (1). Since the ultrasonographic image demonstrated diffuse hypoechoic or focal hypoechoic areas, it is confused with malignancy. Therefore, patients often undergo orchiectomy, and IGO is diagnosed only through histopathological examination (2).

## Case Presentation

A 52-year-old man with testicular swelling was referred to the urology clinic. A palpable mass was detected by physical examination. Ultrasonography revealed a solid heterogeneous mass suspected as a malignancy in the right testes. On biochemical examination, beta human chorionic gonadotropin, alpha-fetoprotein and lactate dehydrogenase levels were within their normal range. The patient underwent elective orchiectomy.

On macroscopic examination, the right testicle contained an exophytic mass which, upon dissection, demonstrated a necrotic nodule measuring 2.5×1.5×1.5 $cm^3$ (Figure 1A). The whole lesion was examined. On microscopic examination, the testicle showed multiple necrotising granulomas and rete testis hyperplasia (Figure 1B). There was granulomatous inflammation accompanied by an inflammatory infiltrate consisting of plasma cells and lymphocytes that destroyed the testicular structure (Figure 2A, B), which was accompanied with rete testis hyperplasia (Figure 3). Microorganisms were not seen in periodic acid-Schiff (PAS) and Ziehl-Neelsen (EZN) staining. Burned-out/regressed germ cell tumours were excluded with immunohistochemical study. The histopathological diagnosis was chronic necrotising granulomatous orchitis. The patient underwent clinical, serological and radiological tests after pathological diagnosis, but no potential factor was detected.

## Discussion

IGO most commonly occurs at age 50-70 years, although cases have been reported in all ages (2). IGO can be acute or chronic. In the acute form, patients present with sudden onset of pain, while in the chronic form, they present with unilateral scrotal swelling. Patients can also present with fever, haematuria, dysuria and hydrocele (3).

The aetiology of IGO is not known exactly, but it is thought to be related to trauma. Additionally, autoimmune diseases and infections have been associated with IGO (2). IGO can clinically mimic malignancy. Testicular trauma, surgery, history

**Cite this article as:** Öztürk Ç, Paşaoğlu E, Bölme Şavlı T. A Lesion Mimicking Malignancy: Granulomatous Orchitis. Bull Urooncol 2021;20(2):126-128

**Address for Correspondence:** Çiğdem Öztürk, Recep Tayyip Erdoğan University Training and Research Hospital, Clinic of Pathology, Rize, Turkey
**Phone:** +90 506 806 95 55 **E-mail:** cigdemtopuksak@gmail.com **ORCID-ID:** orcid.org/0000-0003-2587-214X
**Received:** 10.12.2020 **Accepted:** 31.12.2020

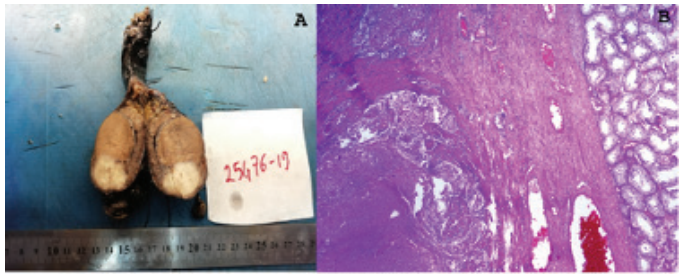


**Figure 1.** A: Macroscopic view of the testicle which demonstrated a necrotic nodule. B: Microscopic view of the normal testicular tissue on the right and lesion area on the left (haemotoxylin and eosin staining, ×40)

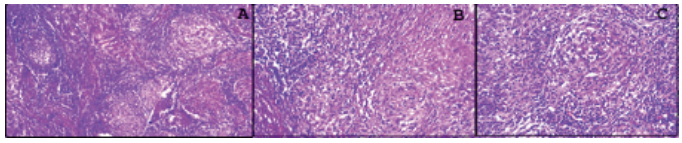


**Figure 2.** A: Multiple necrotising granulomas (hematoxylin and eosin staining (HE), ×100). B: Multiple granuloma structures (HE, ×200). C: Granuloma structure accompanied by an inflammatory infiltrate (HE, ×200)

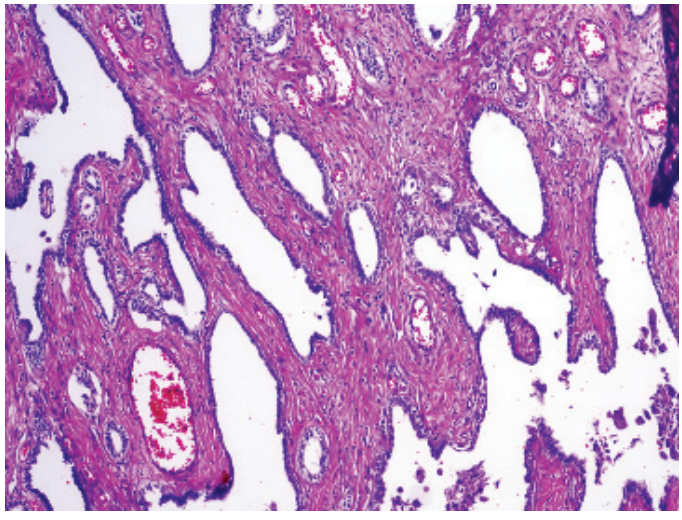

**Figure 3.** Rete testis haemotoxylin (HE, ×100)

of tuberculosis and urinary tract and epididymis infections may raise clinical suspicion for IGO (4).

Distinguishing IGO from malignancy is extremely challenging because of the destruction of the testicular tissue, as shown in ultrasonography. Therefore, orchiectomy is often performed (2). On histopathological examination, the granulomatous inflammatory infiltrate consisting of plasma cells and lymphocytes invade the seminiferous tubules and germ cells degenerate. Fibrosis develops in the later period (5).

Inflammatory and infectious factors should be considered in the differential diagnosis. The most common cause of granulomatous inflammation is tuberculosis. The presence of granulomas with caseification necrosis accompanied by Langhans-type giant cells and the presence of microorganisms in the acid-fast histochemical staining suggest tuberculosis (6). Other factors in the differential diagnosis are syphilis, leprosy, brucella and fungal infections. In these factors, the specific morphological appearance of granulomas; presence of microorganisms in histochemical stains such as Warthin-Starry, EZN and PAS; and clinical laboratory findings are helpful in the diagnosis (7). Sarcoidosis that rarely involves the genitourinary system should be also considered. Non-caseating granulomas, minimal lymphocytic infiltration, Schauman basophilic, asteroid bodies and systemic involvement in patients support the diagnosis of sarcoidosis (8). Granulomatous seminoma on histopathological examination should also be considered in the differential diagnosis. The presence of intratubular germ cell neoplasia, immunohistochemical presence of a tumour such as OCT3/4 and CD117 and placental alkaline phosphatase are also helpful in the differential diagnosis (9). Malignant lymphoma is another neoplasia that should be included in the differential diagnosis. In IGO, lymphoma is excluded if the inflammatory infiltrate is not monotonous and shows polyclonal pattern on immunohistochemical staining and partially preserved tubular structure of the testis (10).

In the present case, malignancy was considered following clinical and ultrasonographic examinations. Histopathologically, the granuloma structure specific to infectious agents was not observed, and organisms were not detected histochemically. On morphological examination, burned-out/regressed germ cell tumour was not considered and was supported by immunohistochemical studies. Thus, the present case was evaluated as IGO after all other causes were excluded. Moreover, rete testis hyperplasia was present. Rete testis hyperplasia is a non-neoplastic lesion that mimics a malignancy of unknown aetiology (11). The accompanying rete testis hyperplasia in our case may be due to degeneration resulting from granulomatous inflammation.

Radiologically, granulomatous orchitis can be confused with malignancy. Thus, sufficient samples should be taken to exclude malignancy. IGO can be diagnosed after excluding all possible causes of granulomatous orchitis.

## Acknowledgements

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

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

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

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

## Ethics

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

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

## Authorship Contributions

Concept: Ç.Ö., Design: Ç.Ö., E.P., Data Collection or Processing: Ç.Ö., T.B.Ş., Analysis or Interpretation: T.B.Ş., Literature Search: Ç.Ö., E.P., Writing: Ç.Ö., E.P., T.B.Ş.

## References


1. Civelli VF, Heidari A, Valdez MC, et al. Case of testicular granulomatous ınflammation mistaken for malignancy: tuberculosis identified post orchiectomy. J Investig Med High Impact Case Rep 2020;8:2324709620938947. doi: 10.1177/2324709620938947.
2. Roy S, Hooda S, Parwani AV. Idiopathic granulomatous orchitis. Pathol Res Pract 2011;207:275-278.
3. Raju GC, Naraynsingh V. Idiopathic granulomatous orchitis. Trop Geogr Med 1985;37:188-189.
4. Sadeghi A, Chaikin D, Calhoun S. Testicular tuberculosis: An uncommon complication after treatment of urothelial carcinoma. Radiol Case Rep 2020;15:2285-2293.
5. Wegner HE, Loy V, Dieckmann KP. Granulomatous orchitis--an analysis of clinical presentation, pathological anatomic features, and possible etiologic factors. Eur Urol 1994;26:56-60.
6. Salmeron I, Ramirez-Escobar MA, Puertas F, et al. Granulomatous epididymo-orchitis: sonographic features and clinical outcome in brucellosis, tuberculosis and idiopathic granulomatous epididymo-orchitis. J Urol 1998;159:1954-1957.
7. Varma R, Baithun S, Alexander S, Goh BT. Acute syphilitic interstitial orchitis mimicking testicular malignancy in an HIV-1 infected man diagnosed by Treponema pallidum polymerase chain reaction. Int J STD AIDS 2009;20:65-66.
8. anda T, Nagai S, Hamada K, et al. Sarcoidosis with bilateral epididymal and testicular lesions. Intern Med 2003;42:92-97.
9. Ulbright TM. The most common, clinically significant misdiagnoses in testicular tumor pathology, and how to avoid them. Adv Anat Pathol 2008;15:18-27.
10. Nistal M, Paniagua R. Non-neoplastic diseases of the testis. In: Bostwick DG, Cheng L, editors. Urologic surgical pathology. 2nd ed. China: Mosby; 2008:712.
11. Ozgur T, Akin MM, Gokce H, Davarci M. Adenomatous hyperplasia of the rete testis: not a true hyperplasia, just proliferation!. Contemp Oncol (Pozn) 2013;17:466-467.