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

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

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

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

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.

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Instructions to Authors

1. General Information

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

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

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.

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

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

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

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

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

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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.

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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.

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

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

(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.

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

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

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7. Manuscript Submission

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

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

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

Submissions must include according to the following sequence:

A-Original Article

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)

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B. Case Reports

1) Copyright Transfer and Author Declaration Statement Form

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

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

4) Table(s)

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C-Review Article

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

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Changes in Metastatic Castration Sensitive Prostate Cancer

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Abstract

Prostate cancer is the second most common cancer in men worldwide, with approximately 1,276,106 new patients and 358,989 new deaths. Metastatic castration-sensitive prostate cancer may be *de novo* metastatic, but also it may be in the localized disease stage at the time of diagnosis, and may present as biochemical relapse and later metastatic disease over time. Purposes of metastatic castration-sensitive prostate cancer treatment are prolonging survival, improving quality of life and reducing complications. In this review, it is aimed to evaluate the current developments in metastatic castration-sensitive prostate cancer treatment.
Keywords: Prostate cancer, castration sensitive, treatment, chemotherapy

Introduction

Overview of Prostate Cancer

Prostate cancer (PC) is the second most common cancer in men worldwide, with nearly 1,276,106 new patients and 358,989 new deaths worldwide (1). PC is responsible for one out of every 5 cancers in men in the United States of America (USA), and is the second most common cause of cancer-related deaths (2). In the USA, according to the Surveillance, Epidemiology and End Results (SEER) database, an estimated 174,650 new patients (9.9% of all newly diagnosed cancers) and 31,620 deaths (5.2% of cancer related deaths) are expected in 2019. Again, according to the SEER database, 5-year survival in PC is 98%, the majority of patients are diagnosed at an early stage and the median age at diagnosis is 66, and the median age at death is 80. Incidence and mortality in PC decrease or stabilize in many parts of the world (3).

In our country, according to 2015 Turkey cancer statistics of the Cancer Agency Presidency, PC is the second most common cancer after lung cancer in men with frequency of 33.1/100,000 according to given standardized rate of 10 cancers by age while in the second frequency; while it is the second most common cancer with 13.2% among men between the ages of 50-69 (4).

Treatment of Metastatic Castration Sensitive Prostate Cancer

Metastatic castration sensitive PC (mCSPC) may be *de novo* metastatic, or may be in the localized disease stage at the time of diagnosis and may present as biochemical relapse and later as metastatic disease over time. The aim of mCSPC treatment is to prolong survival, improve quality of life and reduce complications. The properties of some agents used in mCSPC are summarized in Table 1.

Androgen Deprivation Therapy in mCSPC

PC is a hormone-dependent disease like breast cancer. Androgens are hormones that play a key role in the growth of cancer cells (5). Testosterone and dihydrotestosterone (DHT) are the two main androgens in men. Of testosterone 90-95% is synthesized from testis Leydig cells and 5-10% from the adrenal glands (6). Circulating testosterone is converted into the active form DHT in the cell by the 5-α reductase enzyme, and DHT acts on the androgen receptor (7).

Huggins and Hodges (8) showed that PC was an androgen sensitive disease and that the disease could regress by lowering the testosterone level by performing bilateral orchiectomy. Androgen deprivation therapy (ADT) is the standard treatment in mCSPC. ADT can be performed with surgical castration (bilateral orchiectomy) or it can be performed medically. In medical castration; gonadotropin releasing hormone (GnRH) agonists (e.g., leuprolide, goserelin, buserelin, triptorelin…) or GnRH antagonists (degarelix) can be used. Testosterone synthesis is suppressed through the hypothalamus-pituitary-gonad axis with medical castration (9). Although the majority of patients respond to ADT, resistance to castration develops in most of the patients within 1-3 years (10).

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Table 1. Properties of some agents used in metastatic CSPC				
	Docetaxel	**Abiraterone acetate**	**Enzalutamide**	**Apalutamide**
Route of administration	intravenous	oral	oral	oral
Dosage	75 mg/m^2	1000 mg/d	160 mg/d	240 mg/d
Need for prednisone	√	√		
Decrease in seizure threshold			√	
Liver toxicity		√	Lesser	
Risk of hypertension		√	√	√
Febrile neutropenia	√			
Neuropathy	√			
Rash				√
Treatment duration	6 cures	Until progression	Until progression	Until progression
CSPC: Castration sensitive prostate cancer				

Antiandrogens used in PC treatment are divided into two as steroidal and non-steroidal ones. Steroidal anti-androgens are synthetic derivatives of hydroxyprogesterone. In addition to blocking androgen receptors in the periphery, these agents have testosterone-lowering and progestational properties with pituitary inhibition. In addition to inhibiting gonadotropin release, they also suppress adrenal activity. They are not recommended for use as monotherapy. They are associated with lower overall survival (OS) rate than luteinizing hormone-releasing hormone (LHRH) analogues (11). Non-steroidal antiandrogens (e.g., bicalutamide, nilutamide, flutamide) are agents with better quality of life and compliance as they do not lower testosterone levels. Bone mineral density, physical performance and libido are protected with these agents. In a meta-analysis including 2717 patients with advanced stage PC, it was shown that non-steroidal antiandrogens were associated with lower OS rate compared to LHRH agonists (12). In a randomized study comparing steroidal and nonsteroidal anti-androgens, survival data of flutamide and cyproterone acetate were found to be similar (13).

Chemotherapy in mCSPC

The addition of cytotoxic chemotherapy (CT) to the standard treatment in mCSPC has resulted in improvements in survival and quality of life (14,15). In studies investigating the role of CT in mCSPC, it has been tried to find an answer to the question of whether there is a survival benefit.

In the CHAARTED study by Sweeney et al. (16), 790 patients with mCSPC were randomized one-on-one to either the ADT arm or ADT + docetaxel (75 mg/m^2 every 21 days, 6 cycles) arm. The primary endpoint of the study was OS. In the CHAARTED study, the presence of 4 or more bony lesions, at least one of which was extra-vertebrae or extrapelvic, or extranodal visceral metastasis was defined as a high-volume disease. The median OS was 57.6 vs 49.2 months when all patients were evaluated [95% confidence interval (CI)=0.47-0.80; p<0.001]. Median OS in patients with high volume disease was 49.2 and 32.2 months [hazard ratio (HR)=0.61, 95% CI=0.45-0.81; p<0.001] and there was no statistically significant difference between treatment arms in terms of median OS in patients with low-volume disease (p=0.11). Among grade 3-4 side effects; neutropenia was detected in 12.1%, febrile neutropenia in 6.1% and fatigue in 4.1% of the patients in the combination arm. As a result, adding docetaxel to ADT provided a statistically significant benefit in OS in high-volume disease (16).

In the open-label, randomized, phase 3 GETUG-AFU 15 study, 385 patients with a diagnosis of mCSPC were randomized one-on-one to either the ADT arm or ADT + docetaxel (75 mg/m^2 every 21 days, 9 cycles) arm. The primary endpoint of the study was OS, and the secondary endpoint was biochemical and radiological progression-free survival (PFS). The median follow-up period was 50 months. The median OS was 58.9 vs 54.2 months (95% CI=0.75-1.36) in the treatment groups. Three-year OS was 64.2% in the ADT arm and 62.9% in the combination arm. The most common grade 3-4 side effects in the combination arm were neutropenia, febrile neutropenia, and fatigue. Consequently, the OS benefit of adding docetaxel to standard therapy could not be demonstrated in this study (17).

In arm C of the multi-arm STAMPEDE trial, patients were randomized one-on-one to either standard therapy or standard therapy + docetaxel (6 cycles of 75 mg/m^2 every 21 days). The primary endpoint of the study was OS. The median follow-up period was 43 months. The median OS was 71 months in the standard treatment arm and 81 months in the combination arm (HR=0.78; 95% CI=0.66-0.93; p=0.006). Of the patients, 77% were able to complete 6 cycles of docetaxel treatment in the combination arm. Grade 3-5 side effects were observed in 32% of the standard treatment arm and 52% of the standard treatment + docetaxel arm. The most common grade 3-5 side effects in the combination arm were neutropenia and febrile neutropenia. Similar to the CHAARTED study, in this study, the survival benefit of adding docetaxel to ADT was shown (18).

A meta-analysis of 5 studies investigating the benefit of adding docetaxel CT to standard treatment in patients with PC was published in Lancet Oncology in 2016. In this meta-analysis, the OS benefit of adding docetaxel to standard therapy was demonstrated (HR=0.77, 95% CI=0.68-0.87; p<0.0001). Absolute improvement in four-year survival was 9% (95% CI=5-14). Addition of docetaxel to standard treatment also provided a statistically significant benefit in disease-free survival (DFS) (HR=0.64; p<0.0001). Absolute improvement in four-year DFS

was 16% (95% CI=12-19) (19). Phase 3 ADT + CT studies in mCSPC are shown in Table 2.

mCSPC and Abirateron Acetate

Abiraterone acetate (AA) is an inhibitor of the cytochrome P-450c17 (CYP17) enzyme, which is a critical enzyme in extragonadal and testicular androgen synthesis. It inhibits both 17α-hydroxylase and C17-20-lyase by dual function. Testosterone precursors inhibit the formation of dehydroepiandrosterone and androstenedione (20). Various studies have been carried out to demonstrate the survival benefit, efficacy, and side effects of AA in mCSPC (21,22).

In the double-blind, phase 3, placebo-controlled LATTITUDE study, 1199 patients were randomized one-on-one to either the ADT + AA + prednisolone arm or ADT + placebo arm. The primary endpoint of the study was OS and radiological PFS. Patients with mCSPC who were aged 18 years or older, had an ECOG performance score of 0-2, and had 2 of 3 high risk factors (Gleason's score ≥8, ≥3 bone metastasis, visceral metastasis) were included in the study. While OS endpoint could not be reached in the combination arm, it was 34.7 months (HR=0.62; 95% CI=0.51-0.76; p<0.001) in the ADT arm. Radiological PFS was 33 months in the combination arm and 14.7 months in the ADT arm (HR=0.47; 95% CI=0.39-0.55; p<0.001). All secondary endpoints were statistically significant in favor of the combination arm. Grade 3 or above side effects including hypertension, hypokalemia, increase in alanine aminotransferase and aspartate aminotransferase, and hyperglycemia were more in the AA arm. With this study, the addition of AA + prednisolone to the standard treatment ADT statistically prolonged OS and radiological PFS in patients with a diagnosis of mCSPC (21).

In the multi-arm STAMPEDE study, 1917 patients were randomized individually to either the ADT or ADT + AA + prednisolone arm. The primary endpoint of the study was OS. The median age at diagnosis was 67, the median PSA level was 53 ng/mL, and 52% of the patients were metastatic. The median follow-up period was 40 months. The three-year OS was 76% vs 83% and was in favor of the combination arm (HR=0.63; 95% CI=0.52-0.76; p<0.001). Three-year event-free survival was 75% vs 45% in favor of the AA arm (HR=0.29; 95% CI=0.25-0.34; p<0.001). Grade 3-5 side effects were observed in 47% of the combination arm and 33% of the monotherapy arm. Hypertension, cardiovascular and hepatic disorders were more common in the combination arm. Symptomatic skeletal related events were less common in the combination arm (HR=0.46; 95% CI=0.37-0.58; p<0.001) (22).

There are no studies directly comparing AA with docetaxel, but in a meta-analysis of seven studies, AA + ADT provided a 19% reduction in the risk of death compared to docetaxel + ADT (HR=0.81; 95% CI=0.66-1.00) (23). In the multi-armed, multi-center STAMPEDE study, 189 (14%) of 1348 patients received docetaxel + ADT and 377 (28%) received AA + ADT. In the indirect comparison of docetaxel + ADT and AA + ADT in the STAMPEDE study; median age was 66, median PSA was 56 ng/mL. HR was 1.16 (95% CI 0.82-1.65) for OS; HR was 0.51 (95% CI 0.39-0.67) for event free survival; and HR was 0.65 (95% CI=0.48-0.88) for PFS (24).

mCSPC and Enzalutamide

Enzalutamide, a new generation androgen receptor blocker, blocks the DHT receptor both on the target cell surface and on the nucleus, thanks to its high receptor affinity. It is an orally used agent that has been shown to be effective in patients who have developed resistance to first generation non-steroidal antiandrogens such as bicalutamide, nilutamide, and flutamide (25).

In the double-blind, phase 3 ARCHES study in which the benefit of enzalutamide on survival was investigated, 1150 patients with a diagnosis of mCSPC were randomized either to the enzalutamide + ADT arm or placebo + ADT arm. The primary endpoint of the study was radiological PFS. The risk of radiological progression and death was statistically significantly lower in the enzalutamide + ADT arm (HR=0.39; 95% CI=0.30-0.50; p<0.001). Enzalutamide + ADT therapy reduced the risk of PSA progression, initiation of new antineoplastic therapy, skeletal related events, and CSPC and pain progression. The frequency of grade 3 or above side effects was 24.3% in the enzalutamide + ADT arm and 25.6% in the placebo + ADT arm (26).

In another open-label, phase 3, randomized ENZAMET study in which the survival benefit of enzalutamide was investigated, 1125 patients with mCSPC were randomized either to the ADT + standard non-steroidal antiandrogen (bicalutamide, nilutamide, flutamide) arm or ADT + enzalutamide arm. The primary endpoint of the study was OS. The median follow-up duration was 34 months. There were 102 deaths in the enzalutamide arm and 143 deaths in the standard non-steroidal antiandrogen arm (HR=0.67; 95% CI=0.52-0.86; p=0.002). Three-year OS rate was 80% vs 72%, which was in favor of the enzalutamide arm. Three-year PFS rate was 67% vs 37%, which was in favor of the enzalutamide arm (HR=0.39; 95% CI=0.33-0.47; p<0.001). Treatment discontinuation due to side effects was more in the enzalutamide arm. Seizures were seen in 7 (1%) patients in the enzalutamide arm. In that study, the addition of enzalutamide provided a statistically significant advantage in terms of OS and PFS in patients with a diagnosis of mCSPC (27).

Table 2. Phase 3 ADT + CT trials in mCSPC

Trial name	Number of patients	CT regimen	Primary end point	OS duration	HR (95% CI)
CHAARTED	790	Docetaxel 75 mg/m^2, 6 cures	OS	Median 57.6 vs 44 months	0.61 (0.47-0.80)
GETUG-AFU 15	385	Docetaxel 75 mg/m^2, 9 cures	OS	Median 58.9 vs 54.2 months	1.01 (0.75-1.36)
STAMPEDE- C arm	1776	Docetaxel 75 mg/m^2, 6 cures	OS	Median 81 vs 71 months	0.78 (0.66-0.93)

ADT: Androgen deprivation therapy, CT: Chemotherapy, mCSPC: Metastatic castration sensitive prostate cancer, OS: Overall survival, HR: Hazard ratio, CI: Confidence interval

In a study comparing enzalutamide with AA + prednisone indirectly, in the predosetaxel and postdosetaxel periods, better results were obtained with enzalutamide in terms of radiological PFS, PSA response rate and time until PSA progression; while there was no difference between the two agents in terms of OS (28).

mCSPC and Apalutamide

Apalutamide is a non-steroidal antiandrogen agent used in the treatment of PC. Apalutamide binds directly to the ligand binding portion of the androgen receptor and prevents androgen receptor translocation, DNA binding, and androgen receptor-mediated transcription (29).

In the phase 3, randomized, double-blind, placebo-controlled TITAN trial, 1052 patients with mCSPK were randomized one-on-one either to ADT + apalutamide arm or ADT + placebo arm. Apalutamid was given orally with a dose of 240 mg/day. The primary endpoints were radiologic PFS and OS. Demographic and clinical characteristics of the patients were well balanced. The median age in both groups was 68. Of the patients, 10.7% previously received docetaxel treatment; 62.7% had high-volume disease, and 37.3% had low-volume disease. One of the primary endpoints, the radiologic PFS at 24 months, was 68.2% in the apalutamide arm and 47.5% in the placebo arm (HR=0.48; 95% CI=0.39-0.60; p<0.001). The first interim analysis for OS was performed after 200 deaths were observed (83 in the apalutamide group and 117 in the placebo group). Another primary endpoint, OS at 24 months, was 82.4% in the apalutamide arm versus 73.5% in the placebo arm (HR=0.67; 95% CI=0.51-0.89; p=0.005). The risk of death in the apalutamide arm was lower by 33%. The frequency of grade 3-4 side effects was 42.2% in the apalutamide arm compared to 40.8% in the placebo group, and rash was more common in the apalutamide arm. Forty two patients (8.0%) in the apalutamide arm and 28 patients (5.3%) in the placebo arm could not continue treatment because of adverse effects. As a result, adding apalutamide to ADT significantly prolonged OS and radiologic PFS in patients with a diagnosis of mCSPC, and no significant difference was found between the two arms in terms of side effect profile (30). Phase 3 studies of hormonal treatment agents used in mCSPC are shown in Table 3.

Should Zolendronic Acid be Used in the mCSPC?

Bisphosphonates, which are synthetic pyrophosphate analogues, accumulate in bone binding to hydroxyapatite crystals and suppress the function of osteoclasts (31). Zolendronic acid, a powerful third generation bisphosphonate, has been shown to reduce the incidence of skeletal related events in patients with a diagnosis of mCSPC (32).

In the multi-arm STAMPEDE study, the contribution of adding zolendronic acid to standard therapy was investigated. Patients were randomized either to the standard therapy arm or standard therapy + zolendronic acid arm. The median OS was 71 months in the standard treatment arm and was not achieved in the standard therapy + zolendronic acid arm (HR=0.94, 95% CI=0.79-1.11; p=0.450). There was also no statistical difference in terms of event-free survivals. In this study, the skeletal related event, OS and event-free survival benefits of adding zolendronic acid to standard therapy could not be demonstrated. In a meta-analysis published in Lancet Oncology, the benefit of skeletal related events and OS [95% CI=0.94 (0.83-1.07); p=0.323] of zolendronic acid in mCSPC could not be demonstrated (19).

The Role of Local Treatment in Metastatic Disease

Radical prostatectomy (RP) or radiotherapy (RT) are the standard treatment options in PC with a life expectancy of ≥10 years and organ limited PC (33). ADT + RT is widely used in locally advanced disease. The effect of local treatment to the prostate on survival in patients with metastatic PC has been searched for a long time.

In the multi-center HORRAD study; 432 patients with PC with primary bone metastasis and PSA >20 ng/mL were randomized one-on-one to either the standard ADT arm or ADT + RT arm. In the RT arm, a total of 70 Gy RT was given in 35 fractions within 3 months after ADT. Primary endpoint was OS. The secondary endpoint was time to PSA progression. The median OS was 45 months in the ADT + RT arm and 43 months in the ADT arm (HR=0.90; 95% CI=0.70-1.14; p=0.4), and there was no statistically significant difference. The time to median PSA progression was 15 months in the RT arm and 12 months in the ADT arm (HR=0.78; 95% CI=0.63-0.97; p=0.02), and a statistically significant difference was found (34).

In the phase 3 STAMPEDE study in which 2061 patients with newly diagnosed metastatic PC were included, patients were randomized individually to either the ADT arm or ADT + RT arm. Primary endpoint was OS. Of the patients, 40% had low-volume disease and 54% had high-volume disease. Three-year OS was 62% in the ADT arm and 65% in the RT arm (HR=0.92;

Table 3. Phase 3 trials of hormonal treatment agents used in mCSPC

Trial ame	Number of patients	Agent used	Primary end point	Duration for radiological PFS	OS duration	HR of OS (95% CI)
LATTITUDE	1199	abiraterone acetate	OS Radiological PFS	33 vs 14.8 months	While the median value could not be reached in the AA arm, the median value was 34.7 months in the control arm.	0.62 (0.51-0.76)
STAMPEDE	1917	abiraterone acetate	OS		OS at 36th month %83 vs %76	0.63 (0.52-0.76)
ENZAMET	1125	enzalutamide	OS		OS at 36th month 80% vs 72%	0.67 (0.52-0.86)
TITAN	1052	apalutamide	OS Radiological PFS	At 24th month 68.2% vs 47.5%	OS at 24th month 68.2% vs 47.5%	0.67 (0.51-0.89)

mCSPC: Metastatic castration sensitive prostate cancer, OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, PFS: Progression-free survival, AA: Abiraterone acetate

95% CI=0.80-1.06; p=0.266). The 3-year event-free survival was 23% in the ADT arm and 32% in the RT arm (HR=0.76; 95% CI=0.68-0.84; p<0.0001). When subgroup analyzes were evaluated, it was shown that adding RT to ADT in low-volume disease significantly prolonged OS (HR=0.68; 95% CI=0.52-0.90; p=0.0098) (35). Phase 3 prostate RT studies in metastatic PC are shown in Table 4.

Table 4. Phase 3 prostate RT trials in metastatic PC

Trial name	Number of patients	Primary end point	OS duration	HR (95% CI)
HORRAD	432	OS	45 vs 43 months	0.90 (0.70-1.14)
STAMPEDE	2061	OS	65% vs 62% for 36 months	0.76 (0.68-0.84)

PC: Prostate cancer, OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, RT: Radiotherapy

In a meta-analysis evaluating the results of 3 studies investigating the effect of RT to the prostate on survival in patients with mCSPC, there was no statistically significant difference in terms of OS (HR=0.92; 95% CI=0.81-1.04, p=0.195) and PFS (HR=0.94; 95% CI=0.84-1.05, p=0.238), while there was improvement in terms of biochemical progression (HR=0.74; 95% CI=0.67-0.82) and in event-free survival (HR=0.76, 95% CI=0.69-0.84) in RT arm (36).

The role of local treatment for primary tumor in patients with metatastic PC was investigated in a reprospective study by Culp et al. (37). In the study, data of 8185 patients were scanned. Of those, 7811 patients did not receive local treatment, 245 patients received RP and 129 patients received brachytherapy. Five-year OS was 67.4% in the RP arm and 52.6% in the non-treated arm (p<0.001). In another retrospective study conducted by Gratzke et al. (38), while 1464 of 1538 patients with metastatic PC did not receive local treatment, 245 patients received RP. Five-year OS was 55% in the RP arm and 21% in the non-locally treated arm (p<0.01).

Cost

Various therapeutic agents can be used in the treatment of mCSPC and there is a financial toxicity brought by these agents. The cost of docetaxel CT for 6 cures is approximately 6000 Turkish Liras (TL), but the treatment of conditions such as febrile neutropenia that may arise due to CT-related toxicities may increase this cost. Monthly costs of new generation antiandrogen treatments range between 6,000 and 10,000 TL.

Conclusion

The treatment of PC has been changing rapidly in recent years. Many therapeutic agents are started to be used in the early period of the disease, and the survival results of our patients are happily improving. Since the introduction of docetaxel in 2004, many agents in the groups of CT, new hormonal therapies, immunotherapy and radionuclides have been approved in various stages of PC and have entered clinical use. However, there are no head-to-head randomized controlled trials with these agents. For this reason, many features such as patient characteristics, efficacy, accessibility to treatment, experience, toxicity, drug-drug interactions, expected side effects and cost should be evaluated together in treatment selection.

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Ethics

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Authorship Contributions

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Original Article

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The Effect of an Animation Video and Music on Anxiety and Pain Scores Before TRUS-guided Biopsy

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Abstract

Objective: The aim of this investigation is to investigate the effect of a pre-procedure animated video and music on blood pressure, pain score, anxiety score and pulse rate in patients undergoing transrectal ultrasound (TRUS)-guided biopsy.
Materials and Methods: One hundred and two male patients who underwent a TRUS-guided prostate biopsy were randomised into two groups. A control group: no music or with a video included (n=51) and an experimental group: pre-education with an animation video and music included (n=51) during the procedure. Before and after the TRUS biopsy, the state-anxiety inventory score (STAI), pain visual analogue scale (VAS), heart rate and blood pressure were obtained from each patient and compared. Blood pressure and pulse were recorded by the urologist. Student's t-test and a paired t-test were used for variables with a normal distribution and Mann-Whitney U test and Wilcoxon-rank tests were used for variables that did not show a normal distribution ($p<0.05$).
Results: There were no differences prostate-specific antigen, age and prostate volume between the two groups. VAS, STAI scores and pulses differed between the two groups before and after the procedure. There was no difference in systolic and diastolic blood pressure values before the procedure. However, a significant difference was found between the two groups regarding these values after the procedure. There was a statistically significant difference in the VAS, STAI, blood pressures and pulse rates after the procedure compared with the pre-procedure values ($p<0.05$).
Conclusion: Watching the animation video and listening to music positively affected patients' anxiety, pain score, blood pressure and pulse values. This method is a low-cost, readily available application, which might be preferred by particular patient groups.
Keywords: Anxiety, pain score, transrectal ultrasound-guided prostate biopsy

Introduction

Transrectal ultrasound (TRUS)-guided biopsy is the gold standard for prostate cancer diagnosis. However, the procedure is both painful and uncomfortable for many patients. Therefore, different methods should be applied to relieve the patient's anxiety and pain (1,2). Two factors cause patient discomfort during the biopsy procedure. First is the movement of the ultrasound probe in the rectum, and the other factor is the pain caused by inserting the biopsy needle into the prostate tissue (3). In addition, anal tension and patient anxiety affect the tolerance to pain (4). Various procedures have been applied to reduce pain and anxiety before and during such procedures performed under local anaesthesia (5,6). Music therapy has been used for many years in medicine and has been shown to have a relaxing effect on pain and anxiety in many cases (5,6). Although music therapy is a useful and cost-effective method with positive effects on pain and anxiety, there is not sufficient information about the effect of watching an animation video in addition to music.

Therefore; the aim of this study is to investigate the effect of music video therapy on pain and anxiety in patients who underwent TRUS-guided biopsy, in addition to watching an animation video about the biopsy pre-procedure.

Materials and Methods

A total of 102 patients admitted for TRUS-guided prostate biopsy from February 2018 to February 2020 after obtaining the approval of the Ethics Committee (approval no: 2001/18/108). Patients had either a prostate-specific antigen (PSA) elevation (PSA >4.0 ng/mL) or abnormal findings on a digital rectal examination. They were randomly allocated to the control (group 1, n=51) and experimental groups (group 2, n=51). Exclusion criteria were any anorectal pathology, hearing loss, any psychiatric disease, current analgesic medication, allergy to

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lidocaine or a previous TRUS-guided biopsy. Demographic data, serum PSA and prostate volume were recorded. Physiological indicators (eg, heart rate and blood pressure) were measured, the state-anxiety inventory (STAI) was applied, and pain visual analogue scale (VAS) scores were collected by a blinded urologist pre- and post-biopsy.

All TRUS-guided biopsies were performed by the same surgeon (H.T.). No patients were administered a rectal enema on the day before the biopsy. However, all patients underwent rectal povidone-iodine preparation for biopsy and received antibiotic prophylaxis of Trimethoprim-Sulfametaxol one day before the biopsy (7). The procedure was explained in detail, and all patients signed an informed consent form.

Patients in the experimental group watched and explained the details about a five-minute animation video (Prostate biopsy YouTube animation video, open to everyone, free access. https://www.youtube.com/watch?v=NGh025wYK20) before the procedure, then completed the STAI form. After the biopsy was planned, patients were asked to select the type of music that they would provide them comfort. The patient's musical selection was played continuously during the procedure. Patients were not restricted in the choice of music. Headphones were not used to enable continuous contact with the doctor. A controlled environment was created to minimise the effects of additional variables. All patients were positioned in the lateral decubitus position with knee flexed and hip extended. Four to five minutes before probe introduction, 2% lidocaine and chlorhexidine gel was introduced into the patient's rectum, and 5 cc lidocaine injections were performed in the right and left the periprostatic area. Then, 12 core biopsies of the six right lobes and six left lobes were taken from all patients. The biopsy procedure took an average of 15-20 minutes. VAS values were recorded when injections were given for the periprostatic blockade and immediately after the procedure. Patients self-reported their pain according to the VAS.

VAS scores range from 0 to 10, where 0 =no pain and 10 =intolerable pain (8). The STAI score measures the level of anxiety in patients under certain stress. The scale has 20 items scored using a 4-point Likert scale of patient responses: 1-"not anxious at all", 2-"moderately anxious", 3-"very anxious" and 4-"extremely anxious" The total score can range from 20 to 80, with a lower score indicating a lower anxiety level. The scores were evaluated as 20-39 mild anxiety, 40-59 intermediate anxiety and 60-80 severe anxiety.

Statistical Analysis

Continuous variables were reported as the mean ± standard deviation (SD) and analysed for normal distribution using a histogram and the Kolmogorov-Smirnov test. Variables with normal distribution were analysed using the Student's t-test and paired t-test. Continuous variables not showing a normal distribution were analysed with the Mann-Whitney U test and the Wilcoxon-rank test for the same groups ($p<0.05$).

Results

The patients in the control group had a mean age of 61.2±6.6 years, PSA value of 7.7±1.9 and prostate volume of 54.2±12.4. The experimental group patients had a mean age of 62.1±5.2 years, PSA value of 7.48±1.8 and a prostate volume of 56±10.6. No significant difference was found between the groups regarding age, PSA level and prostate volume (Table 1). The post-biopsy VAS scores were significantly different in both groups compared with the pre-biopsy values ($p<0.05$). A significant difference was found in each group in systolic and diastolic blood pressures post-biopsy compared with pre-biopsy values ($p<0.05$). However, there was no difference between the two groups before the procedure ($p>0.05$). A significant difference was found between the pre- and post-biopsy STAI anxiety scores and pulse values both within the groups and between the two groups ($p<0.05$) (Table 2).

Discussion

Music therapy has been used for many years during surgical procedures under local anaesthesia and is thought to have a relaxing effect on patients. The present study started with the idea that watching a detailed animation video and music about the procedure may have a positive effect on anxiety scores, pain scores and cardiac parameters.

The TRUS-guided prostate biopsy for prostate cancer diagnosis is a routine outpatient procedure. However, despite the application of lidocaine gel combined with the periprostatic blockade, a certain level of fear, anxiety and agitation remains (9).

The avoidance of pain in men undergoing a TRUS-guided prostate biopsy is highly desirable, so various methods have been applied in attempts to control this situation (10).

Many studies have shown that music therapy provides the patient relief after surgery or an invasive procedure (5,11). In clinical studies, music has positive effects on physiological and psychological parameters and has also been reported to have anxiolytic properties and positive effects in stressful interventions (12). In the current study, music therapy and animation video were used in outpatient TRUS-guided prostate biopsy patients, and positive results were obtained on pain scores and anxiety.

The soothing effect of music reduces fear and anxiety in patients and has been shown to make it easier for the patient to tolerate the procedure in re-biopsy cases (13). However, studies are showing that music does not affect anxiety scores, heart rate or blood pressure. In a study by Ebneshahidi and Mohseni (14), music chosen by patients undergoing caesarean section was seen to decrease pain and analgesic requirements in the post-operative period. However, no change in anxiety scores, heart rate and blood pressure were observed (14). Another study showed that the music did not change the STAI and pain scores (15). Although it has been investigated whether pre-procedure training would have an effect with music, no consensus has

Table 1. General information

	Control (MD ± SD)	Experimental (MD ± SD)	p-value
Age (years)	61.2±6.6	62.1±5.2	0.45
PSA (ng/dL)	7.7±1.9	7.48±1.8	0.56
Prostate volume (cm^3)	54.2±12.4	56±10.6	0.19

SD: Standard deviation, PSA: Prostate-specific antigen, MD: Mean difference

been established (6,16). During the procedure, the patient faces the opposite side and cannot see the procedure. Therefore, an animation video explaining the process in detail can be shown to the patient before the process. In this study, the experimental group watched an animation video with music before the process. As a result, a significant difference was observed in systolic and diastolic blood pressure values, pulse and STAI anxiety scores in the patient group informed by animation with music. Although the pre-procedure values were not the same between the two groups, the decrease in STAI scores in the experimental group was significant compared with the post-biopsy value of the control group. This finding is especially important for patients receiving antipsychotic treatment or psychiatric problems. We believe that watching music and animation videos will comfort this group of patients.

TRUS biopsy may cause a rise in blood pressure. This increase may cause hypertensive attacks in patients with uncontrolled hypertension, angina and arrhythmias in patients with coronary artery disease and dyspnoea in patients with heart failure.

In the study, blood pressure values were recorded in both groups before the procedure. Changes in systolic and diastolic blood pressures after the procedure suggest that music and video may be an effective tool for blood pressure (Table 3).

Some studies reported that music might distract patients from anxiety and worries and reduce pain and distress (17,18). However, another study showed that listening to music during or after the biopsy had no significant pain reduction in patients (19). In this study, the VAS score was mild to moderate (mean ± SD, 3.1±1.5) in all patients, attributed to the effective periprostatic blockade. When the two groups were compared, there was a significant difference in VAS values. Likewise, a significant difference was observed between the two groups before and after the procedure (pre-biopsy and post-biopsy). However, this difference was not clinically significant because patients were evaluated regarding low VAS scores (Table 3).

Study Limitations

There were some limitations to this study. This study included only a relatively low number of patients. It was not possible to control pain sensation at every stage of the procedure, such as when the ultrasound probe was inserted into the anus, or the needle was inserted during the periprostatic blockage. The biopsy gun's sound was loud and made patients uncomfortable, although it had been tested before the procedures. Despite these limitations, the present study showed that listening to music and pre-education by watching an animation video

Table 2. Comparisons between the experimental and control groups, pre- and post-test

	Control (n=51)	Experimental (n=51)	P[1]	P[2]	P[3]
VAS			0.008	<0.001	0.02 0.01
Pre-test Post-test	3.72±1.9 4.72±1.2	2.59±0.7 3.7±1.4			
STAI			0.001	<0.001	<0.001 <0.001
Pre-test Post-test	40.1±2.3 37.7±3.3	36.5±36 29.6±1.4			
Systolic Pressure (mmHg)			<0.001	0.001	0.159 0.044
Pre-test Post-test	138.1±9.0 147.9±5.8	140±8.4 145±5.0			
Diastolic Pressure (mmHg)			<0.001	<0.001	0.291 <0.001
Pre-test Post-test	81.3±8.5 96.6±2.3	79±5.6 90.8±5			
Heart Rate			<0.001	<0.001	0.015 0.019
Pre-test Post-test	79.6±2.7 73.2±2.8	77.4±4.1 71.3±3.7			

P[1]: Comparison of pre-test and post-test control group values
P[2]: Comparison of pre-test and post-test experimental group values
P[3]: Comparison of control and experimental group values
VAS: Visual analogue scale, STAI: State-trait anxiety inventory

Table 3. Changes in evaluated variables between the experimental and control groups

	Experimental group	Control group	p-value
ΔVAS	1.13±1.44	1.0±2.3	0.7
ΔSTAI	-6.8±3.9	-2.4±4.0	<0.001
ΔSystolic pressure	5.5±9.4	9.8±10.1	0.048
ΔDiastolic pressure	11.8±7.2	15.3±8.6	0.045
ΔHeart rate	-6.1±5.2	-6.3±3.4	0.086

VAS: Visual analogue scale, STAI: State-trait anxiety inventory

decreased anxiety, heart pressure and heart rate during a TRUS-guided biopsy.

Conclusions

Watching the animation video and listening to music during the TRUS-guided biopsy procedure can be obtained quickly and had positive effects on patients. This method offers a safe option for patients with cardiac pathology, psychiatric problems and indications for re-biopsy in urological procedures.

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Ethics

Ethics Committee Approval: The study has been approved by the Medicalpark Karadeniz Hospital Ethics Committee (approval no: 2001/18/108).

Informed Consent: All patients signed an informed consent form.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Original Article

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Multiparametric MRI Fusion-guided Biopsy for the Diagnosis of Prostate Cancer: Results of the First 100 Consecutive Patients

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Abstract

Objective: Our aim was to compare prostate cancer detection rates according to International Society of Urological Pathology (ISUP) grade group (GG) among magnetic resonance imaging (MRI)-targeted biopsies (TBx), systematic biopsies (SBx) and a combination of both (TBx + SBx).

Materials and Methods: Between July 2018 and Nov 2020, 100 patients undergoing MRI-targeted prostate biopsy and SB were analysed retrospectively. Men with MRI-visible prostate lesions underwent both MRI-targeted (UroNav®) and systematic 12-core biopsy. The primary outcome was cancer detection according to ISUP GG. The secondary outcome were detection of cancers of GG 2 or higher.

Results: The overall cancer detection rate in the study was 43%. Among these, a histopathological ISUP grade of 1 was detected in 44.2%, ISUP grade 2 in 32.5% and higher-grade groups in 23.2% of patients. MRI-TB detected 38 and SBx biopsy detected 30 of the overall study cohort. Combined biopsy led to a cancer diagnoses in 18 more men than with either method alone. Significant cancer detection was 53.4% for TBx, 39.5% for SBx, and highest 55.8% for combination TBx + SBx (p=0.038). Most of the cancers missed by SBx were clinically significant. No significant side effects were recorded. The overall cancer detection rate was 20.4%/46.6% and 90.2% for prostate imaging reporting and data system 3/4/5, respectively.

Conclusion: Our results have shown that among patients with lesions visible on MRI, combined biopsy led to greater detection of all prostate cancers, providing increased detection of clinically significant tumours.

Keywords: Prostate cancer, detection, targeted biopsy, MRI US Fusion, prostate biopsy

Introduction

Prostate cancer (PCa) is the most common cancer among Northern and Western European men (1). To further improve survival in patients with PCa, it is necessary to differentiate between clinically insignificant and clinically significant cancer. In current clinical practice, Transrectal Ultrasound-guided prostate Biopsy (TRUS Bx) is the commonly used technique to further evaluate a suspected PCa diagnosis. The current diagnostic approach including PSA testing and digital rectal examination followed by transrectal ultrasound biopsies lacks both sensitivity and specificity in PCa detection and offers limited information about the aggressiveness and stage of the cancer (2,3,4). Recent scientific work supports the rapidly growing use of multiparametric magnetic resonance imaging (mpMRI) as a promising tool of growing importance in PCa evaluation. With the introduction of mpMRI, the accuracy for the localisation and detection of PCa is improved (3,5,6). Its use may improve many aspects of PCa management, from initial detection of significant tumours using mpMRI-guided biopsies to evaluation of biological aggressiveness and accurate staging, which can facilitate appropriate treatment selection. The use of mpMRI and MRI-targeted biopsy (TB) has been shown to improve PCa detection by increasing the overall PCa detection rate and reducing the detection of insignificant tumours (3,4,5,6,7). However, experience with MRI-targeted biopsies in PCa diagnosis in Turkey has been very limited. Therefore, we carried out this study to evaluate the use of mpMRI in disease detection and the assessment of histopathological aggressiveness.

Materials and Methods

Based on our prospective database, 100 consecutive biopsy-naive patients who underwent MRI-TB combined with systematic 12-core prostate biopsy (TBx + SBx) during the period between July 2018 and November 2020 were identified and included in the

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analysis. Patients with firm palpable prostate nodules suggestive of cancer, any patient who had previously undergone prostate biopsy and patients with known urinary tract infections were excluded from the study. All patients gave informed consent. Patients for whom had complete pathological data were available for each Bx scheme were investigated. The patient's age and PSA level and the highest GS of each Bx scheme were evaluated. Since the study was a retrospective case-control study, IRB approval was not required.

All mpMRI for targeted biopsies were reviewed by the specified radiologist. In patients with a prostate imaging reporting and data system (PI-RADS) lesion ≥3 (according to the PI-RADS"-v2 classification) (8), software-based MRI-targeted ultrasound fusion biopsies using UroNav® (Invivo Corp, Philips, USA) were conducted. All biopsies were performed using a transrectal approach under IV sedation anaesthesia and antibiotic prophylaxis with a single dose of Fosfomycin the night before and IV Gentamycin 120 mg + third Generation Cephalosporin 1 hour before the procedure. MRI image- fusion-targeted biopsies were taken from each target, and at least 2 core samples were taken from each target lesion. In addition to targeted biopsies, SBx were performed using a 12-core approach. The biopsy cores were evaluated by dedicated uro-pathologists. The biopsy Gleason score was defined as the highest Gleason score in at least one core and was reported using the International Society of Urological Pathology (ISUP) Consensus Conference 2014 grading system (9).

Statistical Analysis

Descriptive statistics included continuous variables and frequencies and proportions for categorical variables. Differences were analysed with the use of a chi-square test using SPSS software. Differences were considered statistically significant at $p \leq 0.05$.

Results

Patient demographics of the study cohort stratiŞed by biopsy approach are depicted in Table 1. The median number of TB cores sampled per region of interest was 4 (2,3,4,5,6,7).

The overall cancer detection rate in the study was 43%. Among these 43 patients, a histopathological ISUP grade of 1 was detected in 19 (44.2%) patients, ISUP grade 2 in 14 (32.5%) patients and higher-grade groups in 10 patients (23.2%). Cancer was detected by MRI/US-TB in 38 and by SB in 30 of the overall study cohort of 100 patients. Combined biopsy led to cancer diagnoses in 18 more men than with either method alone. There was a significant difference in the missed cancer ratio between TBx and SBx (11.6% vs 30.2%, p=0.01), in that any grade of cancer detection by SBx alone was significantly lower than by TBx alone.

Many patients had different PI-RADS scores registered by target lesion in the same patient. When the results were divided according to PIRAD grade, the positivity rates were 20.4%, 46.6% and 90.2% for PIRAD 3, PIRAD 4 and PIRAD 5 scores, respectively.

The rate of significant cancer detection was 53.4% for TBx, 39.5% for SBx and 55.8% for combination TBx+SBx, indicating that more significant cancer (ISUP grade 2 or higher) is detected by MRI fusion biopsy. If only SBx biopsies had been performed, 13.9% of clinically significant cancers would have been misclassified. Most of the cancers missed by SBx were clinically significant (Figure 1).

No significant side effects such as fever, urinary retention, urosepsis, and hospitalisation were recorded in any patient, except mild haematuria and hematospermia.

Discussion

In modern times, mpMRI of the prostate is becoming an integrative part of the diagnostic workup of PCa. Several prospective trials demonstrated that TBx can increase PCa

Table 1. Patients characteristics and pathological findings of the study cohort

Variables		**Combined MRI-TBx + SBx method (n=100)**			
Age (year)		58.6±4.1 (48-75)			
PSA (ng/dL)		6.1±3.9 (2.2-27)			
Cancer Detected n=43		**MRI-TBx**	**SBx**	**Combined MRI-TBx + SBx**	-
	Missed Cancer	5	13	0	-
Biopsy ISUP Grades	1	15	13	19	
	2	13	9	14	
	3	8	6	8	
	4	1	1	1	
	5	1	1	1	
PI-RADS 3				20.4 %	
PI-RADS 4				46.6%	
PI-RADS 5				90.2%	

MRI: Magnetic resonance imaging, TBx: Targeted biopsies, SBx: Systematic biopsies, ISUP: International Society of Urological Pathology, PI-RADS: Prostate imaging reporting and data system, PSA: Prostate-specific antigen

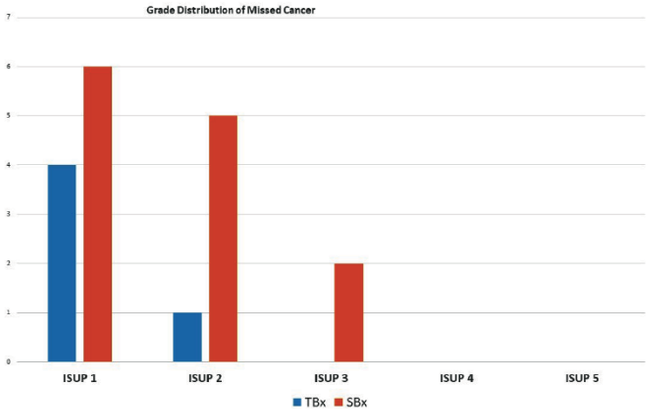

Figure 1. Distributions of ISUP grades of missed cancer according to the biopsy method

ISUP: International Society of Urological Pathology

detection rates, especially that of clinically significant PCa (GGG ≥2), while lowering the detection rate of low-risk PCa (2,10,11,12,13,14).

In this cohort of patients, combined TBx + SBx biopsy provided a more accurate diagnosis than MRI-targeted or SB alone. Consistent with earlier studies, we found higher cancer detection rates on TBx when compared with SBx (7,10). However, 5 out of 43 prostate cancers (11.6 %) went undetected by TBx alone. Missed cancers by TBx may reflect the underlying limitation of mpMRI, which is the possibility of invisible PCa on mpMRI, varying inter-reader agreement on the mpMRI results and missing the target lesion in biopsy.

The combination of TB and SB was superior to either method alone for the detection of clinically significant PCa (ISUP 2 or higher). When TBx alone to SBx alone are compared for the detection rate of significant PCa diagnosis, overall TB alone tends to detect more significant PCa but this superiority does not reach statistical significance. Our result complements previous results favouring MRI-targeted biopsies (15,16). Several other studies have compared MRI fusion-TB with SB with diverging results depending on the type of SB used or number of cores taken. Some found that MRI-TB led to increased detection of high-risk cancer and decreased detection of low-risk cancer but missed up to 6% of higher-risk tumours. On the other hand, others found similar detection rates in systematic and targeted transrectal biopsies (10,16,17). In the present study, SBx had inferior yet important performance to TBx in determining high-grade cancers. This may be a result of the cognitive fusion bias within the SBx that occurred when the urologist performing the SBx was aware of the localisation of the suspicious lesion on mpMRI. In our study, if a pure TBx strategy omitting SBx were to be applied, this would lead to missing up to 5 patients with cancer. Our results support that to obtain the most accurate assessment of the entire prostate gland, SBx remains necessary, in addition to TBx, due to limitations of mpMRI performance/reading and of precision during lesion targeting.

In the current study, we report our experience of biopsied PI-RADS 3,4,5 lesions. We found our detection rate of prostatic adenocarcinoma amongst these lesions to be 20.42%, 46.6% and 90.2% respectively. The results of the current study demonstrate a good correlation between PI-RADS scores and positive biopsy. The cancer detection rate stratified by PI-RADS score is similar to that reported in the published literature (18). However, there are different cancer detection rates according to PI-RADS score. Previous studies reported overall cancer detection rates of PI-RADS v2 categories 3, 4 and 5 of 39%, 72% and 91%, respectively, for all prostate cancers. On the other hand, several studies reported lower detection rates (19). The DWI PI-RADS score alone correlates well with positive biopsies in the peripheral zone, but not the transition zone (20). PI-RADS v2 uses a simplified approach but shows a lower diagnostic accuracy. This could lead to a higher rate of false-negative results with the risk of missing tumours within low PI-RADS score levels. When performing a TB, combination with a SB still provides the highest detection rate of prostate cancer.

Study Limitations

The present study has several limitations. First and foremost, our manuscript was based on a retrospective analysis of only one centre. Our study was limited to a rather small cohort of 100 patients. In all our patients, MRI-TBx was performed by using the transrectal approach. We could not measure the potential positive or negative effects of other platforms on detection rates using transperineally biopsy systems. Moreover, failure of mpMRI fusion biopsy due to incorrect mpMRI image registration or mismatching of image planes, inaccurate sampling and intralesion Gleason score heterogeneity may have impacted on our results. However, our data reflect the real-life picture.

Conclusion

Our study shows that MRI-targeted biopsies in patients with suspected PCa result in a high detection rate and clinical significance of diagnosed tumours. These results suggest that MRI-based diagnosis and subsequent targeted biopsies fulfil an important role in increasing the detection rate and accuracy in the diagnosis of PCa. Since multiparametric MRI still has some risk of missing tumours; additional systematic 12 core biopsies should not currently be omitted.

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Ethics

Ethics Committee Approval: Since the study was a retrospective case-control study, IRB approval was not required.

Informed Consent: All patients gave informed consent.

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Original Article

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Comparison of Prostate Cancer Detection Rates of Cognitive Fusion-targeted Biopsy and Standard Transrectal Ultrasound-guided Biopsy

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Abstract

Objective: The aim of this study is to investigate whether there is a difference between standard prostate needle biopsies and cognitive fusion prostate biopsies (classical 12-core plus 2 cognitive lesions) for any prostate cancer or clinically significant prostate cancer (CSPCa) detection rates.

Materials and Methods: The records of 340 patients who underwent standard transrectal ultrasound-guided biopsy (TRUS-SB) and cognitive targeted biopsy (COG-TB) between June 2015 and January 2020 at our institute were retrospectively reviewed and included in the study. There were 185 patients in the TRUS-SB (12-core) group and 155 patients in the COG-TB (12-core + 2 lesions) group. Patients undergoing COG-TB underwent 3-T multiparametric magnetic resonance imaging before the biopsy procedure and were evaluated with the prostate imaging reporting and data system version 2. The rates of any prostate cancer and CSPCa were compared between groups.

Results: The patient mean ages were determined as 64.02±5.15 and 64.41±3.93 years for the TRUS-SB and COG-TABLO groups, respectively. Any prostate cancer was detected in 38/185 patients (20.54%) in the TRUS-SB group, and 44/155 patients (28.38%) in the COG-TB group. CSPCa rates were determined as 57.80% (22/38 patients), and 56.8% (25/44) for the TRUS-SB and COG-TB groups, respectively. There was no statistically significant difference between the groups regarding cancer (p=0.092) and CSPCa detection rates (p=0.843).

Conclusion: In our study, no significant difference was found between the overall prostate cancer and clinically important prostate cancer detection rates between the TRUS-SB and COG-TB groups.

Keywords: Biopsy, cognitive fusion, standard biopsy prostate cancer, multiparametric magnetic resonance imaging

Introduction

Prostate cancer is the second most common cancer in men and ranks fifth among the causes of cancer-related deaths. It is reported that approximately 1.3 million patients worldwide have been diagnosed with prostate cancer in 2018 (1). The incidence of prostate cancer has started to increase, especially with the introduction of the prostate-specific antigen (PSA) test introduced in the 1980s. Transrectal ultrasound-guided standard prostate biopsy (TRUS-SB) is the gold standard method to diagnose cancer in patients with suspected prostate cancer suggested by increased PSA levels or detection of the prostatic nodule(s) during a digital rectal examination (DRE). Initially, a six-core systematic, sextant biopsy protocol was used (2). However, the number of cores obtained increased over time, with 12-14 cores being taken as standard practise (3). While cancer detection rates were reported to range between 27% and 44% with TRUS-SB, 15% to 34% of cancer cases may be overlooked (4). Although saturation biopsy procedures were started when 20 or more cores were obtained, only a limited increase in prostate cancer detection rates was achieved with this technique (5). TRUS-SB has the advantage of lower cost and faster application; however, it diagnoses an excessive number of clinically insignificant cancer (CISPCa) cases and leads to

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numerous unnecessary treatments. It also detects clinically significant cancers (CSPCa) at a lower rate and has limitations, such as false negativity (6). In parallel with the developments in magnetic resonance imaging (MRI), multiparametric prostate MRI (Mp-MRI), which provides information about the prostate's anatomical and functional structure has been started to be used to prevent these limitations. The aim is to increase clinically significant prostate cancer (CSPCa) detection rates by taking fewer samples from the prostate (7). MRI targeted fusion biopsies are performed in three ways:

1. Real-time MRI-guided biopsy [(MRI in bore- targeted biopsy (TB)].

2. Fusion biopsy (MRI Ultrasound Fusion Software) (MRI/US-TB) combines MRI and ultrasound images using the software.

3. Cognitive biopsy (COG-TB) uses biopsy materials obtained from these suspicious areas after detecting suspicious lesions with Mp-MRI (8).

While performing a biopsy after MRI in all applications, there is also an application unity about adding 12 quadrant standard biopsies. Although there are studies in this direction, it is not recommended to take a biopsy only from the lesion (9). In this study, we aimed to evaluate whether there is a difference between standard TRUS-guided prostate needle biopsies and cognitive fusion prostate biopsies, regarding the detection rates of any prostate cancer and clinically significant prostate cancer.

Materials and Methods

Using our computerised database, the records of 377 patients who underwent TRUS-SB and COG-TB between June 2015 and January 2020 at our institute were retrospectively analysed. Patients with suspicious findings such as induration or nodules suggest prostate cancer on DRE or high PSA levels were included in the study. Patients with a large nodule detected during DRE suggesting suspected metastatic disease (n=12) and patients with a previous history of negative biopsy (n=25) were excluded from the study. A total of 340 patients, including 185 cases in the TRUS-SB group and 155 cases in the COG-TB group, were enrolled in the study. In the COG-TB group patients with suspected lesions detected on prebiopsy MP-MRI were also included in the study. MRI examinations were performed with three Tesla MRI units (Ge Healthcare 3T; Pioneer Signa MLG, Japan). T2-weighted, dynamic contrast diffusion-weighted images and visible diffusion coefficient maps were obtained. MRI images were examined by a single radiologist experienced in the field. Suspicious lesions were identified, and Prostate Imaging Reporting and Data System (PI-RADS) scoring was performed. (PI-RADS 1 =Very low CSPCa is highly unlikely to be present, PI-RADS 2 =Low CSPCa is unlikely to be present, PI-RADS 3 =Intermediate the presence of CSPCa is equivocal, PI-RADS 4 =High CSPCa is likely to be present, PI-RADS 5 =Very high CSPCa is highly likely to be present) (10). All biopsies were performed by the same urologist. Antibiotic prophylaxis with one gramme intravenous ceftriaxone and bowel prep were performed one hour before the procedure. After the patient was discharged, oral treatment with ciprofloxacin (500 mg twice a day) was maintained.

Biopsies were performed in the operating room by applying sedoanalgesia or caudal block. A 12-core systematic standard biopsy was performed in the TRUS-SB group by placing an endorectal TRUS probe (4-9 MHz endorectal probe PVT-781, Toshiba, Japan). Two more core biopsies were taken per suspected area in patients with suspicious findings on DRE or TRUS. In the COG-TB group, after inserting the TRUS probe, the suspicious lesions described on the Mp-MRI attempted to be identified. After taking two core biopsies per lesion from the regions with suspected areas, 12 systematic core biopsies were performed. An 18 Gauge 25 cm biopsy gun (Bard Monopty Biopsy gun) was used for biopsy. Tissues placed in 10% buffered formalin solution were sent to the laboratory for histopathological examination.

Any evidence of cancer, CSPCa and CISPCa rates were compared between the groups. There is still no consensus on the definition of CSPCa. For this reason, we preferred a frequently used definition when determining CSPCa rates. Based on the histopathology reports, prostate cancers with Gleason scores (GS) of ≥7 were accepted as CSPCa. Similarly, GS 6, with a more than 5 mm tumour length in any of the cores, was considered CSPCa (11,12).

Statistical Analysis

SPSS program (SPSS version 20.0; IBM, NY, USA) was used for statistical evaluation. Descriptive statistical methods (mean, standard deviation) and the chi-square test were used to evaluate the data. $P<0.05$ was considered statistically significant. At all stages of the study, families were informed about the procedure, and informed consent forms were obtained. This study was conducted in accordance with the principles of the Helsinki Declaration and approval of the Ethics Committee of our institute was obtained (register no: 2018/15-14).

Results

The mean ages of patients included in the study were determined as 64.02±5.15 and 64.41±3.93 years for TRUS-SB and COG-TB groups, respectively. The mean serum PSA values were 11.83±4.13 ng/mL in the TRUS-SB group, and 9.1±5.37 ng/mL in the COG-TB group. The mean prostate volumes were 72.72±19.1 and 71.51±24.3 g in the TRUS-SB and COG-TB groups. The mean GS were determined as 6.40±0.8 and 6.31±1.1 for TRUS-SB and COG-TB groups. In the COG-TB group, the percentages of patients with PI-RADS 2, 3, 4 and 5 scores in Mp-MRI were 16.7%, 41.9%, 33.5% and 7.74%, respectively. The lesion's mean length in the MRI (mm) was determined as 14.27±3.1 mm (Table 1).

The average number of cores taken were determined as 2.90±0.4 and 3.65±1.1 for TRUS-SB and COG-TB groups, respectively. The median positive cancer core length detected in the cores taken on biopsy was determined as 3.12±0.3 mm in TRUS-SB and 5.22±1.3 mm in COG-TB groups. Any prostate cancer was detected in 38/185 patients (20.54%) in the TRUS-SB group and 44/155 patients (28.38%) in the COG-TB group. The CSPCa rates were determined as 57.80% (22/38 patients) and 56.8% (25/44) for TRUS-SB and COG-TB groups, respectively (Table 2). There was no statistically significant difference between the groups regarding cancer detection (p=0.092) and CSPCa detection rates (p=0.843).

Table 1. Comparison of patient characteristics in the TRUS-SB and COG-TB groups

	TRUS-SB (n=185)	COG-TB (n=155)
Patient age (years)	64.02±5.15	64.41±3.93
PSA value (ng/mL)	11.83±4.13	9.1±5.37
Prostate volume (gramme)	72.72±19.1	71.51±24.3
Mean Gleason score	6.40±0.8	6.31±1.1
Mean length of the lesion in the MRI (mm)	-	14.27±3.1
PI-RADS 2 (n)	-	26 (16.7)
PI-RADS 3 (n)	-	65 (41.9)
PI-RADS 4 (n)	-	52 (33.5)
PI-RADS 5 (n)	-	12 (7.74)

Data are presented as mean ± standard deviation.
Data in parentheses represent percentages; n: Number of patients; mm: Millimetre, TRUS-SB: Transrectal ultrasound-guided biopsy, COG-TB: Cognitive targeted biopsy, PI-RADS: Prostate Imaging Reporting and Data System, MRI: Magnetic resonance imaging

Table 2. Comparison of biopsy results and complications between the TRUS-SB and COG-TB groups

	TRUS-SB (n=185)	COG-TB (n=155)
No. cores (per patient)	2.90±0.4	3.65±1.1
Median positive cancer core length (mm)	3.12±0.3	5.22±1.3
Positive for any cancer (n)	38 (20.54%)	44 (28.38%)
Positive for clinically significant cancer (n)	22 (57.80%)	25 (56.80%)
Complications (n)	30 (16.21%)	21 (13.54%)
Haematospermia	12 (6.48%)	8 (5.16%)
-Urinary tract infections	7 (3.78%)	5 (3.22%)
-Significant haematuria	3 (1.62%)	3 (1.93%)
-Urinary retention	5 (2.70%)	3 (1.93%)
-Sepsis	2 (1.08%)	1 (0.64%)
-Significant rectal bleeding	1 (0.54%)	1 (0.64%)

Data in parentheses represent percentages, n: Number of patients, TRUS-SB: Transrectal ultrasound-guided biopsy, COG-TB: Cognitive targeted biopsy

The complication rates were determined as 16.21% (30 patients) and 13.54% (21 patients) for TRUS-SB and COG-TB groups, respectively. The most common complication in the TRUS-SB group was haemospermia in 12 (6.48%) patients. Infection is another common complication and was detected in seven (3.78%) patients. Other complications were urinary retention in five (2.70%), massive haematuria in three (1.62%), urosepsis in two (1.08%) patients, and massive rectal bleeding only in 1 (0.54%) patient. Similarly, the most common complication in the COG-TB group was haemospermia in eight (5.16%) patients. Infection was observed in five (3.22%), urinary retention in three (1.93%), massive haematuria in three (1.93%), urosepsis in one (0.64%) and massive recurrent rectal bleeding in only one (0.64%) patient. In both groups, mild and moderate self-limiting haematuria and rectal bleeding were not considered complications and not included in the complication rates (Table 2). The mean operation time was determined as 9.2±0.8 min in the TRUS-SB and 11.3±1.8 min in the COG-TB groups.

Discussion

Prostate cancer is the second most common cancer in men (1) In the 1980s, the PSA was introduced, and the number of patients diagnosed started to increase. In a case of high PSA or the detection of prostatic induration on DRE, a biopsy is performed with suspicion of prostate cancer. Even asymptomatic patients undergo biopsy after the detection of increased PSA. Pathological examinations of patients who were operated for benign prostatic hyperplasia or the detection of undiagnosed cancer on autopsy have increased the prostate cancer incidence (1,13). TRUS-SB was first introduced in 1989 by Hodge et al. (2) to assist in prostate cancer diagnosis. It is now used as the gold standard method in the diagnosis of prostate cancer. Although it has the advantage of quick application at low cost, it has disadvantages such as overestimating CISPCa and underestimating CSPCa. This leads to unnecessary and excessive treatment. These disadvantages were eliminated with the developments in MRI when the Mp-MRI started to be used. Suspected lesions regarding malignancy in the prostate were identified before the biopsy and started to be targeted during the procedure (14). The ideal prostate biopsy has been defined as being minimally invasive by taking fewer cores, having a low side effect profile, determining CSPCa in a high rate of patients, and minimising the CISCPCa detection rate to reduce unnecessary overtreatment (14).

In a recent systematic review and meta-analysis, Hu et al. (15) stated that MRI-guided biopsies are more useful than TRUS-Bx in detecting any cancer and CSPCa. They also reported that MRI-guided biopsies had a significantly higher detection rate in detecting any prostate cancer in patients with an initial biopsy. They reported that they did not detect a significant difference between the two groups regarding detecting any cancer and CSPC for patients with a previously negative biopsy (15). Schoots et al. (14) reported no significant difference in the rates of any cancer detection compared with TRUS-SB in biopsies performed with MRI guidance. However, the CSPCa detection rate was higher in the MRI group. In another study, Kasivisvanathan et al. (16) reported that in prostate cancer diagnosis that has not been previously biopsied, risk assessment with MRI, and then performing MRI-TB before the biopsy is more advantageous than TRUS-SB. Contrary to these studies, Baco et al. (17) reported no significant difference in the detection rate of CSPC between MRI-guided biopsies and TRUS-SB. In our study, no significant difference was found between COG-TB and TRUS-SB regarding detecting any prostate cancer and CSPCa in accordance with the results of Baco et al. (17). Although higher rates of any prostate cancer were detected in the COG-TB group, this was not significantly different from those detected in the TRUS-SB group (p=0.092).

Although transrectal prostate needle biopsy is a safe procedure, it can sometimes cause serious complications, such as sepsis, which will require hospitalisation. Serious complications are rare and minor complications such as haematuria is more common (18). The most common complications after prostate biopsy

are haematuria, haematospermia rectal bleeding, urinary tract infections and acute urinary retention (19). It has been reported that the rates of major complications such as massive haematuria, rectal bleeding or sepsis vary between 0.5% and 6.6%, and the rates of complications requiring hospitalisation range between 0.5% and 4.8% (19,20). Our study's overall complication rates were 16.21% in the TRUS-SB group and 13.54% in the COG-TB group. Major complication rates were 3.24% and 3.22%, respectively, in the TRUS-SB and COG-TB groups, consistent with the literature findings.

Study Limitations

The most important limitation of this study is its retrospective design. Prospective randomised studies comparing MRI COG and standard 12-core biopsy would help in this regard. However, only 12-core standard biopsies might not be ethically possible for this patient when an MRI report is available.

Conclusion

Our study did not find any significant difference between the overall prostate cancer and CSPCa detection rates between TRUS-SB and COG-TB. Therefore, considering the costs and the country's economy, standard systematic TRUS-SB may be sufficient, especially in patients who initially underwent prostate biopsy. However, we think that it would be more appropriate to perform rebiopsy under MRI guidance in patients with a previous history of a negative biopsy.

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Ethics

Ethics Committee Approval: This study was conducted in accordance with the principles of the Helsinki Declaration and approval of the Ethics Committee of our institute was obtained (register no: 2018/15-14).

Informed Consent: Informed consent forms were obtained.

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Authorship Contributions

Concept: O.A., M.E., M.N.B., E.D., B.K., S.Ç., S.S.Ç., A.H.T., Design: O.A., M.E., M.N.B., B.K., S.Ç., S.S.Ç., A.H.T., Data Collection or Processing: O.A., M.E., M.N.B., E.D., S.Ç., S.S.Ç., Analysis or Interpretation: O.A., M.E., M.N.B., A.H.T., Literature Search: O.A., M.E., M.N.B., E.D., B.K., S.S.Ç., Writing: O.A., M.E., E.D., S.Ç.

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Are the Recommended Criteria for Clinically Insignificant Prostate Cancer Applicable to 12-core Prostate Biopsy Scheme? A Multicentre Study of Urooncology Association, Turkey

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Abstract

Objective: The aim of this study is to investigate the relevance of the Epstein criteria for the 12-core transrectal prostate biopsy (TRUS-Bx) scheme with the evaluation of clinicopathologic data recorded in the Urologic Cancer Database - Prostate (UroCaD-P), Urooncology Association, Turkey (UOAT).

Materials and Methods: Patients with detailed pathological 12-core TRUS-Bx data for each biopsy core and who underwent RP due to PCa were included in this study. A total of 1167 patients from seven different centres were analysed. TRUS-Bx pathological findings were separately evaluated in the areas matching the sextant biopsy (6-core paramedian-lateral) scheme and in all 12-core biopsy areas (12-core biopsy scheme). Overall detection rates of PCa and ratios of clinically significant (sPCa) and insignificant PCa (insPCa) after RP were defined and compared between the biopsy schemes. Biopsy findings, according to the Epstein criteria, were also compared between the two schemes. A model for each biopsy scheme was created, including the Epstein criteria and additional biopsy findings using logistic regression analysis to predict clinically sPCa after RP.

Results: There was a high correlation for the prediction of clinically insPCa between the two biopsy schemes in the same population. However, 7.3% of PCa could not be diagnosed in the 6-core TRUS-Bx scheme. Also, 69.4% of these had clinically sPCa according to the Epstein criteria in 12-core TRUS-Bx scheme and 51.8% of these were clinically sPCa after RP. The presence of perineural invasion (PNI) in 12-core biopsy was also significant regarding predicting sPCa ($p<0.001$).

Conclusion: The Epstein criteria in 12-core prostate biopsy provide a better prediction of clinically sPCa than the 6-core biopsy scheme. Biopsy PNI findings appeared to improve the effectiveness of 12-core prostate biopsy, in addition to the Epstein criteria.

Keywords: Prostate cancer, radical prostatectomy, clinically insignificant prostate cancer, Epstein criteria, 12-core prostate biopsy scheme

Introduction

Prostate cancer (PCa) is the most common cancer in men (1). Currently, diagnosis is via TRUS-guided biopsy (TRUS-Bx) based on prostate-specific antigen (PSA) level and digital rectal examination. However, not all forms of PCa will progress, and detection of clinically insignificant PCa (insPCa) may cause over-treatment in some patients. Although active surveillance

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is an increasingly adopted management approach preventing unnecessary treatment in this patient category (very low-risk localised PCa), a substantial number of patients are still subjected to surgical or radiation-based interventions (2). Therefore, accurate identification of the clinical significance of tumours is crucial in avoiding unnecessary treatment with potential side effects or delay of curative therapy for whom it is required.

Initial attempts for a valid definition of clinical significance were based on tumour volume in 1993 by Stamey et al. (3). Later, preoperative criteria for the prediction of insPCa were defined in 1994 by Epstein et al. (4). Based on sextant biopsy findings, it was defined as a tumour <0.2 mL, organ-confined disease and a Gleason score (GS) <7. This comprised 16% of all PCa in their series (4). The initial report's positive and negative predictive values were 95% and 66%, respectively, for insPCa (4). Subsequently, the Epstein criteria began to be used to predict insPCa to categorise patients for surveillance. However, diverse concordance ratios (37%-96.9%) were reported for the predictive ability of the Epstein criteria in various studies over time (5). During the same period, optimisation studies of TRUS biopsy schemes resulted in a general acceptance of obtaining 12 cores for biopsy. Although the Epstein criteria are assumed to be valid for 12-core biopsies, very scarce information is available in the current literature to support this view.

Therefore, we investigated the validity of the Epstein criteria, as defined according to the sextant biopsy scheme, for the currently utilised 12-core prostate biopsy protocol by analysing the clinicopathologic data recorded in the Urologic Cancer Database - Prostate (UroCaD-P), Urooncology Association, Turkey (UOAT).

Materials and Methods

In this study, we retrospectively reviewed the data of 3,300 patients in the UroCaD-P, UOAT between 2007 and 2019. Data were anonymised entirely in compliance with the local regulations at the source centre before being recorded in the UroCaD-P. Patients who had detailed 12-core TRUS-Bx pathologic data for each biopsy core and subsequently underwent radical prostatectomy (RP) (open, laparoscopic or robotic) due to PCa were included in the study. Patients with incomplete data for TRUS-Bx and/or RP were excluded. As a result, 1,167 patients from 7 different centres were evaluated in the study. Pathological findings were separately evaluated in the areas matching the sextant biopsy (6 cores paramedian-lateral) scheme and all 12-core biopsy areas (6 cores paramedian-lateral and 6 cores far-lateral) and were separately entered into the database for each patient. Detection rates of PCa and ratios of clinically significant (sPCa) and insPCa after RP were separately evaluated and compared between the biopsy schemes. Prediction levels of clinically insPCa were defined according to the Epstein criteria. Also, true clinically insPCa was defined according to the final pathology report after RP (organ-confined PCa and no GS 4 or 5) (4). Proportions of patients who met the Epstein criteria (clinical stage T1c, PSA density ≤0.15 ng/mL/cm^3, ≤6 GS (or Gleason grade group 1), ≤2 positive biopsy cores and ≤50% percentage of tumour in positive biopsy core) were compared between the biopsy schemes. Accordingly, GS (according to 2005 modified Gleason grading system), the number of positive cores and percentage of tumour in positive cores were compared between the sextant and 12-core TRUS-Bx schemes. In addition, PSA, PSA density, age and RP pathological findings of all patients were evaluated.

Two different models were created for each biopsy scheme based on the Epstein criteria alone and additional biopsy findings to predict the clinical significance of the tumours after RP.

Statistical Analysis

The non-parametric paired Wilcoxon test and chi-square test were used to analyse the relationships between categorical and independent variables. Also, the chi-square test, McNamer test and correlation analysis were used for the analysis of categorical variables and p-value, estimated risks (OR), Kappa score, Pearson's R correlation coefficient (R) and confidence intervals (CI), positive predictive values (PPV) and accuracy rates were given. The ability of the two different biopsy schemes to predict clinically insPCa after RP was evaluated using a logistic regression model. The Statistical Package for the Social Sciences version 22.0 was used for all statistical analysis. P-values less than 0.05 were considered statistically significant.

Results

A total of 1,167 patients with a median age of 63 years and a PSA level of 7.5 ng/mL were investigated in the study. The patients' demographic data, 12-core biopsy pathologic data and RP pathologic data are given in Table 1. Among patients, 767 (65.7%) had clinically sPCa, and 400 (34.3%) had clinically insPCa after RP. According to the prediction of the Epstein criteria, there were 143 patients with clinically insPCa after the evaluation of the 6-core TRUS-Bx scheme. In contrast, there were 111 patients, according to the 12-core TRUS-Bx scheme (Table 2). In evaluating 143 clinically insPCa patients who were predicted with the 6-core TRUS-Bx scheme, 33 of these patients were predicted as clinically sPCa according to the 12-core TRUS-Bx scheme. In addition, although PCa was diagnosed in the 12-core TRUS-Bx scheme, 85 (7.3%) patients had no cancer according to the 6-core TRUS-Bx scheme. Also, 59 (69.4%) of these 85 patients were predicted as clinically sPCa according to the Epstein criteria in the 12-core TRUS-Bx scheme, and 44 (51.8%) of them were found to have clinically sPCa after RP. The results of predicting clinically sPCa and insPCa according to the Epstein criteria and analysis of additional pathological findings in the 6- and 12-core TRUS-Bx schemes are given in Table 3. The sensitivity, specificity, PPV and negative predictive values (NPV) of the sextant TRUS-Bx scheme for true clinically sPCa after RP was 94.9%, 26%, 71.1% and 72.7%, respectively (p<0.001, OR: 6.559 CI: 4.43-9.71). The sensitivity, specificity, PPV and NPV of the 12-core TRUS-Bx scheme for the true clinically sPCa after RP were 97%, 22%, 70.5% and 79.3%, respectively (p<0.001, OR: 9,124 CI: 5,65-14,71). There was a high correlation between the two biopsy schemes (p<0.001; Pearson's R: 0.859). The model results for both 6-core and 12-core TRUS-Bx schemes according to the Epstein criteria and the model results of additional pathological findings added to the nomograms as predictive

Table 1. Demographic data, 12-core biopsy pathologic data and RP pathologic data of the patients		
Data, mean ± standard deviation (minimum-maximum)		**n=1167**
Age (years)		62.7±6.5 (42-86)
BMI (kg/m^2)		26.7±3.1 (18.5-34.9)
PSA (ng/mL)		10.5±11.5 (1-125.7)
fPSA (ng/mL)		1.31±2.06 (0.1-24.67)
PV (cm^3)		52.1±27.2 (14-200)
PSA density (ng/mL/cm^3)		0.23±0.23 (0.01-1.88)
Clinical T stage, n (%) (n=1123)	T1c	265 (22.7)
	T2a	212 (18.2)
	T2b	37 (3.2)
	T2c–T3	609 (52.2)
GS of 12-core prostate biopsy		6.65±0.83 (4-10)
ISUP grade of 12-core prostate biopsy, n (%)	1	591 (50.7)
	2	334 (28.6)
	3	115 (9.9)
	4	68 (5.8)
	5	59 (5.1)
PNI presence of 12-core prostate biopsy, n (%) (n=1096)		319 (29.1)
LVI presence of 12-core prostate biopsy, n (%) (n=1074)		92 (8.6)
HGPIN presence of 12-core prostate biopsy, n (%) (n=1048)		254 (24.2)
RP pathological T stage, n (%) (n=1166)	pT2	777 (66.6)
	pT3a	234 (20.1)
	pT3b	151 (12.9)
	pT4	4 (0.3)
GS of RP specimen		6.81±0.85 (4-10)
ISUP grade of RP specimen, n (%)	1	437 (37.4)
	2	437 (37.4)
	3	148 (12.7)
	4	65 (5.6)
	5	80 (6.9)
True clinically sPCa after RP, n (%)		767 (65.7)
True clinically insPCa after RP, n (%)		400 (34.3)

BMI: Body mass index, PSA: Prostate-specific antigen, fPSA: Free PSA, PV: Prostate volume, GS: Gleason score, ISUP: International society of urological pathology, PNI: Perineural invasion, LVI: Lymphovascular invasion, HGPIN: High grade prostatic intraepithelial hyperplasia, RP: Radical prostatectomy, sPCa: Significant prostate cancer, insPCa: Insignificant prostate cancer

Table 2. Pathological findings and data of clinically sPCa/insPCa according to the Epstein Criteria in 6- and 12-core biopsy schemes, separately				
Biopsy results		**12-core TRUS-Bx scheme group (n=1167)**	**6-core TRUS-Bx scheme group (n=1167)**	**p***
Diagnosis, n (%)	Benign pathology	0 (0)	85 (7.3)	-
	PCa	1167 (100)	1082 (92.7)	
	Clinically insPCa according to the Epstein criteria	111 (9.5)	143 (12.3)	
	Clinically sPCa according to the Epstein criteria	1056 (90.5)	1024 (87.7)	
Percentage of tumour in positive biopsy core		50.5±31.7 (1-100)	44.8±32.6 (0-100)	<0.001
Number of positive biopsy core		3.34±2.45 (1-12)	2.32±1.6 (0-6)	<0.001

PCa: Prostate cancer, insPCa: Insignificant PCa, sPCa: Significant PCa, TRUS-Bx: Transrectal prostate biopsy
*Paired t-test

Table 3. Prediction of clinically sPCa and insPCa after RP according to the Epstein criteria and analysis of additional pathological findings in the 6- and 12-core biopsy schemes

	All patients (n=1167)	Patients with true clinically sPCa after RP (n=767)	Patients with true clinically insPCa after RP (n=400)	p*
Prediction of the Epstein criteria in 6-core TRUS-Bx scheme				p<0.001 OR: 6.559 (CI: 4.43-9.71) Pearson's R: 0.303 Kappa: 0.247 McNemar <0.001
• Clinically insPCa, n (%)	143 (12.3)	39 (5.1)	104 (26)	
• Clinically sPCa, n (%)	1024 (87.7)	728 (94.9)	296 (74)	
Prediction of the Epstein criteria in 12-core TRUS-Bx scheme				p<0.001 OR: 9.124 (CI: 5.65-14.7) Pearson's R: 0.307 Kappa: 0.230 McNemar <0.001
• Clinically insPCa, n (%)	111 (9.5)	23 (3)	88 (22)	
• Clinically sPCa, n (%)	1056 (90.5)	744 (97)	312 (78)	
PNI presence in 12-core biopsy, n (%) (n=1096)	319 (29.1)	263 (36.5)	56 (14.9)	p<0.001 OR: 3.3 (CI:2.38-4.54) Pearson's R: 0.226
LVI presence in 12-core biopsy, n (%) (n=1074)	92 (8.6)	79 (11.2)	13 (3.5)	p<0.001 OR: 3.5 (CI: 1.91-6.36) Pearson's R: 0.131
HGPIN presence in 12-core biopsy, n (%) (n=1048)	254 (24.2)	175 (25.7)	13 (21.5)	p=0.133 OR: 1.3 (CI: 0.93-1.71) Pearson's R: 0.046

RP: Radical prostatectomy, PCa: Prostate cancer, insPCa: Insignificant PCa, sPCa: Significant PCa, ISUP: International society of urological pathology, PNI: Perineural invasion, LVI: Lymphovascular invasion, HGPIN: High grade prostatic intraepithelial hyperplasia, OR: Odds ratio, CI: Confidence interval
*chi-square test, McNemar test and Correlation were used. Estimated risk are given as odds ratio and Correlation is given as Pearson's R

Table 4. In the same patients, created model results of predicting clinically sPCa and insPCa after RP according to the Epstein criteria and additional pathological findings in both 6- and 12-core biopsy schemes

	p-value	Exp (B)	CI
Predictive model of the Epstein criteria in 6-core TRUS-Bx scheme (Model p<0.001)			
• PSA	0.383	1.055	0.935-1.191
• PSA density	**0.008**	0.383	0.188-0.777
• Clinical T Stage	**0.028**	0.234	0.064-0.856
• Biopsy GS	<**0.001**	0.015	0.003-0.073
• Tumour percentage of positive core	**0.014**	0.346	0.149-0.804
• Number of positive cores	0.976	0.988	0.442-2.207
Predictive model of the Epstein criteria in 12-core TRUS-Bx scheme (Model p<0.001)			
• PSA	0.413	1.052	0.932-1.118
• PSA density	**0.013**	0.401	0.196-0.822
• Clinical T Stage	**0.032**	0.238	0.064-0.884
• Biopsy GS	<**0.001**	0.017	0.004-0.078
• Tumour percentage of positive core	**0.002**	0.259	0.110-0.612
• Number of positive cores	0.565	1.268	0.565-2.847
New modelling of findings in 12 core prostate biopsy (Model p<0.001)			
• Epstein criteria	<**0.001**	7.379	4.447-12.242
• PNI presence in prostate biopsy	<**0.001**	2.514	1.771-3.568
• LVI presence in prostate biopsy	0.093	1.734	0.913-3.296

PSA: Prostate-specific antigen, GS: Gleason score, PNI: Perineural invasion, LVI: Lymphovascular invasion, RP: Radical prostatectomy, PCa: Prostate cancer, CI: Confidence interval
*Analysis results are given with creation of Logistic regression models

factors for the sextant and 12-core TRUS-Bx scheme are given in Table 4. Analysis of data revealed the presence of perineural invasion (PNI) in the 12-core biopsy scheme as a significant predictor in both univariate and multivariate analyses in terms of sPCa (p<0.001; OR: 3.3 CI: 2.38-4.54; Pearson's R: 0.226).

Discussion

The widespread use of PSA testing has led to over-diagnosis because of increased prostate biopsy rates and increased number of cores in each biopsy (6,7). At the same time, over-treatment rate of RP also increased over time. After the published reports about RP series, 26-33% of RP specimens were clinically insPCa (organ-confined PCa, tumour volume less than 0.2 cc, and no Gleason pattern 4 or 5) (4,8). Our series found that 34.3% of patients had clinically insPCa after RP, consistent with the literature. Therefore, it is becoming more important to distinguish the clinically significant disease from clinically insPCa in the decision-making process before treatment to avoid unnecessary treatment interventions. Therefore, identification of insPCa for active surveillance became a major topic of interest. The Epstein criteria have been widely used for that purpose in clinical practice despite some deficiencies (9). Based on the final pathology results, predictive variables were suggested as ≤0.15 ng/mL/cm^3 PSA density, T1c clinical stage and favourable features on 6-core prostate biopsy [≤6 GS (Gleason grade group 1), ≤2 positive biopsy cores and ≤50% percentage of tumour in positive biopsy core] (4,10).

When we look at each predictive factor evaluated in the Epstein criteria, PSA density was previously found to be useful to differentiate more aggressive PCa (11). It was also used as an inclusion criterion for AS (12,13). Cut-off values of PSA density were defined as 0.15 ng/mL/cm^3 and 0.2 ng/mL/cm^3 in previous studies. In our evaluation and validation of the Epstein criteria with the 12-core biopsy scheme, the threshold of PSA density was taken at the level of 0.15 ng/mL/cm^3, like the original study, to predict clinically insPCa. The clinical stage T1c is a main factor for the Epstein criteria because it predicts about 30% of clinically insPCa after RP (4,8).

One of the questions we aimed to answer is the optimal number and percentage of positive biopsy cores from a 12-core biopsy to predict a significant tumour at RP. In this context, some protocols recommend the threshold as the percentage of positive cores (14). In such protocols Dall'Era et al. (15) recommended the presence of <6 total GS, <10 ng/mL PSA level, ≤33% positive cores and tumour presence in ≤50% of each positive core as indicators of insPCa. Similarly, van AS et al. (16), included clinical stage T1-2a, ≤7 total GS (3+4) or ≤ International Society of Urological Pathology grade 2, <15 ng/mL PSA level and <50% positive biopsy cores. In summary, the primary purpose of all these criteria is to predict clinically insPCa and to avoid over-treatment in eligible patients. Many publications suggested that a low number of positive cores was associated with favourable pathological findings at RP specimens (17,18,19). However, there are important studies questioning the role of a number of positive cores on biopsy as a predictive factor for insPCa (18,19). In the current study, we found that the average number of positive biopsy cores was higher in the 12-core biopsy scheme than the 6-core biopsy scheme (3.34 vs 2.32, p<0.001). In the regression model for our population, the ≤2 positive biopsy core finding was not a predictive factor for clinically insPCa in both 6- and 12-core biopsy schemes within the context of the Epstein criteria.

Presence of tumour in <50% of the positive biopsy core was the best factor correlated with the prediction of insPCa among the Epstein criteria in the literature (17). In a recently published study, very low-risk patients (≤6 GS, ≤2 positive biopsy core and ≤50% of tumour in positive core) and other low-risk patients (≤6 GS, >2 positive core and/or >50% percentage of tumour in positive core) were compared and a risk stratification, including tumour volume on biopsy was recommended for low-risk patients (20). In the current study, we found that the mean percentage of tumour in positive biopsy cores were higher in the 12-core biopsy scheme than in the 6-core biopsy scheme (50.5% vs 44.8%; p<0.001). When we look at the regression model in our study, the presence of ≤50% of tumour in positive biopsy core was an independent predictive factor for clinically insPCa in both 6- and 12-core biopsy schemes, consistent with the literature.

The current study aimed to evaluate the performance of the Epstein criteria for the 12-core prostate biopsy scheme. We also investigated the role of possible additional predictive factors that can be added to the criteria such as prostate biopsy PNI, lymphovascular invasion and others. In our cohort, the Epstein criteria in both 6-core and 12-core biopsy schemes significantly predicted clinically sPCa (or insPCa) and were found to correlate with each other. However, the 12-core biopsy scheme was superior for this prediction. However, despite the better performance of 12-core biopsy, only 88 of 400 (22%) patients with true clinically insPCa at final pathology could be predicted. This finding indicates a major room for improvement. Thus, additional analysis of our data highlighted the presence of PNI at the biopsy specimen as a promising predictive factor. The finding of PNI in biopsy is shown as the extension of PCa cells along the nerve bundle in prostate tissue (21). It is reported in 20% of all biopsies harbouring PCa, which is generally accompanied by high GS and PSA levels (22).

Additionally, a high correlation level was shown between PNI on biopsy and extra prostatic extension and surgical margin positivity after RP (22,23,24,25,26,27). However, PNI on biopsy was not always an independent predictive factor of sPCa (28,29). Nevertheless, prostate biopsy PNI presence was an independent predictive factor for clinically sPCa at RP in our study when we incorporated this variable into the Epstein criteria.

In summary, there was a high correlation for the prediction of clinically sPCa/insPCa between the two biopsy schemes in the same patient population. Nevertheless, 7.3% of patients could not be diagnosed with PCa in 6-core TRUS-Bx scheme. Also, 69.4% of these patients (5.1% of all) were clinically sPCa according to the Epstein criteria in the 12-core TRUS-Bx scheme, and 51.8% of them (3.8% of all) were clinically sPCa after RP. According to our results, using the Epstein criteria with 12-core prostate biopsy provides better results in predicting clinically

sPCa than 6-core biopsy. Furthermore, PNI on biopsy can be a useful predictive factor in addition to the Epstein criteria.

Study Limitations

The major limitations of our study are its retrospective nature and analysis. Therefore, indications for surgery were at the physician's discretion. Another important limitation is that there was no centralised pathological examination and the proposed changes in the Gleason grading system over time. However, multicentric pathological examinations by uropathologists at respective centres and long-term data acquisition may reflect a real-life nationwide picture.

Conclusions

The Epstein criteria in sextant prostate biopsy scheme predicted clinically significant PCa with high sensitivity in our cohort in concordance with the original publication and subsequent literature. The performance of biopsy the Epstein criteria in predicting insPCa at final pathology was better with 12-core prostate biopsy scheme in our cohort. In addition, incorporation of the biopsy PNI finding to the prediction model improved the performance of the Epstein criteria.

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Ethics

Ethics Committee Approval: We investigated the validity of the Epstein criteria, as defined according to the sextant biopsy scheme, for the currently utilised 12-core prostate biopsy protocol by analysing the clinicopathologic data recorded in the Urologic Cancer Database - Prostate (UroCaD-P), Urooncology Association, Turkey (UOAT).

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Authorship Contributions

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

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Original Article

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Prognostic Significance of Surgical Margin Status and Gleason Grade at the Positive Surgical Margin in Predicting Biochemical Recurrence After Radical Prostatectomy in a Turkish Patient Cohort

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Abstract

Objective: To investigate the prognostic role of positive surgical margin (PSM) features in addition to well-defined risk factors in predicting biochemical recurrence (BCR) after radical prostatectomy.

Materials and Methods: This study used the prostate cancer database from the Urooncology Association in Turkey. Clinical, surgical, pathological and follow-up data were recorded from the database. PSM features, including number, location, linear length and Gleason grade (GG) were also recorded. Kaplan-Meier survival analyses were performed to assess differences in BCR-free survival (BCR-FS). In order to identify prognostic factors affecting BCR-FS, univariate and multivariate Cox regression analyses were performed.

Results: The study included 984 patients who met the eligibility criteria. The median follow-up time was 29 (minimum: 6, maximum: 210) months, and BCR was detected in 178 (18.1%) patients. BCR-FS was found to be significantly lower in patients with higher total prostate-specific antigen, higher International Society of Urological Pathology (ISUP) grade, extraprostatic extension (EPE), seminal vesicle invasion, lymphovascular invasion, lymph node involvement, PSM and GG at PSM (PSMGG) ≥4 (log-rank p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, p<0.001 and p=0.005). ISUP grade, EPE and PSM were identified as independent prognostic factors in predicting BCR-FS [Hazard ratio (HR): 1.89, p=0.035 and HR: 4.65, p<0.001, HR: 1.82, p=0.030, HR: 1.77, p=0.042, respectively]. Unlike the univariate analysis, in multivariate analysis, PSMGG did not prove to be an independent prognostic factor in predicting BCR-FS.

Conclusion: PSM GG ≥4 was found to be significantly associated with shorter BCR-FS. There is a need for large, randomised prospective studies to clarify the role of PSMGG to be used in nomograms as an independent predictor to determine patients who would benefit from adjuvant radiation therapy.

Keywords: Radical prostatectomy, positive surgical margin, Gleason grade

Introduction

Prostate cancer, the most common newly diagnosed cancer in men, is the second leading cause of cancer-related deaths (1). Biochemical recurrence (BCR), the most common pattern of disease relapse, is seen in nearly 30% of patients who have undergone radical prostatectomy (RP) (2). Numerous risk factors, including preoperative total prostate-specific antigen (PSA) level, pathological stage, Gleason grade (GG), perineural invasion (PNI), lymphovascular invasion (LVI) and positive surgical margin (PSM) have been identified in predicting BCR. PSM is seen in 10%-48% of patients after RP (3). Moreover, half of all patients with PSM develop BCR (4). The absence of BCR in a significant proportion of patients with PSM necessitates

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the examination of surgical margin features, including number, linear length, location and GG at the site of positive resection margin. This study investigates the prognostic role of surgical margin features in addition to well-defined risk factors in predicting BCR.

Materials and Methods

Study design

This study used the prostate cancer database from the Urooncology Association in Turkey, to which participating institutions submit data online. Data obtained from 984 patients who underwent RP with localised and locally advanced prostate cancer and met eligibility criteria for this study (Figure 1). Since our study was a retrospective study using a database, informed consent and ethics committee approval was not obtained.

Data Collection and Definitions

Clinical (age, preoperative total PSA), surgical (type of operation, lymphadenectomy status), pathological [International Society of Urological Pathology (ISUP) grade, extraprostatic extension (EPE), LVI, PNI, seminal vesicle invasion (SVI), surgical margin status, lymph node involvement (LNI)], PSM (number, linear length, location and GG) and follow-up (PSA outcome, BCR status) data were requested and recorded from the prostate cancer database. PSM features including linear length (<1 mm and ≥1 mm), number (single and multiple), location (apex, anterior, posterolateral, bladder neck and seminal vesicle) and GG (1-5) were recorded as submitted in the prostate cancer database. The ISUP grading system as identified in the 2014 ISUP consensus conference was used (5). BCR is defined as PSA >0.2 ng/mL after the RP (6). BCR-free survival (BCR-FS) is defined as the time from the date of RP to the date of BCR. In patients without BCR, BCR-FS is defined as the time from the date of RP to the date of the last follow-up visit.

Statistical Analysis

The normal distribution of continuous variables was evaluated through visual (histogram and probability plots) and analytical (Kolmogorov-Smirnov and Shapiro-Wilk tests) methods. For continuous variables, the statistical difference among the groups was determined using the Mann-Whitney U test. For categorical variables, statistically significant differences among groups were determined using chi-square tests. To assess differences in BCR-FS, Kaplan-Meier curves were generated and compared using the log-rank test. Univariate and multivariate Cox regression analyses were performed to identify the prognostic factors affecting BCR-FS. Statistical significance was accepted as $p<0.05$. IBM SPSS Statistics 15.0 was used for the statistical analysis.

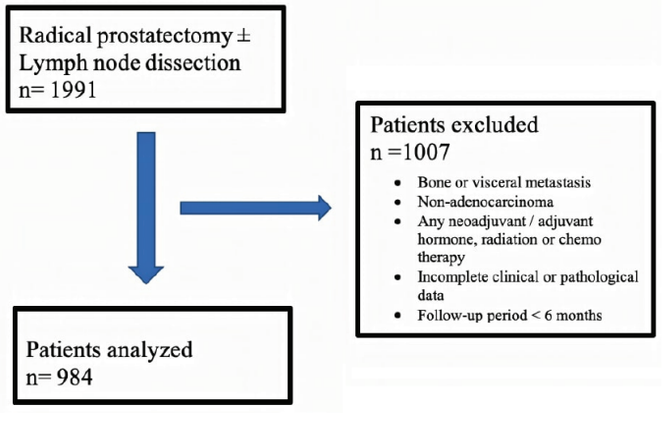

Figure 1. Flow chart of the patients who met study eligibility

Results

Clinicopathological Characteristics

Patients' clinical, surgical and pathological data are summarised in Table 1. BCR was detected in 178 (18.1%) patients. The median follow-up time for all patients was 29 (6-210) months, and it was significantly higher in the BCR group (36 months vs 28 months). The total PSA was significantly higher in the BCR group (8.3 ng/mL vs, 6.7 ng/mL; $p<0.001$). Data analysis showed that a higher ISUP grade had a significant relationship with BCR ($p<0.001$). Moreover, EPE, SVI, LVI and LNI were all significantly higher in the BCR cohort ($p<0.001$).

Surgical Margin Features

The PSM was significantly higher in the BCR group (53.4% vs 29.5%; $p<0.001$). Surgical margin status was evaluated in terms of surgical margin features, including number, location, linear length and GG at PSM. There was no statistically significant difference between the BCR and disease-free group in terms of number, location and linear length of PSM ($p>0.05$). Patients were separated into two groups according to positive surgical margin Gleason grade (PSMGG) as PSMGG ≤3 and PSMGG ≥4. We found a significant relationship between higher PSMGG and BCR ($p=0.043$). We also analysed the PSMGG status in three groups-downgrade, same and upgrade-according to the difference from the index tumour GG. We found a significant relationship between the downgrade of PSMGG and disease-free status (Table 2).

Relationship Between BCR-FS and Clinicopathological Features

The median follow-up period was 28 (6-210) months in the disease-free group. According to Kaplan-Meier survival analysis, BCR-FS was found to be significantly lower in the group with the higher total PSA level, higher ISUP grade, EPE, SVI, LVI and LNI (log-rank $p<0.001$). Kaplan-Meier survival curves, including 2-year, 5-year and 10-year BCR-FSs, are shown in Figure 2.

Relationship Between BCR-FS and Surgical Margin Features

In 333 (33.8%) patients, PSMs were observed. Since PSMGG was not routinely reported in every patient with a PSM, 120 patients were included in the analysis involving PSMGG. According to Kaplan-Meier survival analysis, BCR-FS was found to be significantly higher in the group with a negative surgical margin (NSM) (log-rank $p<0.001$) (Figure 3a). The NSM group was compared separately from the PSMGG ≤3 and PSMGG ≥4 groups in terms of BCR-FS. It was shown that patients with NSM

Table 1. Clinical and pathological data of the patients			
	Disease-free	**Biochemical recurrence**	**p-value**
Age (year) [median (min-max)]	63 (30-83)	63 (46-75)	0.334
Total PSA (ng/dL) [median (min-max)]	6.7 (0.82-87.0)	8.3 (0.73- 64.1)	<0.001
Type of operation n (%)			
Open	617 (79.3)	146 (86.4)	0.033
Robotic	131 (16.8)	15 (8.9)	
Laparoscopic	30 (3.9)	8 (4.7)	
Lymph node dissection n (%)			
Yes	318 (39.5)	97 (54.5)	<0.001
No	488 (60.5)	81 (45.5)	
ISUP grade n (%)			
1	306 (38.0)	47 (26.4)	<0.001
2	347 (43.1)	51 (28.7)	
3	93 (11.5)	34 (19.1)	
4	36 (4.5)	15 (8.4)	
5	24 (3.0)	31 (17.4)	
Extraprostatic extension n (%)			
Yes	167 (22.1)	65 (45.5)	<0.001
No	590 (77.9)	78 (54.5)	
Seminal vesicle invasion n (%)			
Yes	49 (6.1)	47 (26.7)	<0.001
No	748 (93.9)	129 (73.3)	
Lymphovascular invasion			
Yes	24 (3.0)	24 (13.8)	<0.001
No	776 (97.0)	150 (86.2)	
Perineural invasion			
Yes	497 (62.3)	110 (63.6)	0.748
No	301 (37.7)	63 (36.4)	
Lymph node involvement n (%)			
Yes	13 (4.2)	18 (18.9)	<0.001
No	296 (95.8)	77 (81.1)	
Follow-up (month) [median (min-max)]	28 (6-210)	36 (6-196)	<0.001
BCR time (month) [median (min-max)]		12 (6-166)	

BCR: Biochemical recurrence, Min: Minimum, Max: Maximum, PSA: Prostate-specific antigen, ISUP: International Society of Urological Pathology

had a significantly better BCR-FS than patients with PSMGG ≥4 (log-rank p=0.005). However, there was no significant difference between patients with NSM and PSMGG ≤3 in terms of BCR-FS (log-rank p=0.662). On account of this finding, we combined NSM and PSMGG ≤3 groups into a single cohort, and then compared with PSMGG ≥4 group. According to Kaplan-Meier survival analysis, BCR-FS was still significantly lower in the PSMGG ≥4 group (Figure 3b). Kaplan-Meier survival curves, including 2-year and 5-year BCR-FSs, are shown in Figure 3.

Prognostic Factors in Predicting BCR-FS

Univariate Cox regression analysis indicated that total PSA, ISUP grade, EPE, SVI, LVI, LNI, PSM and PSMGG are significantly associated with BCR-FS (p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, p<0.001 and p=0.007, respectively). Multivariate Cox regression analysis was performed to identify the independent prognostic factors for predicting BCR. For this purpose, we created two different predictive models. We included total PSA, ISUP grade, EPE, SVI LVI and LNI in both models. In addition to these predictive factors, Model 1 included surgical margin status, and Model 2 included PSMGG. When evaluating PSMGG in multivariate Cox regression analysis, we combined patients with NSM and PSMGG ≤3 into the same group, and then compared them with PSMGG ≥4. In multivariate Cox regression analysis of Model 1, ISUP grade, EPE and PSM were found to be independent prognostic factors in predicting BCR-FS [Hazard ratio (HR): 1.89, p=0.035 and HR: 4.65, p<0.001, HR: 1.82, p=0.030, HR: 1.77, p=0.042, respectively]. However, in Model 2, only ISUP grade was found to be an independent prognostic factor in predicting BCR-FS (HR: 10.04, p<0.001, Table 3).

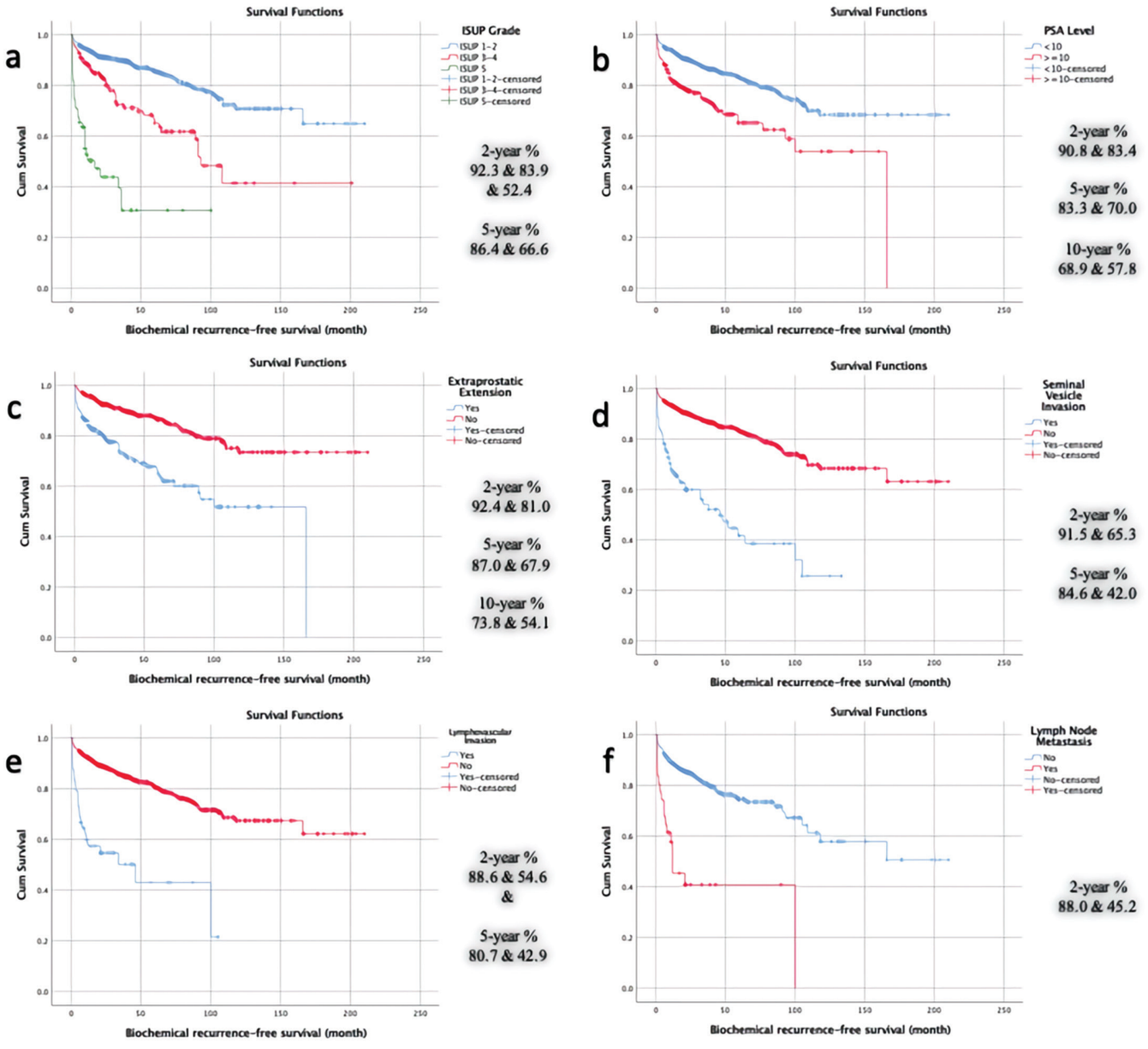

Figure 2. Kaplan-Meier curves in predicting biochemical recurrence-free survival, and 2, 5 and 10-year survival probability, groups categorised in terms of (a) ISUP grade, (b) PSA level, (c) extraprostatic invasion status, (d) seminal vesicle invasion status, (e) lymphovascular invasion status and (f) lymph node involvement status

ISUP: International Society of Urological Pathology, PSA: Prostate-specific antigen

Discussion

Patients with BCR after RP have a worse prognosis. In these patients, the risk of metastatic disease and cancer-related death increases significantly (2). Cancer-specific survival declines significantly in patients with a shorter PSA doubling time and shorter interval to BCR after RP as well as in patients with higher Gleason scores (GSs). A PSM and higher pathologic tumour stage were also found to increase the risk of metastatic disease (7). Prediction of BCR-FS plays an important role in determining which patients would benefit from adjuvant treatment, especially radiation therapy (ART). In a meta-analysis including three randomised-controlled trials (EORTC22911, SWOG8794, ARO96-02/AUO-AP09/95) in which ART was compared with a wait-and-see strategy, metastasis-FS was found to be significantly higher in the ART group (Odds ratio=0.77, p=0.02). Clinical progression-FS was found to be significantly lower in patients with SVI or PSM (HR=0.73, p=0.0003) (8). In another multi-institutional study, no significant difference was found in terms of metastasis-FS and overall survival when early salvage radiotherapy and ART were compared (92% vs 91%, p=0.9, and 89% vs 92%, p=0.9, respectively) (9).

Table 2. Surgical margin data			
	Disease-free	**Biochemical recurrence**	**p-value**
Surgical margin status n (%)			
Positive	238 (29.5)	95 (53.4)	<0.001
Negative	568 (70.5)	83 (46.6)	
Number of PSM n (%)			
Single	151 (77.0)	52 (74.3)	0.642
Multiple	45 (23.0)	18 (25.7)	
Location of PSM n (%)*			
Apex	47 (31.1)	15 (28.8)	0.950
Anterior	23 (15.2)	10 (19.2)	
Posterolateral	71 (47.0)	24 (46.2)	
Bladder neck	8 (5.2)	2 (3.8)	
Seminal vesicle	2 (1.3)	1 (1.9)	
Linear length of PSM n (%)			
<1 mm	39 (37.5)	7 (31.8)	0.615
≥1 mm	65 (62.2)	15 (68.2)	
Gleason grade of PSM n (%)			
1	7 (7.6)	0	*0.043
2	16 (17.4)	0	
3	45 (48.9)	9 (50.0)	
4	18 (19.6)	6 (33.3)	
5	6 (6.5)	3 (16.7)	
Comparison of PSMGG with index tumor GG n (%)			
Downgrade	32 (34.8)	1 (5.6)	0.042
Same	35 (38.0)	9 (50.0)	
Upgrade	25 (27.2)	8 (44.4)	

*Positive surgical margin at single location, **Positive surgical margin Gleason grade 3 vs 4-5 was compared, PSM: Positive surgical margin, GG: Gleason grade

Preoperative PSA, pathological GS, EPE, SVI, PSM and LNI are included in nomograms as independent predictive factors for BCR (10). Kattan et al. (11) created the first nomogram in 1999, including these predictors, and external validations of this nomogram have been performed subsequently (12,13). In our study, we found a statistically significant relationship between high preoperative PSA, high pathological ISUP grade, EPE, SVI, PSM, LVI and LNI and a shorter BCR-FS in univariate analysis. In a meta-analysis evaluating the prognostic significance of six clinicopathological features including PSM, EPE, SVI, LVI, PNI and LNI, all these factors were found to be statistically significant for BCR-FS (HR: 1.79, p<0.001; HR: 2.03, p<0.001; HR: 1.97; p<0.001; HR: 1.85, p<0.001; HR: 1.59, p<0.001; HR: 1.88, p<0.001, respectively) (14). LVI and PNI are not involved in current prostate cancer nomograms. The prognostic role of PNI in predicting BCR is controversial. In a large multicentre study, Kraus et al. (15) found that PNI was not an independent predictor for BCR. However, it can be an indicator of unfavourable histology, such as high G. In our study, we found no statistically significant relationship between PNI and BCR. However, LVI was found to have a significant association with a higher BCR risk in a meta-analysis evaluating its prognostic value (16). We found a statistically significant relationship between high total PSA, high ISUP grade, PSM, EPE, SVI, LVI and LVI and BCR. Kaplan-Meier analyses also showed shorter BCR-FS in these groups. However, PNI was not statistically associated with BCR.

PSM is a well-known predictor for BCR (17,18,19). However, there is limited evidence about PSM subgroups, including number, location, linear length and GG/GS. Apical and posterolateral prostate were the most common locations in terms of PSM (20). Although the prognostic effect of location and number of PSM on BCR is controversial (20,21,22,23), the relationship between both extended positive surgical margin linear length (PSMLL) and higher PSMGG/SMGS with BCR has been previously reported. Mainly PSMLL ≥3 mm and PSMGG ≥4 have been shown to be the most prominent factors in predicting BCR (24,25,26,27,28,29). Unlike most studies, we grouped PSMLL as <1 mm and ≥1 mm since the database was designed in this way. We found no significant relationship between number, linear length and location of PSM and BCR. However, we found a statistically significant relationship between PSMGG and BCR. PSMGG ≥4 was found to be associated with a significantly shorter BCR-FS. Iremashvili et al. (27) designed a study in which they provided different "PSM GS" definitions (GS at the margin, high-grade Gleason pattern present at the margin, predominantly high-grade GS at the margin, GS at the margin higher than overall GS and GS at the margin lower than overall GS) and were used to evaluate BCR-FS. Their results showed that all the definitions of GS at PSM were independently associated with the risk of BCR. It was stated that a "high-grade Gleason pattern at a PSM" could be used as the most useful definition since it provided at least as much prognostic benefit as the others. We also found a statistically significant relationship between a lower PSMGG than the overall GG and disease-free status.

We developed two predictive models by using total PSA, ISUP grade, EPE, SVI, LVI, LNI, surgical margin status and PSMGG. In Model 1, which included surgical margin status instead of PSMGG, ISUP grade, EPE and surgical margin status were found to be independent prognostic factors in predicting BCR-FS. However, in Model 2, which included PSMGG instead of surgical margin status, only ISUP grade was found to be an independent prognostic factor in predicting BCR-FS. In Model 1, the expected results were determined in accordance with the current literature except for the SVI (10,12,14). Since there were only 120 patients with PSMGG data, we had to evaluate patients with NSM and PSMGG ≤3, which have similar BCR-FS, in the same group against patients with PSMGG ≥4. A possible explanation for the unexpected result in Model 2 may have been due to the smaller number and the shorter follow-up time of the patients who have the PSMGG data in contrast to previous studies which identified the independent prognostic role of PSMGG in predicting BCR-FS (24,25,26,27,30).

Study Limitations

The study is retrospective. There were limited data, including LND and PSM features. Since the type of LND was not always recorded, they were all evaluated in the same group. Not performing LND in almost half of the patients led to these patients not being able to be included in the multivariate

analyses. Although the study included 333 patients with PSM, PSMGG data were only available for 120 patients. Since the PSMGG data had been reported relatively recently, these patients had a shorter follow-up. We thought that the lack of PSM data caused less accurate results in multivariate analysis, which included PSMGG. Moreover, there might have been a difference

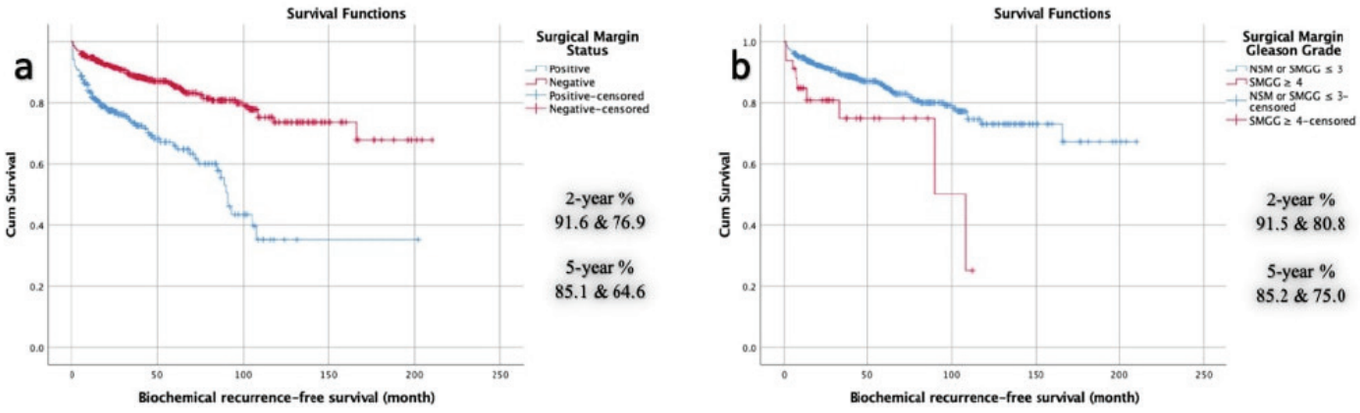

Figure 3. Kaplan-Meier curves in predicting biochemical recurrence-free survival, and 2- and 5-year survival probability, groups categorised in terms of (a) surgical margin status and (b) positive surgical margin Gleason grade

Table 3. Univariate and multivariate Cox regression analyses of prognostic factors for biochemical recurrence-free survival

	Univariate analysis			Multivariate analysis Model 1*			Multivariate analysis Model 2**		
	CI 95%	HR	p-value	CI 95%	HR	p-value	CI 95%	HR	p-value
Total PSA									
<10	1.62-3.01	1.00 (ref.)	<0.001						
≥10		2.21							
ISUP grade									
1-2		1.00 (ref.)			1.00 (ref.)			1.00 (ref.)	
3-4	1.70-3.39	2.40	<0.001	1.04-3.42	1.89	0.035			
5	5.62-12.8	8.50	<0.001	2.08-10.39	4.65	<0.001	3.35-30.02	10.04	<0.001
Extraprostatic extension									
No	2.10-4.06	1.00 (ref.)	<0.001	1.06-3.12	1.00 (ref.)	0.030			
Yes		2.92			1.82				
Lymphovascular invasion									
No	2.93-6.98	1.00 (ref.)	<0.001						
Yes		4.52							
Seminal vesicle invasion									
No	3.13-6.13	1.00 (ref.)	<0.001						
Yes		4.38							
Lymph node involvement									
No	2.70-7.68	1.00 (ref.)	<0.001						
Yes		4.55							
Surgical margin status*									
Negative	2.2-4.02	1.00 (ref.)	<0.001	1.02-3.10	1.00 (ref.)	<0.042			
Positive		2.98			1.77				
PSMGG**									
NSM or PSMGG ≤3	1.28-5.06	1.00 (ref.)	0.007						
PSMGG ≥4		2.55							

*Only included in Model 1, **Only included in Model 2, NSM: Negative surgical margin, PSMGG: Positive surgical margin Gleason grade, CI: Confidence interval, HR: Hazard ratio

in pathologic interpretation, especially when evaluating PSM features, due to the lack of central pathologic review. We also used a cut-off value of 1 mm for PSM linear length, since it was categorised in the database as such. Continuous linear length data could produce more accurate results.

Conclusion

The present study shows that ISUP grade, EPE and PSM as independent prognostic factors in predicting BCR-FS. Although BCR-FS was significantly shorter in the patients with PSMGG ≥4, in multivariate analysis, PSMGG was not found as an independent prognostic factor in predicting BCR-FS. There is a need for large, randomised prospective studies to identify the role of PSMGG to be used in nomograms as an independent predictor in order to determine patients who would benefit from ART.

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Contribution: There is an other contributor who may not be listed as authors: Saadettin Eskiçorapçı, Acıbadem University Faculty of Medicine, Department of Urology, İstanbul, Turkey, Çağ Çal, Ege University Faculty of Medicine, Department of Urology, İzmir, Turkey, Volkan İzol, Çukurova University Faculty of Medicine, Department of Urology, Adana, Turkey.

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Ethics

Ethics Committee Approval: Since our study was a retrospective study using a database, informed consent and ethics committee approval was not obtained.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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Predictive Value of Duration and Frequency of Macroscopic Haematuria for Stage, Prognosis and Recurrence in Bladder Cancer Patients

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Abstract

Objective: We aimed to investigate the predictive value of duration and frequency of macroscopic haematuria for the stage, prognosis and recurrence rates in primary bladder cancer.

Materials and Methods: We retrospectively reviewed the data of our patients diagnosed with primary bladder cancers during 2000-2014. Patients with history of macroscopic haematuria were included. Their haematuria duration and frequency and stage and grade of bladder cancer, recurrence rates, time until recurrence, time until progression and pre-operative use of anticoagulants were evaluated.

Results: A total of 331 patients comprising 276 males (83%) and 55 females (16%) were included in the study. The mean age of the patients was 64.0±11.8 (28-93) years. The average haematuria duration was 18.5±33.5 (0-260) months. There were 173 (52%), 106 (32%) and 52 (15.7%) patients with cancer stages of Ta, T1 and T2, respectively. The average follow-up time was 54.0±41.8 (1-268) months. The frequency of haematuria was significantly higher in patients with muscle-invasive bladder cancers than in those with superficial bladder cancers (p=0.010). Similarly, patients with tumour diameter >3 cm reported significantly higher frequency of haematuria than in those with tumour diameter <3 cm (p=0.045). Five patients exclude from study because they did not attend their follow-up. During follow-up recurrences were seen in 89 (32.3%) out of 326 patients, while 237 (72.7%) patients did have any recurrences. Disease progression was reported in 28 (8.5%) patients. The average time periods until recurrence and progression were 25.8±34.7 months and 27.1±34.9 (1-144) months, respectively.

Conclusion: We found a significant difference between the frequency of haematuria in patients with muscle-invasive cancers and those with superficial cancers. Also, we found a negative correlation between smoking and the time until recurrence in patients with macroscopic haematuria. No significant relationships were observed between the duration of haematuria and cancer recurrence rates and prognosis.

Keywords: Haematuria, bladder cancer, haematuria frequency, haematuria duration

Introduction

Bladder cancers are one of the most common cancers of the urinary system and comprise 2%-3% and 6%-8% of malignant cancers in women and men, respectively (1,2). Owing to their low prevalence in the general population, their screening is not recommended (3). Factors affecting their prognoses are tumour burden, diameter, composition, histology, stage, grade and accompanying carcinoma *in situ* (CIS) (4). Among the various diagnostic tools, cystoscopy is the best modality available for urologists to diagnose bladder cancers (5). The most common symptom of bladder cancer is painless macroscopic haematuria. It is seen in 85% of bladder cancer patients. Microscopic haematuria can be found in almost all patients. The second most common symptom comprises irritable bladder symptoms that are seen in 20% of patients. These indicate the presence of CIS or invasive bladder cancer (6). Haematuria is commonly seen in the general population, with a prevalence of 2.5%-20% (7,8). The diagnosis and degree of haematuria can be found by counting red blood cells in each 1 mL of urine sample (chamber count), via sediment count, or through an indirect dipstick test (9). An underlying urinary tract cancer is present in 40% and

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approximately 5% of patients with macroscopic and microscopic haematuria, respectively (10). No underlying illness is seen in 40% of patients with microscopic haematuria (7). Haematuria may not always be a cause for alarm; studies have shown that 9%-18% of healthy individuals may report this symptom (11).

Many studies have showcased the importance of microscopic haematuria; unfortunately, there are limited publications investigating macroscopic haematuria. Some studies have explored the association between macroscopic hematuria and bladder cancer.

However, no previous study has explored the relationship between the frequency and duration of haematuria with the stage, degree, recurrence, prognosis, tumour burden, diameter, cigarette use, age, body mass index (BMI) and pre-operative anticoagulant usage. We aimed to determine the effect of the frequency and duration of macroscopic haematuria on primary bladder cancers; primarily with the stage, prognosis and recurrence rate.

Materials and Methods

The study was approved by the ethics committee of our hospital, the Şişli Hamidiye Etfal Training and Research Hospital. All patients included in the study were informed about the study and written consents were obtained. Data of the patients with primary bladder cancers attending the urology clinic at the hospital during 2000-2014 were retrospectively evaluated. A total of 331 patients were included in the study and divided into two groups based on the presence and absence of macroscopic haematuria. Haematuria duration and frequency, tumour characteristics namely; stage, grade, recurrences, time until recurrence, time until progression and pre-operative anticoagulant usage were reviewed.

Furthermore, patients were tested for CIS. Then the tumour burden and intravesical therapies [Bacillus Calmette-Guerin (BCG) or chemotherapy] were noted. Patients with macroscopic haematuria were divided into four groups, based on prior studies, considering the duration of the symptom as: group 1: less than 3 months, group 2: 3-5 months, group 3: 6-12 months and group 4: longer than 12 months. Duration of haematuria was calculated from the time of its first appearance until the date of operation, while its frequency was defined as the number of days on which haematuria occurred. Pre-operative Hb and Htc values were noted for all patients. Patients were followed up for 5 years. Their controls were planned as per the EAU guidelines.

Statistical Analysis

SPSS 15.0 for Windows was used for the statistical analysis. Descriptive statistics were employed for the evaluation of results: for categorical variables, numbers and percentages and for numerical variables, mean, standard deviation, minimum, maximum and median values were used. The Mann-Whitney U test was used for continuous variables. The ratio of the categorical variables between the groups was tested by chi-square analysis. A p-value <0.05 was considered as statistically significant.

Results

A total of 331 patients were included in our study. Demographic data of the patients are listed in Table 1. There were 276 (83%) men and 55 (16%) women. Data are presented as mean ± standart deviation. The average age was 64.0±11.8 (28-93) years and the average BMI was 26.7±4.2 (16-39) kg/m^2. Mean cigarette usage per year was 33.8±28.5 (0-150) packs/year. Sixty-one patients (21.9%) showed no signs of macroscopic haematuria, while 218 patients (78.1%) did. The mean haematuria duration was 18.5±33.5 (0-260) months. Patients with haematuria were divided into four groups according to their symptom duration as mentioned earlier. Groups I-IV had 121 (43.4%), 35 (12.5%), 15 (5.4%) and 47 (16.8%) patients, respectively. Frequency of haematuria was 10.4±31.9 (0-365) days. Pre-op Hb values were 13.5±2.1 gm/dL and pre-op Hct values were 40.7±6.0 (13.7-51.8)%. Pathological staging of Ta, T1, and T2 bladder cancers were seen in 173 (52%), 106 (32%) and 52 (15.7%) patients.

The average follow-up time was 54.0±41.8 months. There were 40 (30.5%) and 91 (69.5%) patients with tumours smaller and larger than 3 cm, respectively. Regarding tumour focality, 92 patients (66.7%) had unifocal, 36 (26.1%) had 2-7 foci and 10 (7.2%) patients had bulky tumours.

Table 1. Demographic data of patients included in the study

Age		64.0±11.8/28-93
Sex	Male	276 (83.4)
	Female	55 (16.6)
Height		168.7±7.7/150-190
Weight (kg)		75.8±12.2/48-113
BMI		26.7±4.2/16-39.0
Cigarettes (packs/year)		33.8±28.5/0-150
Comorbid Illness	**HT**	117 (36.7)
	DM	61 (19.1)
	IHD	40 (12.5)
	CBF	9 (2.8)
	COPD	26 (8.2)
	Other	10 (3.1)
Hematuria interval		18.5±33.5/0-260
Hematuria interval	Negative	61 (21.9)
	Positive	218 (78.1)
	<3 months	121 (43.4)
	3-5 months	35 (12.5)
	6-12 months	15 (5.4)
	>12 months	47 (16.8)
Days with hematuria		10.4±31.9/0-365
Pre-op Hb		13.5±2.1/6.1-17.8
Pre-op HCT		40.7±6.0/13.7-51.8

BMI: Body mass index, Hb: Haemoglobin, HCT: Hematocrit, HT: Hypertension, DM: Diabetes mellitus, IHD: Ischaemic heart disease, CBF: Chronic bladder failure, COPD: Chronic obstructive pulmonary disease

Recurrences were observed in 89 out of 326 patients (27.3%) during their follow-up; while 237 patients (72.7%) remained in remission. Disease progression was observed in 28 (8.5%) patients. Average time periods until recurrence and progression were 25.8±34.7 and 27.1±34.9 (1-144) months, respectively. Furthermore, while 46 (15.8%) patients underwent intracavitary chemotherapy, 63 (21.6%) patients received intracavitary BCG.

Anticoagulants were received by 27 patients pre-operatively, while 174 (86.6%) did not receive any (Table 2).

On statistical analyses, the relation between age and haematuria duration was negatively significant (p=0.024). The average haematuria duration was significantly higher in men than in women (p=0.035).

Tumours larger than 3 cm in diameter were found to be significantly more in patients with haematuria than in those without it (p<0.001).

No meaningful differences were determined between tumour burden and haematuria duration. The same was true for frequency of haematuria, recurrence ratio, time until recurrence, number of recurrences, progression rate and time until progression.

Frequency of haematuria was significantly higher in patients with a tumour diameter >3 cm than in those with tumour diameter <3 cm (p=0.045). However, such an association was not seen with haematuria duration. Also, frequency of haematuria, recurrence rate, time until recurrence, the number of recurrences, progression rate and time until progression are not significantly associated with haematuria duration.

Frequency of haematuria was significantly associated with the pathological staging of the tumour (p=0.022). Stage Ta patients had a significantly lower frequency compared with that of stage T2 patients (p=0.021). Haematuria duration, recurrence rate, time until recurrence, progression rate and time until progression were not significantly correlated with the pathological staging.

The grade of tumours were found to be significantly different among the groups based on the haematuria duration (p=0.033). In patients with grade 1 tumours, the ratio of those with a haematuria interval of 6-12 months was determined to be highest. There was no significant difference in frequency of haematuria, recurrence rate, recurrence quantity and progression rate and time until progression among the different grades.

Superficial bladder cancers were further divided into three groups: low, intermediate and high risk; and their characteristics were analysed. No significant differences were found among the groups in terms of haematuria duration, frequency, recurrence rate, time until recurrence, number of recurrences and progression rate and time until progression.

A positively significant correlation was observed between haematuria duration and cigarette usage (packs/year; p=0.016), while a negatively significant correlation was found between recurrences and cigarette usage (packs/year; p=0.024). Age and BMI were shown to have no significant effect on haematuria duration and frequency, number of recurrences, time until recurrence, number of recurrence, and time until progression.

Haematuria duration was not found to be significantly correlated with recurrence rates, progression rates, time until recurrence and time until progression. The same was true for pre-operative anticoagulant use.

In patients without haematuria, no significant differences were observed with regards to burden, tumour diameter, stage, grade, recurrence and progression rates.

In patients with superficial bladder cancers without haematuria, no significant differences were observed in low, intermediate and high-risk groups (Table 3).

Frequency of haematuria was observed to be more statistically significant in muscle-invasive bladder cancer patients than in those with superficial tumours (p=0.010). The tumour burden in patients with superficial tumours was significantly higher than in those with muscle-invasive tumours (p=0.020).

Table 2. Comparison of patients in relation to stage, grade, recurrence, tumour diameter and progression

Stage	Ta	173 (52.3)
	T1	106 (32.0)
	T2	52 (15.7)
Superficial (non-T2) risk	Low risk	119 (36.0)
	Intermediate risk	34 (10.3)
	High risk	127 (38.1)
Grade	1	19 (5.8)
	2	163 (50.0)
	3	144 (44.2)
CIS	Negative	278 (86.6)
	Positive	43 (13.4)
RE-TUR	Negative	184 (65.2)
	Positive	98 (34.8)
Recurrence	Negative	237 (72.7)
	Positive	89 (27.3)
Time until recurrence (months)		25.8±34.7/1-206
Progression	Negative	303 (91.5)
	Positive	28 (8.5)
Time to progression (months)		27.1±34.9/1-144
Follow-up period		54.0±41.8/1-268
Intracavitary treatment	Negative	136 (46.6)
	CT	46 (15.8)
	BCG	63 (21.6)
	CT+BCG	47 (16.1)
Pre-op anticoagulant use	Negative	174 (86.6)
	Positive	27 (13.4)
Tumour count	1	92 (66.7)
	2-7	36 (26.1)
	>7	10 (7.2)
Tumour diameter	<3 cm	40 (30.5)
	>3 cm	91 (69.5)

CIS: Carcinoma *in situ*, RE-TUR: Re-transurethral resection, CT: Chemotherapy, BCG: Bacillus Calmette-Guerin

Table 3. relation to hematuria interval, days with hematuria and recurrence				
		Stage		
		Superficial	T2	p
Hematuria interval mean ± SD		18±33.6	21.1±33.4	0.055
Hematuria interval n (%)	Negative	55 (23.8)	6 (12.5)	0.254
	<3 months	98 (42.4)	23 (47.9)	
	3-5 months	29 (12.6)	6 (12.5)	
	6-12 months	10 (4.3)	5 (10.4)	
	>12 months	39 (16.9)	8 (16.7)	
Days with hematuria mean ± SD		9.6±33.3	14.5±23.3	0.010
Tumour diameter n (%)	<3 cm	34 (33.0)	6 (21.4)	0.238
	>3 cm	69 (67.0)	22 (78.6)	
Tumour count n (%)	1	68 (61.8)	24 (85.7)	0.020
	2-7	34 (30.9)	2 (7.1)	
	>7	8 (7.3)	2 (7.1)	
Recurrence n (%)	Negative	192 (70.1)	45 (86.5)	0.015
	Positive	82 (29.9)	7 (13.5)	
Time till recurrence (ay) mean ± SD		27.1±35.9	11.4±7.1	0.250
Recurrence quantity mean ± SD		0.7±1.5	0.3±1.0	0.020
Progression n (%)	Negative	254 (91.0)	49 (94.2)	0.593
	Positive	25 (9.0)	3 (5.8)	
Time till progression (months) mean ± SD		28.7±36.5	13.3±9.7	0.710
SD: Standard deviation				

Patients with superficial bladder cancers showed significantly higher recurrent tumours (p=0.020) and recurrence rates (p=0.015) compared with those in patients with muscle-invasive bladder cancers.

Discussion

Haematuria is one of the most common symptoms of bladder cancer with majority of bladder cancer patients presenting with macroscopic haematuria. Upon detailed inquiry it has been determined that it is not taken seriously and that most patients seek medical care only after suffering recurrent episodes of haematuria.

Although, microscopic haematuria has been studied in detail, there are limited studies about macroscopic haematuria. Edwards et al. (12) reported that 82.4% of patients presenting with macroscopic haematuria were diagnosed with bladder cancers. Gandrup et al. (13) studied 150 patients with macroscopic haematuria and reported bladder cancers in 30 patients. Another study stated that if each patient presenting with macroscopic haematuria received a complete urological examination; approximately 10% will be diagnosed with bladder cancers (14).

The examples above are from studies in which bladder cancer is determined cumulatively from the presence of macroscopic haematuria. However, unlike our study, the association between the duration and frequency of macroscopic haematuria with the stage, grade, recurrence, prognosis, tumour count and diameter, cigarette use, age, BMI and anticoagulant use has not been examined. We aimed to determine the predictive value of the duration and frequency of macroscopic haematuria for the stage, prognosis and recurrence of bladder cancer.

Delayed diagnosis and treatment of bladder cancer can affect survival (15). Further, patients who ignore preliminary symptoms and undergo treatment later have higher tumour grades and decreased survival rates (16). It has also been determined that delays in diagnosis increase the mortality risk related to the stage and grade of the disease (17). Superficial (non-muscle invasive) tumours comprise 60%-80% of the newly diagnosed bladder cancers and majority of them are low grade. Our study detected a ratio of 84.3% superficial bladder cancers and 15.7% muscle-invasive bladder cancers, which is concordant with the current medical literature. Our study also determined that frequency of haematuria was more statistically significant in muscle-invasive tumours compared with that in superficial tumours. According to the data from the USA, men were 2.5 times more likely to be diagnosed with bladder cancer than women. In Turkey, this ratio is 7:1. Bladder cancer is a disease of old age; the average age of diagnosis is 72 years (18). Our study sample comprised 276 men (83.4%) and 55 women (16.6%), which is concordant with the national data.

The average age of patients in our group was 64, which is a bit lower than the national average. The increase of industrial and environmental carcinogens in the last 50 years is to blame for the decrease in the age of bladder cancer patients. Since

our patients were of advanced age, comorbid pathologies such as hypertension, diabetes mellitus, ischaemic heart disease, chronic bladder failure) and chronic obstructive pulmonary disease were also present. Previous studies have shown that delay in bladder cancer diagnosis in men and women (especially delays >6 months after the diagnosis and >12 weeks from the diagnosis to cystectomy) negatively affects survival rates (19,20). In recent studies, women were found to be at a higher risk of delayed diagnosis and presented with more advanced sickness compared with that in men (21). A study in women with bladder cancer revealed that urological consultations were not performed immediately upon complaints of symptoms and that these patients were given three or more doses of antibiotics first (22). The period between initial haematuria and bladder cancer diagnosis was statistically significant in women (23).

Our study differed from other similar studies in showing that haematuria duration was significantly higher in men than in women (p=0.035). This may be due to the lower ratio of female patients nationally. There were 276 (83.4%) men and 55 (16.6%) women, and this was concordant with the national data.

Age and haematuria duration were negatively significant when patients were analysed according to age (p=0.024).

When comparing patients with haematuria and those without it, the number tumours >3 cm in size were significantly higher in the former (p=0.045). When patients with haematuria were divided into subgroups according to tumour diameter, stage and quantity, patients with Ta tumours were found to have statistically lower frequency of haematuria than in those with T2 tumours. Studies that have examined microvascular invasion of advanced stage tumours support our findings.

A significant association was seen between haematuria duration of 6-12 months and grade 1 toumors. We found that in such patients with long-term macroscopic haematuria, since there was no physical discomfort, diagnoses could not be established either clinically or radiologically. That leads us to stress the importance of cystoscopic controls for definite diagnosis.

The correlation between cigarettes and bladder tumours is clear in medical literature and The European Association of Urology (EAU) guidelines. The emergence of a positive relationship of haematuria duration with cigarette usage (packs/year) in our study supports these findings. Additionally, cigarette use and recurrence of bladder tumours in the macroscopic haematuria group showed a negative correlation. In other words, patients with macroscopic haematuria who also smoked had early recurrences.

We found no relationship between haematuria duration and number of recurrences and tumour prognosis. Age and BMI were also not significantly associated with progression and recurrence in patients with haematuria.

Among the different groups based on the haematuria duration, no significant differences were observed regarding the use of pre-operative anticoagulants and the tumour stage, grade, burden and diameter, number of recurrences, time until recurrence, time until progression. Findings from previous studies differ from ours in this respect.

The incidence of haematuria in patients treated with fibrinolytic agents varies between 20% and 30% (24). Despite these findings, it is unclear if anticoagulant-related haematuria causes asymptomatic genitourinary lesions to be detected earlier (25).

Generally, the degree of haematuria depends on the amounts and dosage of anticoagulants used. Nevertheless, haematuria may be the only uropathological finding. Therefore, some authors recommend a complete urological evaluation of all patients with non-traumatic anticoagulant-related haematuria. Furthermore, it has also been seen that 30% of patients receiving anticoagulants were diagnosed with a malignancy (25).

Some authors have claimed that bleeding episodes in patients receiving anticoagulant therapy correlate with PT (26).

One particular study showed that patients attending the emergency room with first time macroscopic haematuria and those on anticoagulant therapy, newly diagnosed with bladder cancers, have a high probability of early-stage and low-grade bladder cancer (27).

The reason that no statistically significant differences in stage and grade, and anticoagulant use emerged in our study may be attributed to the small sample size. Although patients with haematuria numbered 270, only 27 received anticoagulants. This number may be insufficient for meaningful statistical analysis.

Study Limitations

Although we are proud of the contribution we have made, we feel that this is a topic that should be made the subject of a larger sample size and longer-term prospective randomised studies than ours.

Conclusion

Haematuria is a severe symptom that motivates patients to seek early treatment. Macroscopic haematuria usually signals an underlying pathology in that 50% of patients with the symptom are diagnosed with significant urogenital system pathology. Therefore, advanced evaluation is needed to determine its underlying cause. Our study intended to emphasise the most widely known diagnostic symptom of bladder cancers, which is macroscopic haematuria, and to assess it according to its duration and frequency.

Our study determined that frequency of haematuria was significantly higher in muscle-invasive tumours than in superficial tumours. In patients with haematuria, the incidence of tumours >3 cm was higher than in those without it.

A positive correlation was determined between haematuria duration and cigarette packs smoked per year. A negative correlation was determined between cigarette use by patients with haematuria and time until recurrence.

Age and haematuria duration were found to be negatively significant. In males, the mean haematuria duration was significantly higher than in females.

We could not find a significant relation between haematuria duration and number of recurrences and tumour prognosis. Also, in patients with haematuria, age and BMI were not significantly associated with tumour progression and recurrence.

In patients with pre-operative anticoagulant usage, there was no meaningful correlation between haematuria duration and tumour stage, grade, burden, diameter, recurrence and progression.

In contemporary medical literature, a detailed analysis of macroscopic haematuria is lacking, especially regarding its relationship with features of bladder cancers, such as stage, size, recurrence and prognosis. With this study, we hope to contribute to this vital area.

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Authorship Contributions

Critical Review: C.Y., Supervision: S.L.K., Concept: A.H.Y., Design: A.T.A., Data Collection or Processing: E.A., Analysis or Interpretation: G.B., Literature Search: G.B., Writing: H.A.

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Original Article

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The Factors Affecting Recurrence and Prognosis in Patients with Low-grade Stage Ta Bladder Cancer

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Abstract

Objective: This study aims to review the parameters affecting tumour recurrence, tumour progression and cancer survival of patients with low-grade non-muscle invasive bladder cancer.
Materials and Methods: We retrospectively reviewed 262 patients with primary, low-grade Ta bladder cancer. Recurrence was defined as the occurrence of a new tumour in the prostatic urethra or bladder. Tumour progression was defined as confirmed high-grade Ta, all T1 or carcinoma *in situ*, upper tract recurrence or progression to T2. The associations between factors that affect recurrence and progression were analysed.
Results: Tumour recurrence and progression occurred in 119 (45.4%) and 25 (9.5%) patients during follow-up (median follow-up: 50.9±36.3 months), respectively. Univariate and multivariate analyses demonstrate that smoking, multiple tumours and large tumours (3 cm<) were significant. A Cox regression analysis revealed that progression was identified as a significant risk factor on survival. There was no effect of smoking on recurrence-free survival. A Kaplan-Meier analysis showed that one-, five- and ten-year progression-free survival rates were 99.6%, 88.2% and 70%, respectively.
Conclusion: Multiple tumours, large tumours (>3 cm) and smoking were risk factors for recurrence and progression. Prevention of smoking and routine cystoscopic examination are essential in bladder cancer.
Keywords: Bladder cancer, progression, recurrence, risk factors

Introduction

Bladder cancer is a complex disease with high morbidity and mortality rates if it is left untreated. Approximately 75%-85% of bladder cancer is non-muscle invasive at the time of the diagnosis. Stage Ta tumours constitute approximately 70% of non-muscle invasive bladder cancers (NMIBC) at presentation. About 50%-70% of NMIBC relapsed and 5%-30% showed progression (1,2).

Although stage Ta tumours are generally low grade, the high-grade disease rate has been 6.9%. However, recurrence rates are high, especially in multiple tumours; progression is rare (3). Stage Ta tumours often relapse or progress after the first five years of treatment. The recurrence rate is approximately 50%-60%, and the progression rate is between 7%-20%. Ta tumours usually show recurrence or progression within five years of initial treatment, but a longer follow-up (10-15 years) is needed (4,5). Low-grade stage Ta tumours rarely progress; however, they often recur. Therefore, knowing the patient's tumours characteristics, treatment and demographic characteristics may prevent recurrence and progression. This study aimed to review the parameters affecting recurrence and progression in patients with bladder cancer diagnosed with primary low-grade stage Ta.

Materials and Methods

This retrospective study has been approved by the Clinical Research Ethics Committee (2017/294), and all participants provided written informed consent to participate in this study. In this study, we retrospectively reviewed 308 patients who underwent transurethral bladder resection (TUR-B) between January 2009-January 2018 for initial diagnoses of low-grade stage Ta bladder tumours at least one year follow-up. The following factors were analysed for each individual from medical

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records: age, gender, smoking, systemic disease, tumour characteristics in cystoscopy (such as papillary, solid, multiple and solitary), tumour diameter in radiological image and time to progression.

Tumour stage was evaluated according to the 2009 American Joint Committee on Cancer tumor node metastasis classification, and tumour grade was evaluated according to 2004 WHO classification (2).

Forty-six patients with a history of TUR-B in other centres, high-grade pathology, upper urinary tract cancer, outpatient follow-up and incomplete data in their medical records were excluded from this study. The surgical procedure was performed under spinal anaesthesia with bipolar or monopolar resectoscope after the patients' informed consent. In addition to the main tumour specimen obtained from TUR-B, the tumour base was also sampled and sent separately for histopathological examination. Small tumours (<1 cm) observed in cystoscopy were removed as en-block (2). The patients were hospitalised for an average of one day. The foley catheter was removed within a mean of two days. All patients received an intracavitary single dose of epirubicin/mitomycin within the first six hours. The patients' follow-up was performed with flexible cystoscopy at three or six months intervals for the first two years, and then every year later (2).

Radiological evaluation (computed tomography/magnetic resonance) was performed to detect upper urinary tract cancer or distant metastasis when positive urinary cytology, the suspicious invasive appearance was detected in the bladder. Recurrence was defined as the occurrence of a new tumour in the prostatic urethra or bladder and cured by transurethral resection. Progression of the tumour was defined as confirmed high-grade Ta, all T1, or carcinoma *in situ* (CIS), upper tract recurrence, or progression to T2.

Statistical Analysis

Data were analysed with statistical software package IBM SPSS V23. Chi-square test was used to compare categorical data. Recurrence-free, progression-free survival analyses were performed using the Kaplan-Meier method. The log-rank test was applied to compare survival between a group of patients. Univariate regression, multivariate regression analysis and Cox regression analysis were used to predict variables that affect recurrence and progression. The significance level was considered as $p<0.05$.

Results

Of the 308 patients whose medical records were examined, 262 (72.4%) were included in this study.

Of these, 92.4% (242) were male, and 7.6% (20) were female. The mean age was 67.58±10.1 years (range 38-92 years), and 140 patients (53.4%) had a history of smoking.

The presenting complaint was haematuria in 238 (90.8%) cases and irritative symptoms in the remaining 24 patients. Twelve patients had diabetes mellitus, 16 had hypertension, four had chronic obstructive lung disease and three had coronary heart disease according to the medical records. During the follow-up period, a total of 15 patients (three of them due to metastatic bladder cancer) died. Ultrasonography and contrast/non-contrast tomography was used in preoperative radiological imaging.

A solitary tumour was detected in 162 (61.8%) cases and multiple tumours in 100 (38.2%).

In 49 patients (18.7%), the tumour was larger than three cm (Table 1).

The mean follow-up period was 50.9±36.3 months (range, 12-204). Recurrence was observed in 119 patients (45.4%). The mean time to recurrence was 22.4 months (range, 2-176 months).

Univariate and multivariate analyses demonstrated that recurrence [Odds ratio (OR) 1.366 95% confidence interval (CI), 0.389-4.801 p=0.021, OR 0.626 95% CI, 0.116-3.38 p=0.036)] and progression (OR 5.760 95% CI, 1.249-26.566, p=0.007, OR 8.317 95% CI, 0.728-94.954 p=0.017) rates of the patients with a smoking history were significant. The recurrence rate was 75% in multiple tumours and 38.4% in solitary tumours. In the multivariate analysis, patients with multiple tumours, recurrence (OR 4.078, 95% CI 0.899-18.491, $p<0.001$) and progression (OR 12.213, 95% CI 0.785-19.039, $p<0.001$) rates were statistically significant compared with solitary tumours. Recurrence and progression ($p<0.001$) rates were found to be significant in tumours larger than three cm compared with

Table 1. Clinical and demographic characteristics of patients

Variable		Total n (%)	Recurrence (+)	Recurrence (-)	p-value	Progression (+)	Progression (-)	p-value
n		**262**	**119 (45.4)**	**143 (54.6)**		**25 (9.5)**	**237(90.5)**	
Gender	Male	**242 (92.4)**	**113**	**129**	**0.143**	**23**	**212**	0.736
	Female	**20 (7.6)**	**6**	**14**		**2**	**18**	
Smoking	Yes	**140 (53.4)**	**72**	**68**	**0.035**	**19**	**121**	0.002
	No	**122 (46.6)**	**47**	**75**		**6**	**116**	
Tumour multiplicity	Solitary	**162 (61.8)**	**45**	**117**	**0.001**	**3**	**159**	0.001
	Multiple	**100 (38.2)**	**74**	**26**		**22**	**78**	
Tumour size	>3 cm	**49 (18.7)**	**27**	**22**	**0.021**	**1**	**48**	0.001
	3 cm	**213 (81.3)**	**79**	**134**		**24**	**189**	

Categorical data is expressed as number (%)

Table 2. Analysis of recurrence and progression according to univariate and multivariate analyses								
	Recurrence				Progression			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Tumour (multiple/solitary)	3.375 (0.608-18.747)	0.057	4.078 (0.899-18.491)	0.001	2.167 (0.476-9.860)	0.055	12.213 (0.785-19.039	0.001
Gender (male/female)	1.342 (0.701-2.315)	0.918	1.456 (0.765- 2.401)	0.151	1.205 (0.957-0.745)	0.674	0.915 (0.608-0.455)	0.942
Smoking (yes/no)	1.366 (0.389-4.801)	0.021	0.626 (0.116-3.38)	0.036	5.760 (1.249-26.566)	0.007	8.317 (0.728-94.954)	0.017
Tumour size (<3 cm/>3 cm)	3.879 (0.908-16.747	0.001	5.078 (0.1899-16.444)	0.001	5.167 (0.976-11.538)	0.001	13.213 (0.989-21.011	0.001
OR: Odds ratio, CI: Confidence interval								

tumours smaller than three cm. According to the multivariate analysis, gender was not an influential factor in patients' recurrence and progression (Table 2).

According to the Kaplan-Meier survival analysis, recurrence-free survival at one, five and ten years was 98%, 65.2% and 27%, respectively. The 5-year recurrence-free survival in multiple tumours was 46% and 71% in solitary tumours (p=0.003). There was no effect of smoking on recurrence-free survival (Figures 1,2).

There was no statistically significant difference between the mean survival times, according to recurrence (p=0.177) (Figure 1). The mean survival time was 176.76 months in patients with recurrence and 150.27 months in patients without recurrence. A total of 25 patients (9.5%) had progression, and the time to progression was 27.3±25.2 months (range, 6-110 months). Both univariate and multivariate analyses demonstrated that smoking and multiple tumours had a high progression rate (p=0.017, p<0.001). The Kaplan-Meier analysis showed that one-, five- and ten-year progression-free survival rates were 99.6%, 88.2% and 70%, respectively. When the factors affecting the Kaplan-Meier 5-year progression-free survival were examined, it was found that only the multiple tumours (79%) were compared with the solitary tumours (98%) (p=0.003) (Figures 3,4).

The Cox regression analysis revealed that smoking, tumour characteristics, and recurrence status were not independent risk factors. Progression status was identified as a significant risk factor on survival, and the presence of progression increased the mortality risk by 18.018 times compared with non-progression (p<0.001). The Cox regression analysis is shown in Table 3.

Recurrence was observed in three patients, progression was observed in one of 23 patients who had been followed for more than 10 years.

Recurrence was observed in three patients, progression was observed in one of 23 patients who had been followed for more than 10 years. High-grade Ta/T1, T2-T4, CIS, Upper urinary tract tumour progression rates were 13 (4.9%), 8 (3%), 2 (0.7%), 2 (0.7%), respectively. Progression significantly affected the mean survival time. The mean survival was 101.48 months in patients with progression and 200.19 months in patients without progression (p<0.001). Survival graphs are presented in Figure 1 and Figure 3.

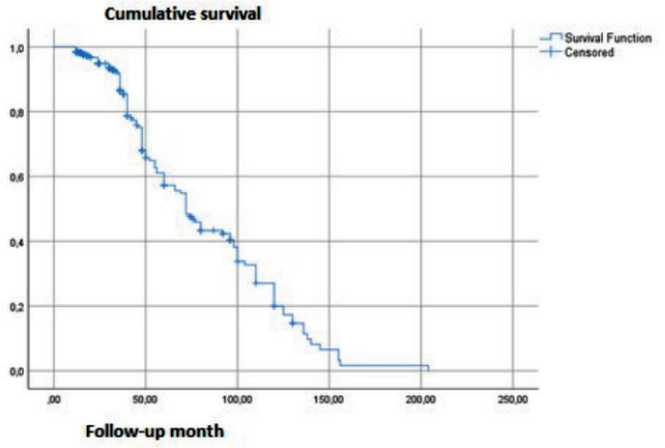

Figure 1. Reccurence-free survival rates, reccurence-free survival 1 and 5 years; 98%, 65.2%

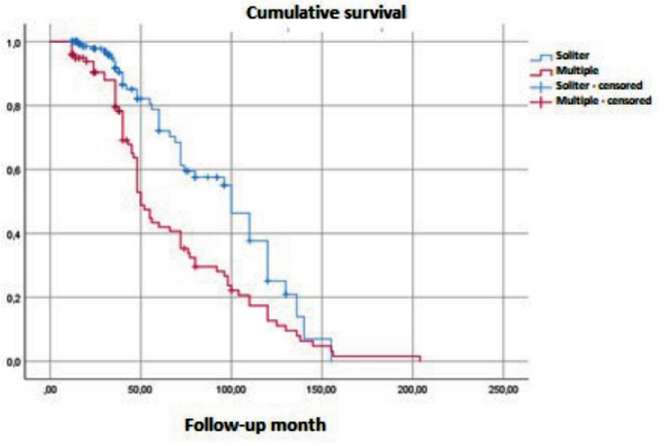

Figure 2. Reccurence-free survival rates in multiple & soliter tumors, reccurence-free survival rates soliter tumors 71% and multiple tumors 46%

Discussion

This study is a retrospective review of 262 patients with primary low-grade stage Ta bladder cancer. Patient-related parameters that could affect recurrence and progression rates (age, sex, smoking, tumour characteristics) were analysed. Multivariate

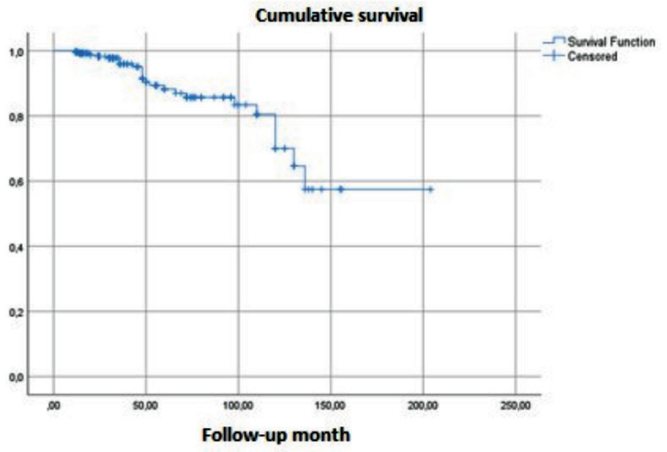

Figure 3. Progression-free survival rates, progression-free survival 1 and 5 years 99.6%, 88.2%

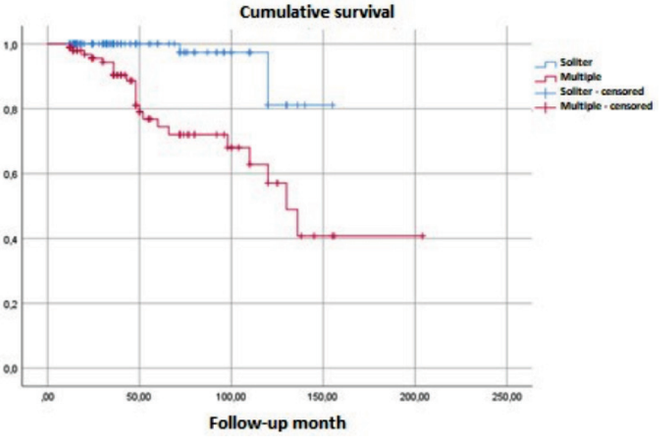

Figure 4. Progression-free survival rates in multiple & soliter tumors, progression-free survival rates multiple tumors 79%, soliter tumors 98%

Table 3. Cox regression analyses		
	OR (95% CI)	**p**
Smoking (yes/no)	3.255 (0.979 - 10.826)	0.054
Tumour (multiple/solitary)	1.994 (0.547 - 7.266)	0.295
Tumour size (≤3 cm, >3 cm)	2.108 (0.653 - 5.615)	0.145
Recurrence (yes/no)	0.945 (0.217 - 4.114)	0.940
Progression (yes/no)	18.018 (4.804 - 67.581)	**<0.001***
*Statistically significant p<0.05, OR: Odds ratio, CI: Confidence interval		

analysis showed a high risk of recurrence and progression in patients with multiple focal tumours and smokers. While solitary tumours had a risk of recurrence of less than 48%, multiple stage Ta tumours had a risk of approximately 50%-70% (5,6). In Golabesk et al.'s (4) single-centre retrospective study, 704 NMBC Ta/G1-G2 T1/G1-G2 patients were followed up for a mean of 64.9 months. Recurrence was observed in 188 (34.3%) of 548 Ta patients. Rieken et al. (5), in their multicentre retrospective analysis, 1436 low-grade Ta-stage patients were divided into two groups as low and moderate risk. After a mean follow-up of 33.5 months, recurrence was found in 613 patients (42.7%), and 5-year recurrence-free survival was 56%. According to the Cox regression analysis, advanced age, tumour size larger than three cm and recurrence rate of multiple tumours were significant. In this study, progression was observed in 164 patients (11.4%) after a mean follow-up of 67.2 months. However, the 5-year progression-free survival was 95% (5).

In a single-centre retrospective analysis conducted by Kobayashi et al. (7), 190 patients with low-grade Ta were evaluated for long-term, tumour recurrence was 43.2%, and progression was 11.1% in 101.5 months. Multiple tumour and intravesical instillation were risk factors for recurrence in multivariate analysis, whereas multiple tumour progression was the only risk factor for recurrence. After five years of tumour-free survival, nine patients had a late recurrence, and 10 years later, two patients had late recurrence after gross haematuria. Similarly, Matsumoto et al. (8) observed recurrence in 39 patients (14.9%) and progression in five patients (1.9%) during the follow-up of patients who did not have a 5-year recurrence in their retrospective studies.

Our study was consistent with Kobayashi (7) and Matsumoto's (8) findings since 10 patients (3.8%) had a late relapse after five years of recurrence, and two (0.76%) patients had late progression. There were 23 patients whose follow-up periods were over 10 years, three patients had a recurrence, and one patient had progression. To our knowledge, although there are no studies described in the literature for late recurrence, it is recommended that low-grade Ta tumours should be under routine follow-up for up to 10 years. However, there are also publications in the literature indicating that follow-up with cystoscopy is unnecessary in low-risk bladder cancer (9).

In Nerli et al.'s (10) single-centre retrospective study, 42 patients with low-grade, multiple, stage Ta bladder cancer were followed for a mean of 57.38±28.4 months (range 12 to 118 months). Recurrence was seen in 23 patients (54.76%) and progression in eight patients (19.04%) (10). In our study, the recurrence rate was 74%, and the progression rate was 22% in multiple tumours. In a multivariate analysis, the recurrence rate was significant in smoking patients, and 5-year relapse-free survival was significantly higher than in non-smokers (74% - 42.5%, p=0.0001).

In Zieger et al.'s (11) a single-centre prospective study, 212 patients with stage Ta G1-2 tumours were followed for 20 years, and only 14 patients received intravesical treatment. Ten patients (4.7%) had TaG3 CIS, 18 (8.5%) had stage T1, 23 patients (10.8%) had muscle invasion and distant metastasis (11). Similarly, Prout et al. (12) followed 178 stage Ta G1 patients for 10 years and observed progression in 13 patients (7.3%). In Akagashi et al.'s (13) study, none of the patients with TaG1-2, muscle invasion were not observed, 9.7% T1 and CIS progression were observed, and patients received intravesical treatment for two years. Also, in our study, the progression rate was 9.5%, which is consistent with the literature.

In the study of 245 low-grade Ta patients selected in the low-risk group in 2018 regarding the number and size of tumours, it was concluded that 1.5 cm might be the cut-off value. It also reported a higher recurrence rate of eight or more tumours (14). Also, in our study, the recurrence rates were higher in tumours larger than 3 cm. Tobacco use is a known risk factor for bladder

cancer. There are publications in the literature that tobacco use increases recurrence rates. In a retrospective analysis published in 2017, patients were categorised as non-smokers, smokers and former smokers. It is suggested that high cumulative exposure may increase smokers' recurrence rate, whereas people who stop smoking may have lower recurrence rates than smokers (15). Our study shows that recurrence and progression rates were significantly higher in smokers.

Although it is not included in the EAU and AUA guidelines, in recent years, as in prostate cancer, active monitoring has been conducted in NMIBC. In the study conducted in 181 cases followed by active surveillance in 2018, recurrence was observed in 61 (33.7%), 20 had benign lesions, and 41 (22.6%) had tumour recurrence. The authors suggest that active monitoring may be performed in NMIBC (16). Further prospective studies on active surveillance are needed.

Study Limitations

There are some limitations to our study. Since our study is retrospective, there may be incorrect and conflicting information in the medical records. Conflicting and incomplete data are excluded from this study as much as possible. Second, we could not find any information in the patient medical records regarding smoking behaviour, such as how many packs of cigarettes smoked per day, how many years they smoked. Third, it is stated in the literature that the recurrence rate decreased in people who receive postoperative intracavitary chemotherapy (ICT) (17). However, all of our patients received postoperative ICT, and there was no control group, so no comparison was made. Similarly, patients with high-risk bladder tumours who received ICT and BCG treatment were not in the control group, and those who received ICT treatment were statistically insignificant. Therefore, we believe that prospective comparative studies with high patient numbers will provide more accurate results.

Conclusion

In our study, recurrence and progression rates were 45.4% and 9.5% in primary low-grade Ta tumours, respectively. Smoking, tumours larger than three cm and multiple tumours increase the risk of recurrence and progression. Therefore, the prevention of smoking and routine cystoscopic examination is essential in the diagnosis and treatment of bladder cancer.

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Ethics

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Informed Consent: All participants provided written informed consent to participate in this study.

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Authorship Contributions

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

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Original Article

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5-Hydroxyuracil Incision Activity Varies According to the Histological Grade of Non-muscle-invasive Bladder Cancer

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Abstract

Objective: High levels of endonuclease III-like 1 (NTHL1) DNA glycosylase, which plays a role in the first step of the base excision repair pathway, has been related to cancer initiation and progression. 5-hydroxyuracil (5-OHU) oxidative base damage is a substrate for NTHL1 and endonuclease VIII-like 1 enzyme 1 (NEIL1) DNA glycosylases. This study investigates the association of 5-OHU incision activity with the risk of disease progression in patients with non-muscle-invasive bladder cancer (NMIBC) regarding grade and stage.

Materials and Methods: During transurethral resection of 17 NMIBC patients, the papillary tumour before monopolar resection and healthy bladder mucosal tissue from the same person were obtained using cold cup biopsy. Both the normal mucosa and NMIBC tumour were pathologically confirmed. The histological grade and stage were also determined. The 5-OHU incision activity of all tissues was measured using a radiolabelled 5-OHU modified base containing DNA substrate.

Results: 5-OHU incision activity was significantly higher in all high-grade NMIBC tissue extracts compared with the corresponding normal tissues (p=0.001). However, we found no significant difference in 5-OHU incision activity in low-grade NMIBC tissues (p=0.89). There was also a significant increase in 5-OHU incision activity at the Ta/T1 stage compared with the corresponding normal tissue (p=0.001).

Conclusion: The increase in 5-OHU incision activity according to the histological grade of NMIBC tissue indicates that this activity (mainly performed by NTHL1 and NEIL1 DNA glycosylases) might play a role in NMIBC prognosis. Thus, it could be used as a potential prognostic biomarker for NMIBC.

Keywords: Non-muscle-invasive bladder cancer, base excision repair, 5-hydroxyuracil incision, progression

Introduction

Bladder cancer is one of the most frequent (approximately 430,000 new cases per year) and most lethal (165,000 per year) cancers of the urinary system. Although its prevalence differs geographically, it is within the first five most prevalent and ten most lethal cancers (1). Bladder cancer is mainly grouped as non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive (MIBC). Around 80% of newly diagnosed cases are NMIBC (2,3). Although bladder cancer's exact aetiology is unknown, environmental, genetic and epigenetic risk factors are thought to be related to the disease's aetiology and pathogenesis (4,5). As an initial step in diagnosing and treating the disease, a complete transurethral resection (TUR) of the tumour is performed. In moderate and high-risk NMIBC patients, Bacillus Calmette-Guerin (BCG) installation remains the gold standard treatment regarding preventing disease recurrence and progression. However, approximately 40% of patients do not respond to BCG treatment (6,7). Although conventional histopathological criteria, such as histological grade and stage, provide information to determine NMIBC progression and metastasis risk, patients with similar pathological features may have different disease courses (3,8). This illustrates the importance of having an individualised therapeutic approach to bladder cancer. The present criteria are not adequate to define the risk factors for recurrence, progression and treatment response.

Recent preclinical and clinical cancer studies have shown that proteins involved in the base excision repair (BER) pathway

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can be promising prognostic and predictive biomarkers and therapeutic targets to determine cancer risk, recurrence, progression and drug resistance. The BER pathway is the primary repair mechanism responsible for repairing oxidative base damages, monofunctional base modifications and single-strand breaks in DNA caused by environmental and endogenous agents. BER is a multistep pathway, and DNA damage-specific DNA glycosylase enzymes are involved in the first step of this pathway. DNA glycosylase enzymes recognise modified or damaged bases and form an apurinic/apyrimidinic (AP) site in the DNA chain by the cleavage of the N-glycosidic bond. A single nucleotide gap is formed by the cleavage of the abasic AP site by AP endonuclease 1 (APE1), and the gap is filled by DNA polymerase β. The repair is completed by ligation of the nick (9,10). Although DNA glycosylase enzymes are specific to DNA damage, they can also repair the same base damage. For example, the main DNA glycosylase that repairs 5-hydroxyuracil (5-OHU) base damage is the endonuclease III homologue (NTHL1). Endonuclease VIII-like 1 enzyme 1 (NEIL1) also uses this base damage as a substrate. 5-OHU base modification is the most common base modification resulting from oxidative deamination of cytosine by reactive oxygen species (11). 5-OHU DNA lesions are bypassed by DNA polymerases and pair with other bases during DNA replication, resulting in mutations. BER mechanism impairment causes mutagenic and/or cytotoxic DNA damage to accumulate in the genome and causes genomic instability. This situation is one of the main reasons for susceptibility to various cancers, such as bladder, lung and breast cancer. On the other hand, it has been shown that cancer cells have a very active BER mechanism that causes cancer cell viability, recurrence, progression, metastasis and resistance to genotoxic anticancer drugs (10,11,12,13). For example, NTHL1 DNA glycosylase's overexpression has been associated with cancer progression and lymph node metastasis (14,15,16). Therefore, this study investigated the association of 5-OHU activity with the risk of progression in patients with NMIBC using low-grade and high-grade NMIBC tissue and their corresponding normal tissues from the same person.

Materials and Methods

NMIBC and Normal Bladder Tissue Samples from the Same Patient

Before the TUR procedure, cold cup biopsies were acquired separately, first from healthy-appearing mucosa and then from cancer tissue in 17 newly diagnosed, treatment-naive bladder cancer patients at the Acibadem Maslak Hospital urology department. The samples were snap-frozen by immediately placing them in liquid nitrogen. A piece of the normal mucosa and cancer tissue were separated for conventional pathology to confirm the normal mucosa and diagnose and grade cancer cells (17). Ethical board approval was obtained from the Acibadem University medical ethics committee (ATADEK-2018/12). The informed consent form was filled in by all participants.

Tissue Lysates Preparation of Normal and NMIBC Tissue

Tissue lysates were prepared as previously described (18). Briefly, the tissue was homogenised by a Dounce glass homogeniser in cold whole-cell extraction buffer. The tissue homogenate was centrifuged at 16,000 x g at 4 °C for 15 min. The pellet was dissolved, and tissue lysates were incubated at 4 °C for two hours in a shaking incubator. Then, they were centrifuged at 130,000 x g at 4 °C for one hour. The supernatant was dialysed at 4 °C overnight and centrifuged at 16,000 x g to remove the salts. The tissue lysates were kept at -80 °C. The tissue lysate protein content was measured with the Bradford protein assay at 595 nm using bovine serum albumin as a standard.

Preparation of Radiolabelled 5-OHU Containing DNA Substrate

The oligodeoxynucleotide sequences of DNA substrate containing 5-OHU base modification are as follows: (X = 5-OHU)

5′-GCTTAGCTTGGAATCGTA TCATGTAXACTCGT GTGCCGTGTA GACCGTGCC-3′;3′-CGAATCGAACCTTAGCATAGTACATGTGAG CACACGGCA CATCTGGCACGG-5′.

The oligodeoxynucleotides were purchased from DNA Technology, Denmark. The 51 mer upper primer sequence of the substrate was labelled with [γ-32P]ATP using a polynucleotide kinase reaction protocol from the 5`-end (Perkin Elmer, USA). The annealing reaction was completed by incubating [γ-32P] ATP labelled 51 mer primer and 51 mer template at 90 ºC for 5 min, and then slowly cooling to room temperature (18).

5-OHU Incision Activity

Incision of 5-OHU was performed in a reaction mixture containing 70 mM HEPES-KOH, pH 7.4, 5 mM EDTA, 1 mM DTT, 50 mM NaCl, 10% glycerol and 50 fmol of 32P-labelled double-stranded 5-OHU-containing the DNA substrate. The reactions were initiated by adding 0.5 µg whole tissue extract and incubating at 37 °C for 30 min. The reactions were stopped by adding formamide stop dye with 100 mM NaOH. Samples were heated at 95 °C for 10 min and then run on 20% PAGE-urea gel. Gels were visualised by Typhoon FLA 9500 PhosphorImager (GE Healthcare, USA). The experiments were performed in triplicate, and the incision activity is presented as fmol of substrate converted to product per min per µg protein.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 6.1 software. Differences in NMIBC tissue activities and the same individual's corresponding normal tissue were analysed using the Wilcoxon matched-pairs signed-rank test. A $p<0.05$ was considered statistically significant. All statistical tests were two-sided.

Results

The mean age of the patients was 68.65±15.02 years. A total of 6 patients had low-grade, and 11 patients had high-grade NMIBC. Of the patients, 14 had Ta stage and three of them had T1 disease. 5-OHU incision activity was measured as the incision of double-stranded oligodeoxynucleotide substrate containing 5-OHU at position 26. 5-OHU incision activity in all high-grade NMIBC tissue extracts was significantly higher than the corresponding normal tissues (Figure 1A, p=0.001). In contrast, no statistically significant difference in the activity was observed in low-grade NMIBC tissues (Figure 1B, p=0.89). The median of

5-OHU incision was 0.20 fmol/min/µg (range 0.15 to 0.44 fmol/min/µg) in high-grade NMIBC tissues and it was 0.10 fmol/min/µg (range 0.06 to 0.17 fmol/min/µg) in their corresponding normal tissues. In low-grade NMIBC tissues, the median of the activity was 0.16 fmol/min/µg (range 0.07 to 0.25) and it was 0.18 fmol/min/µg (range 0.08 to 0.2 fmol/min/µg) in their corresponding normal tissues. NMIBC tissue at the Ta/T1 stage exhibited a significant increase in 5-OHU activity (Figure 1C, p=0.001; median: 0.17 fmol/min/µg; range, 0.07 to 0.44 fmol/min/µg) compared to the corresponding normal tissues (median: 0.12 fmol/min/µg; range, 0.06 to 0.2 fmol/min/µg). 5-OHU incision activity was 2.01±0.42-fold higher in high-grade NMIBC tissue (Figure 1A and Figure 2), whereas the activity was 0.97±0.2-fold in low-grade NMIBC tissue (Figure 1B and Figure 2). Figure 2C shows the inter-individual variation among NMIBC and normal tissue. 5-OHU incision activity is different in NMIBC and normal tissues, and each individual (Figure 2C).

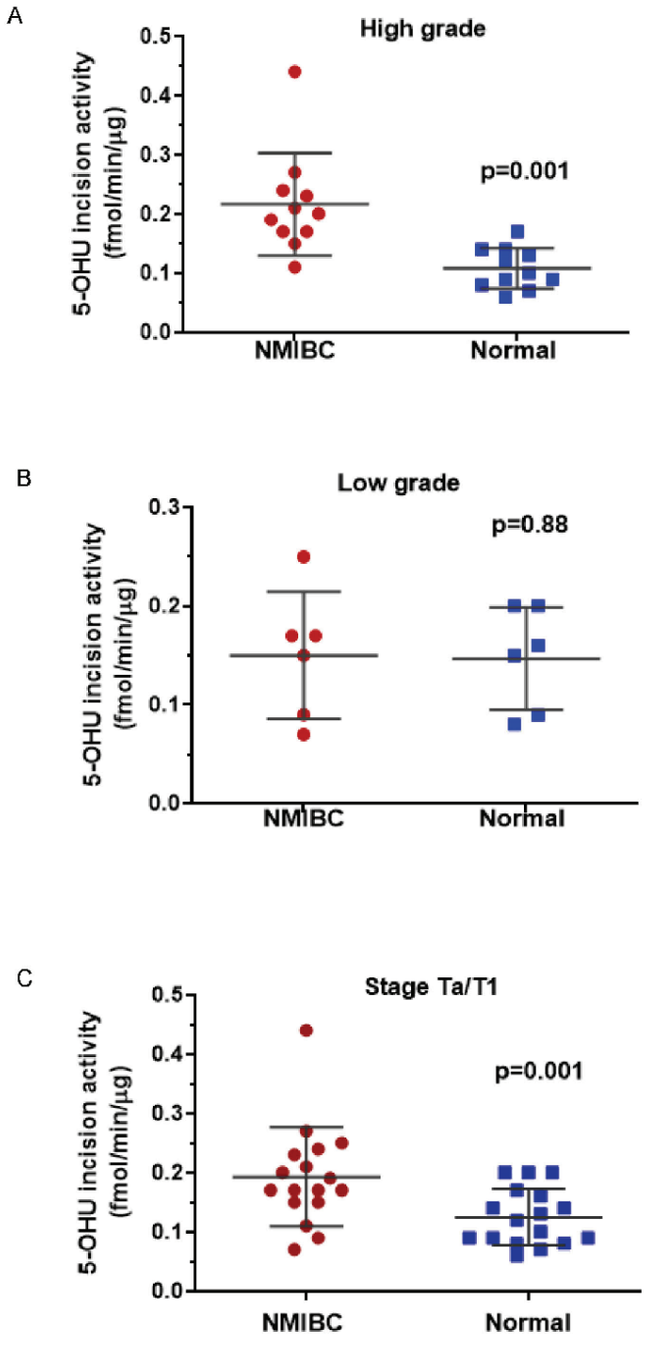

Figure 1. 5-OHU incision activity in NMIBC and their corresponding normal tissues. Quantitation of 5-OHU incision from high-grade (A), low-grade (B) and Ta/T1 stages (C) of all NMIBC and their corresponding normal tissues (fmol/µg/min)

5-OHU: 5-hydroxyuracil, NMIBC: Non-muscle-invasive bladder cancer

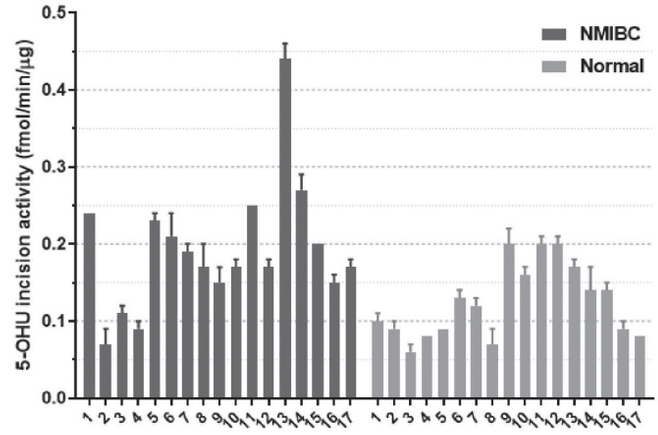

Figure 2. Inter-individual variability of 5-OHU incision activity in BER capacity of seventeen NMIBC and their corresponding normal tissues. Low-grade sample numbers are 2, 4, 9-12; high-grade sample numbers are 1, 3, 5-8, 13-17

5-OHU: 5-hydroxyuracil, NMIBC: Non-muscle-invasive bladder cancer, BER: Base excision repair

Discussion

In this study, it has been shown that 5-OHU incision activity of high-grade NMIBC tissue is very high compared with that of healthy bladder tissue of the same individual. In contrast, the activity does not change in low-grade NMIBC tissues. Thus, the increased activity correlates with the grade of NMIBC tissues. 5-OHU is the substrate for both NTHL1 and NEIL1 DNA glycosylase enzymes (19), suggesting that these enzymes might play an important role in the progression and recurrence of NMIBC. Cells with high levels of NTHL1 and NEIL1 DNA glycosylase enzymes have been shown to protect themselves by preventing mutations induced by 5-OHU modified base (16). Similarly, the aggressiveness and lymph node metastasis are related to increased levels of NTHL1 expression in colorectal cancers (15). In another study, high levels of *NTHL1* gene expression were shown to cause genomic instability and tumour formation (14).

In NMIBC tissues, uracil DNA glycosylase activity, which repairs uracil base damage, was high. However, no difference was reported in 8-oxoguanine DNA glycosylase activity, which repairs 8-oxoguanine base damage. In the same study, total BER activity and APE1 and Pol β activities of the BER pathway were increased in NMIBC tissues. These activities were statistically significant in both high-grade and low-grade NMIBC tissues than

the corresponding normal tissues (18). A study comparing the expression levels of the *APE1* gene in patients with high- and low-grade NMIBC showed that *APE1* gene expression was at a very high level in high-grade NMIBC tissue, and this increase was associated with the prognosis and recurrence of the disease (20,21,22). In this study, the increase in 5-OHU incision activity depended on the degree of NMIBC, thereby demonstrating that this activity can also be used as a prognostic biomarker for NMIBC.

Every individual has a different DNA repair capacity. The emergence of BER capacity differences between individuals and even between normal and cancer tissues helps to personalise cancer treatment by enabling the individual to understand their sensitivity to environmental toxins and their response to certain chemotherapeutic agents (23). Determining each NMIBC patient's BER capacity will facilitate their selected treatment approach that will provide the maximum benefit for NMIBC patients and predict the cancer cells' response to treatment.

Study Limitations

The limitation of this study was its small sample size. The number of patients could be increased for future biomarker studies.

Conclusion

In this study, the increase in 5-OHU incision activity in high-grade NMIBC tissues was determined and associated with NMIBC tissue grade. This activity and DNA glycosylase enzymes using a 5-OHU modified base as a substrate (mainly NTHL1 and NEIL1) might play a role in the progression of NMIBC. It could be used as a potential prognostic biomarker for NMIBC.

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Ethics

Ethics Committee Approval: Ethical board approval was obtained from the Acibadem University medical ethics committee (ATADEK-2018/12).

Informed Consent: The informed consent form was filled in by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.K., M.M., Design: S.K., C.Ö., Ü.İ., A.R.K., M.M., Data Collection or Processing: S.K., F.M.A., B.S., Y.S., T.D., C.Ö., Ü.İ., A.R.K., M.M., Analysis or Interpretation: S.K., F.M.A., B.S., Y.S., Ü.İ., A.R.K., M.M., Literature Search: A.A., Ç.D., A.E., Writing: M.M., S.K.

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Original Article

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Second Primary Malignant Tumours in Patients with Renal Cell Carcinoma

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Abstract

Objective: The primary aim of our study is to establish the frequency and clinicopathological features of seconder primary malignant tumours (SPMTs) in cases with renal cell carcinoma (RCC).

Materials and Methods: Pathology reports of 1129 RCC cases were checked retrospectively, and 70 RCC cases with SPMTs were included in the study. One patient had two and the other had three different SPMTs, so the total number of SPMTs was 73. According to occurrence times of SPMTs, the cases were classified as the antecedent, synchronous, subsequent and unknown. The first three groups were compared according to their clinicopathological features.

Results: The incidence of SPMTs with RCC in our study was 6.2% and lower than that reported by many other studies. The most common SPMTs were gastrointestinal, breast, prostate, lung, thyroid carcinomas and haematolymphoid malignancies. Sixty-two per cent of SPMTs were developed as synchronous and subsequent. There was no statistically significant difference among groups regarding age, histological subtype and RCC size. Male patients had a higher percentage in the synchronous group. In all groups, the most common RCC subtype was clear cell carcinoma. The RCC subtype in cases with multiple SPMTs was papillary. The prostatic adenocarcinoma rate was remarkable in males with papillary type RCC.

Conclusion: RCC can coexist with secondary malignancies. Therefore, when a new tumour appears in a patient with RCC in clinical follow-up, it is appropriate to evaluate that tumour histopathologically or cytopathologically regarding SPMT before accepting it as a metastatic spread.

Keywords: Renal cell carcinoma, seconder primary malignant tumour, synchronous neoplasms, metachronous neoplasms

Introduction

The number of multiple primary malignancies has increased because of improvements in early detection and specific treatment of tumours (1,2). For seconder primary malignant tumours (SPMTs), some criteria (Warren and Gates criteria) were accepted. Each tumour must arise from a different location, have distinct histology and metastasis possibility of the other must be excluded (3). They were classified as the antecedent, synchronous or subsequent in the literature. Synchronous tumours are defined as two or more primary cancers diagnosed at the same time or within six months (1,3,4). SPMTs, in cases with renal cell carcinoma (RCC), are frequent, and the reported incidence varies from 4.5% to 27.4% (5,6,7,8).

Rabbani et al. (6) found the most five common SPMTs in cases with RCC were the prostate, breast, colon, bladder carcinomas and non-Hodgkin lymphoma (NHL). In another study, it was reported that the most common other primary tumours were those of the prostate, bladder, lung, breast, colon, rectum, melanoma and NHL (7). Gastrointestinal carcinomas were the most common in Japanese people (1).

The association between histopathological RCC subtype and SPMTs was evaluated. It was reported that papillary type RCC

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(PRCC) was associated with an increased risk of developing SPMT in the prostate and bladder (6).

SPMTs contribute to the prognosis. The presence of antecedent or synchronous SPMTs is the second most significant prognostic factor, following the pathological stage of RCC (1). In addition, it was reported that RCC cases with antecedent or synchronous SPMTs had significantly poorer overall survival than those without (7).

The primary aim of our study is to establish the frequency and types of SPMTs in cases with RCC. In addition, we classified SPMTs according to occurrence times as antecedent, synchronous or subsequent and investigated the differences among these groups regarding available data.

Materials and Methods

We retrospectively checked the pathology reports of 1,129 cases diagnosed as RCC, in pathology archives of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, between January 2000 and June 2018. All were evaluated for the possibility of having SPMTs. Only the tumours, whose diagnosis were confirmed histopathologically and/or cytopathologically, were included as SPMTs in this study.

Clinicopathological parameters including age, gender; diagnostic method, histological subtype and size of RCC; location and histological type of SPMT were recorded for each case. The time of the diagnosis of RCC was considered for patients' ages. In addition, according to occurrence times of SPMTs, all RCC cases with SPMTs were classified as the antecedent, synchronous, subsequent and unknown. Synchronous tumours were defined as those diagnosed concurrently or within six months of the operation as in the literature (1,3,4). The first three groups were compared among each other regarding clinicopathological features.

Statistical Analysis

Descriptive statistics were used to describe the data. Normal distribution was tested by the Shapiro-Wilk test and graphical methods. Categorical data were compared using the chi-square test. Non-parametric groups comprising more than two groups were compared with the Kruskal-Wallis test. The confidence intervals were calculated at the 95% confidence level. Differences at $p<0.05$ were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0.

Results

SPMT was detected in 70 of 1,129 (6.2%) RCC cases; 47 (67%) of these patients were male, and 23 (33%) were female. Two patients had multiple secondary malignancies (one patient had two malignancies, and the other had three malignancies). Therefore, 73 SPMTs were included in the study. The distribution of SPMTs accompanying RCCs by gender is summarised in Figure 1. The time of the diagnosis of RCC was considered for patients' age; the median age was 60.5 (24-82) years.

In 61 of 70 cases, the diagnosis of RCC was made in the partial or radical nephrectomy material. The other nine patients were

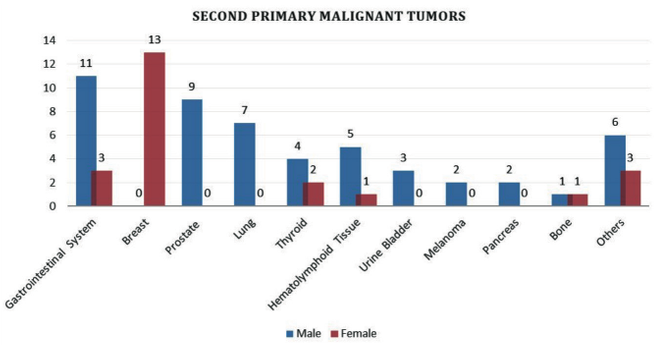

Figure 1. Distribution of SPMTs accompanying renal cell carcinomas by gender

SPMT: Sekonder primary malignant tumour

diagnosed as RCC by fine-needle aspiration (FNA) and/or core biopsy. These patients were not operated at our centre. The diagnosis of the most SPMTs was made by FNA and/or tissue (core or surgical) biopsy (TB) at our centre (FNA: 2, FNA+TB: 2, TB: 62). One SPMT was diagnosed by pleural fluid aspiration. Six cases did not have any biopsy at our centre, and the presence of SPMT was learned from clinical information.

Clear cell RCC (CCRCC) was the most common RCC subtype (in 41 cases: 58.6%), and one had sarcomatoid changes. The second and third common subtypes were PRCC (in 13 cases: 18.6%) and chromophobe (CHRCC) (in 12 cases: 17.1 %). Two cases had mucinous-tubular-spindle cell carcinoma, and two cases were unclassified RCC.

According to occurrence times, 73 SPMTs were divided into four groups: 25 in the antecedent (34.2%), 27 in synchronous (37%), 18 in subsequent (24.7%) and three in unknown (4.1%). Two SPMTs-antecedent nasopharyngeal mantle cell lymphoma and synchronous squamous cell carcinoma of the lung belonged to the same patient. In addition, another patient had three different secondary malignancies-prostate adenocarcinoma, papillary thyroid carcinoma and chronic lymphocytic leukaemia-which were in the group of unknown occurrence times.

After excluding the group of unknown occurrence times, antecedent, synchronous and subsequent groups were compared. There was no statistically significant difference between the three groups in terms of patient age ($p=0.538$, Kruskal-Wallis test). Because the median age was 60.5, age values were divided into two groups as ≤60 and >60, and the number of antecedent, synchronous and subsequent cases in each group were determined. When these parameters were compared using the chi-square test, there was no statistically significant difference between them ($p=0.742$) (Table 1).

Male patients were observed to have a higher percentage in the synchronous group than antecedent and subsequent groups (88,9%, 56%, 50%, respectively) and there was a statistically significant difference between the three groups regarding gender ($p=0.008$) (Table 1).

The most common RCC subtype in all three groups was CCRCC (56%, 66.7%, 50%, respectively), but this was not statistically significant ($p=0.298$) (Table 1).

We could not reach the clinical stage information of the cases. Since the most reliable data available for the pathological stage was

tumour size, we found it appropriate to evaluate this parameter statistically. Tumour size was known for 66 RCC, and one of them was accompanied by two different secondary malignancies. Tumour size could not be determined for four cases, and one of them had three different secondary malignancies. So, 67 SPMTs were analysed for RCC size. There was no statistically significant result between antecedent, synchronous and subsequent groups regarding RCC size (p=0.718, Kruskal-Wallis test). Then, RCC diameters were divided into four categories: ≤4 cm, >4-7 cm, >7-≤10 cm and >10 cm. The cases with ≤4 cm in RCC size were more frequently in the antecedent (13/24, 54.2%) and synchronous (11/25, 44%) groups. In the following group, the RCC size was >4 cm in most cases (13/18, 72.3%). However, the results were not statistically significant (p=0.353, chi-square test) (Table 2).

The most common SPMTs were gastrointestinal malignancies (19.1%), breast carcinomas (17.8%) and prostate carcinomas (12.3%). The distribution of SPMTs according to locations, histological types and occurrence times are listed in Tables 3 and 4.

When we compared the common SPMTs according to occurrence times, we found that gastrointestinal system (GIS) and lung tumours were most frequent in the synchronous group (57.1% and 71.4%, respectively), and breast tumours most frequently appeared as an antecedent (61.5%).

When we compared the histopathological RCC subtypes and SPMTs, CCRCC was the most common RCC subtype that accompanied SPMTs in all the series. CCRCC percentages were higher in the GIS, breast, lung, urinary bladder and pancreas (78.6%, 69.2%, 85.7%, 66.7% and 100%, respectively). In the CCRCC group, the occurrence times of the cases were parallel to characteristics of the general group: GIS and lung tumours most frequently appeared as synchronous (54.5% and 66.7%, respectively), and breast tumours were most frequent in the antecedent group (55.5%).

The proportion of prostatic adenocarcinoma in men with PRCC was remarkable, one of which also had two more SPMTs in addition to prostatic adenocarcinoma (papillary thyroid carcinoma and chronic lymphocytic leukaemia). In nine cases, prostatic adenocarcinoma was detected as SPMT. Renal carcinoma in five (55.6%) of them was PRCC. There was no

Table 1. Classification of SPMTs based on occurrence time and comparison of each group according to clinicopathological features

		Antecedent	Synchronous	Subsequent	Total	p
		n (%)				
		Median (min-max)				
Age (years)		60 (24-82)	64 (40-81)	59.5 (44-73)	60 (24-82)	0.538
Age (years)	≤60	13 (52)	12 (44.4)	10 (55.6)	35 (50)	0.742
	>60	12 (48)	15 (55.6)	8 (44.4)	35 (50)	
Gender	Female	11 (44)	3 (11.1)	9 (50)	23 (32.86)	0.008
	Male	14 (56)	24 (88.9)	9 (50)	47 (67.14)	
Histological type of RCC	Clear cell	14 (56)	18 (66.7)	9 (50)	41 (58.6)	0.298
	Papillary	3 (12)	4 (14.8)	6 (33.3)	13 (18.6)	
	Chromophobe	5 (20)	5 (18.5)	2 (11.1)	12 (17.1)	
	Others	3 (12)	0 (0)	1 (5.6)	4 (5.7)	
TOTAL		25 (100)	27 (100)	18 (100)	70 (100)*	

*: The RCC case with three SPMTs of unknown occurrence time was not included in the statistical analysis, Min: Minimum, Max: Maximum, SPMT: Seconder primary malignant tumours, RCC: Renal cell carcinoma

Table 2. Comparison of the antecedent, synchronous and subsequent groups according to RCC size

		Antecedent	Synchronous	Subsequent	Total	p
		n (%)				
		Median (min-max)				
RCC size (cm)		4 (1.6-14)	5 (1.7-15.50)	5 (1.5-15)	4.5 (1.5-15)	0.718
RCC size (cm)	≤4	13 (54.2)	11 (44)	5 (27.7)	29 (43.3)	0.353
	>4-≤7	8 (33.3)	8 (32)	11 (61.1)	27 (40.3)	
	>7-≤10	1 (4.2)	4 (16)	1 (5.6)	6 (8.9)	
	>10	2 (8.3)	2 (8)	1 (5.6)	5 (7.5)	
TOTAL		24 (100)	25 (100)	18 (100)	67 (100)*	

*Tumour size could be determined in 66 RCC cases. One had 2 SPMTs. Therefore, the statistical analysis was performed based on 67 SPMTs, RCC: Renal cell carcinoma, SPMT: Seconder primary malignant tumours, Min: Minimum, Max: Maximum

Table 3. Distribution of locations and histological types of SPMTs			
SPMTs	**Histological Type of SPMT**	**n**	**%**
Gastrointestinal system		14	19.1
Colorectum	Adenocarcinoma	11	
Stomach	Adenocarcinoma	1	
Stomach	Gastrointestinal stromal tumour	1	
Small Intestine	Neuroendocrine carcinoma	1	
Breast		13	17.8
	IDC*	6	
	Mixed IDC + mucinous carcinoma	2	
	Mixed IDC + lobular carcinoma	1	
	Mixed IDC + micropapillary carcinoma	1	
	Mucinous carcinoma	1	
	In-situ ductal carcinoma	1	
	Unknown**	1	
Prostate	Prostatic adenocarcinoma	9	12.3
Lung		7	9.6
	Small cell carcinoma	3	
	Adenocarcinomas	2	
	Squamous cell carcinoma	2	
Thyroid		6	8.2
	Papillary thyroid carcinoma	5	
	Hurthle (oncocytic) variant of follicular carcinoma	1	
Haematolymphoid tissue		6	8.2
	Chronic lymphocytic leukaemia	3	
	Mantle cell lymphoma (1 of them is nasopharyngeal)	2	
	Large B cell lymphoma of the skin	1	
Urinary bladder	Urothelial carcinoma	3	4.1
Melanoma		2	2.7
	Uveal melanoma	1	
	Skin melanoma	1	
Pancreas		2	2.7
	Ductal adenocarcinoma	1	
	Low-grade neuroendocrine tumour	1	
Bone		2	2.7
	Chondrosarcoma	1	
	Ewing sarcoma	1	
Lip	Squamous cell carcinoma	1	1.4
Larynx	Unknown**	1	1.4
Liver	Adenocarcinoma	1	1.4
Cervix	Squamous cell carcinoma	1	1.4
Ovary	Endometrioid adenocarcinoma	1	1.4
Testis	Germ cell tumour	1	1.4
Abdominal wall	Synovial sarcoma	1	1.4
Skin	Basal cell carcinoma	1	1.4
Metastasis in pleural fluid	Signet ring cell carcinoma of unknown primary origin	1	1.4
Total		73	100

*: IDC: Invasive ductal carcinoma (invasive carcinoma of no special type).
**: These cases were diagnosed at another hospital, and pathology reports could not be reached, SPMT: Seconder primary malignant tumour

significant difference regarding occurrence time in all prostatic adenocarcinomas developing as SPMT. However, the time of occurrence of four prostate adenocarcinomas associated with PRCC was known, and half of them occurred subsequently. Also,

Table 4. Distribution of SPMTs according to occurrence times						
SPMTs	**antecedent**	**synchronous**	**subsequent**	**unknown**	**n**	**%**
Gastrointestinal system	4	8	2	-	14	19.1
Colorectal	3	6	2	-	11	15.0
Stomach	-	2	-	-	2	2.7
Small Intestine	1	-	-	-	1	1.4
Breast	8	1	4	-	13	17.8
Prostate	3	2	3	1*	9	12.3
Lung	1	5**	1	-	7	9.6
Thyroid	-	1	4	1*	6	8.2
Haematolymphoid tissue	2**	2	1	1*	6	8.2
Urinary bladder	1	2	-	-	3	4.1
Melanoma	1	1	-	-	2	2.7
Pancreas	-	2	-	-	2	2.7
Bone	2	-	-	-	2	2.7
Lip	1	-	-	-	1	1.4
Larynx	1	-	-	-	1	1.4
Liver	-	-	1	-	1	1.4
Cervix	-	-	1	-	1	1.4
Ovary	-	1	-	-	1	1.4
Testis	1	-	-	-	1	1.4
Abdominal wall	-	1	-	-	1	1.4
Skin (BCC)***	-	1	-	-	1	1.4
Metastasis in pleural fluid****	-	-	1	-	1	1.4
Total	**25**	**27**	**18**	**3***	**73**	**100**

*: One case had three different secondary malignancies including prostatic adenocarcinoma, papillary thyroid carcinoma and chronic lymphocytic leukaemia. Occurrence times of SPMTs were unknown.
**: One case had two different secondary malignancies, including antecedent nasopharyngeal mantle cell lymphoma and synchronous squamous cell carcinoma of the lung.
***: BCC: Basal cell carcinoma.
****: Signet ring carcinoma metastasis of unknown primary origin in pleural fluid, SPMT: Seconder primary malignant tumour

Table 5. Distribution of histopathological RCC subtypes in SPMTs groups										
SPMTs	**Clear cell RCC**		**Papillary RCC**		**Chromophobe RCC**		**Others**		**Total**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Gastrointestinal system	11	78.6	1	7.1	2	14.3	0	0.0	14	100.0
Breast	9	69.2	1	7.7	1	7.7	2	15.4	13	100.0
Prostate	1	11.1	5	55.6	3	33.3	0	0.0	9	100.0
Lung	6	85.7	1	14.3	0	0.0	0	0.0	7	100.0
Thyroid	2	33.3	2	33.3	1	16.7	1	16.7	6	100.0
Haematolymphoid tissue	2	33.3	4	66.7	0	0.0	0	0.0	6	100.0
Urinary bladder	2	66.7	1	33.3	0	0.0	0	0.0	3	100.0
Melanoma	1	50.0	0	0.0	1	50.0	0	0.0	2	100.0
Pancreas	2	100.0	0	0.0	0	0.0	0	0.0	2	100.0
Bone	1	50.0	0	0.0	1	50.0	0	0.0	2	100.0

RCC: Renal cell carcinoma, SPMT: Seconder primary malignant tumour

RCCs in two patients with multiple secondary malignancies were PRCC. The distribution of histological subtypes of RCC in the SPMT groups that have many cases is shown in Table 5.

Discussion

The incidence of SPMTs in cases of RCC varies from 4.5% to 27.4% (5,6,7,8). It was found as 12% in Japanese patients. These differences in frequency might be because of the nature of the institutions and the pattern of the studies (1). Genetic and environmental differences can contribute to a higher or lower risk of SPMT in a given population (8). The incidence of second cancers among patients with RCC in our study was 70/1129 (6.2%) and lower than that reported by many other studies. This may be due to our data being limited to pathology reports.

Beisland et al. (7) reported that the most common other primary tumours were those of prostate, bladder, lung, breast and colon. Sato et al. (1) showed that gastrointestinal carcinomas were the most common SPMTs accompanying RCC. In another study, it was found that the largest number of SPMT arose in male genital (particularly the prostate gland), digestive and respiratory systems (8). In a population-based study, the incidence of RCC was found higher among men with many kinds of carcinomas, whereas the incidence of prostate cancer was increased only in men who had RCC (9). In our study, the most common SPMTs were respectively gastrointestinal cancer (mostly colorectal adenocarcinoma), breast carcinoma (mostly invasive ductal carcinoma/invasive carcinoma of no special type), prostatic adenocarcinoma, lung carcinomas (mostly small cell carcinoma), thyroid carcinoma (mostly papillary type) and haematolymphoid malignancies (mostly chronic lymphocytic leukaemia).

In the literature, it was reported that the small intestine was the most common location for gastrointestinal stromal tumor (GIST) that accompanied a second primary neoplasm (10,11). However, in our series, there was only one patient with GIST as SPMT, and it was localised in the stomach. Mendonca et al. (11) found nine RCC cases with GIST as SPMT that had a high frequency of CCRCC (4/9) and PRCC (4/9) subtypes. In our case, renal carcinoma was also CCRCC.

In a study, the association between NHL and RCC was evaluated. Race and gender were found significantly associated with an increased cumulative incidence of RCC after NHL. White males with NHL are at increased risk for RCC (12). In our small series, six cases had haematolymphoid malignancy as SPMT, and five were male.

The association between the histological subtype of RCC and SPMTs was investigated by some authors. Abdel-Rahman (13) found that PRCC had the highest standardised incidence ratios for subsequent kidney cancers. Rabbani et al. (6) reported that the PRCC is associated with an increased risk of developing SPMT in the prostate and bladder. Thampson et al. (14) found that cases with PRCC were significantly more likely to have colon and prostate cancer or any second malignancy compared with CCRCC. Cases with CHRCC were significantly more likely to have colon cancer than CCRCC. Cases with PRCC were more likely to have bladder cancer, but this result was not significant compared with CCRCC and CHRCC.

In our series, CCRCC was the most common RCC subtype that accompanied SPMTs. CCRCC percentages were higher in the GIS, breast, lung, urinary bladder and pancreas. We found a close relationship between PRCC and prostatic adenocarcinoma in our study: 55.6% of prostatic adenocarcinoma cases had PRCC. There were two cases with multiple secondary malignancies in our study, and one of these cases had prostatic adenocarcinoma. The kidney carcinoma of both cases with multiple secondary malignancies was PRCC.

SPMTs contributes to the prognosis of RCC cases. Sato et al. (1) found that the presence of antecedent or synchronous malignancies was the second most significant prognostic factor, following the pathological stage of RCC. Beisland et al. (7) reported that RCC cases with an antecedent or synchronous other cancer had significantly poorer overall survival than those without. Among the clinicopathological data we could obtain in our study, we compared the time of occurrence of SPMTs and the tumour size, since the tumour size was the most valuable prognostic parameter. The cases with ≤4 cm in RCC size were usually in the antecedent and synchronous groups, whereas tumours >4 cm in most cases were in the subsequent group. However, there was no statistically significant result between the occurrence time of SPMT and RCC size.

In our study, when the antecedent, synchronous and subsequent SPMT groups were compared with each other regarding clinicopathological parameters, no significant difference was found between the groups, except for the gender parameter. We thought that this was related to the limited number of cases and the clinicopathological parameters that could be reached. More comprehensive studies are required to determine the clinical and pathological characteristics of SPMTs with RCCs.

Study Limitations

Since the clinical information we obtained was limited, we could not comment on some topics, such as etiological factors, stage and survival.

Conclusion

In this study, the incidence of SMPTs with RCC was 6.2% and lower than that reported by many other studies. The most common locations for SPMTs were the GIS, breast and prostate. When SPMTs were categorised according to occurrence times, there were no statistically significant differences among antecedent, synchronous and subsequent groups regarding patient age, histological RCC subtype and RCC size. Male patients had a higher percentage in the synchronous group than antecedent and subsequent groups. CCRCC was the most common RCC subtype that was accompanying SPMTs in all our series. The proportion of prostatic adenocarcinoma in men with PRCC was remarkable. Two patients' RCCs with multiple secondary malignancies were PRCC. RCC can coexist with secondary malignancies. Our findings indicate that more comprehensive studies are required to determine the clinical and pathological characteristics of SPMTs with RCCs. However, for our practical application, we can say that: When a new tumour appears in a patient with RCC who is in clinical follow-up, it is appropriate to evaluate that tumour histopathologically or cytopathologically regarding SPMT before accepting it as a metastatic spread.

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Authorship Contributions

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Oncological Outcomes of Bilateral Testicular Germ Cell Tumors and Evaluation of Prognostic Risk Factors

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Abstract

Objective: The incidence of bilateral testicular germ cell tumours (TGCT) is low and constitutes 0.5%-7% of all testicular tumours. We aimed to evaluate the clinical and pathological features of unilateral and bilateral TGCT, as well as prognostic factors in bilateral cases that may have an impact on oncological outcomes.

Materials and Methods: Bilateral TGCT were detected in 10 (11.4%) of 87 patients between January 2010 and July 2016. Patients with 68 unilateral and 10 bilateral tumours (4 synchronous, 6 metachronous) had completely accessible data. We retrospectively evaluated their clinical-pathological data and postoperative follow-up results.

Results: Four patients with bilateral synchronous tumours had a seminoma and three (75%) of them had a stage III disease. At a median follow-up of 31.50 (29-37) months, local recurrence, distant metastasis and death were observed in two patients with stage III disease. No recurrence or metastasis was seen in six patients with unilateral TGCT at 33 (24-50) months of follow-up, but metachronous tumours occurred in the contralateral testicles. At a median follow-up of 25 (11-39) months after metachronous tumour development, local recurrence, distant metastasis and death were observed in the contralateral testis of patients with stage III disease. There was no significant difference in bilateral and unilateral cases for disease-free survival, progression-free survival (PFS) and overall survival (OS). PFS and OS were significantly shorter (p=0.039) in bilateral synchronous tumours than in metachronous tumours. Moreover, stage III disease was more common (75% vs 33.3%) in synchronous tumours. Family history (OR: 6.556, p=0.035), testicular dysgenesis syndrome (OR: 3.876, p=0.031), disorders of semen parameters (OR: 2.879, p=0.037), undescended testis (OR: 2.561, p=0.026), monocyte/lymphocyte ratio >0.31 [odds rotio (OR): 2.234, p=0.022], testicular microlithiasis (OR: 2.015, p=0.015) and neutrophil/lymphocyte ratio >3.23 (OR: 1.348, p=0.025) increased the risk of contralateral tumour development.

Conclusion: Bilateral synchronous tumours are detected at a more advanced stage and have lower PFS and OS durations, but survival rates are similar to those of unilateral tumours. Long-term follow-up is necessary for patients with unilateral TGCT having certain risk factors due to the possibility of metachronous tumour development in the contralateral testis.

Keywords: Bilateral, metachronous, synchronous, testicular dysgenesis syndrome, testicular germ cell tumour

Introduction

Although testicular germ cell tumor (TGCT) constitutes 1% of all male malignancies and 5% of urological tumors, it is the most common solid tumor detected in men aged 15-44 years (1). In the treatment of TGCT, which accounts for more than 95% of all testicular malignancies, the standard first approach is radical orchiectomy, and as a result of the developments in adjuvant chemotherapy (CT), high rates of cure can be achieved today (2).

Well-known risk factors in the etiology are testicular dysgenesis syndrome (TDS) components (undescended testis, hypospadias, decreased spermatogenesis), familial TGCT history in first-degree relatives, a history of tumor in the contralateral testicle, and the presence of intratubular germ cell neoplasia (ITGCN) (3). Bilateral TGCT accounts for 0.5-7% of all testicular tumors (1,4). Synchronous (simultaneous bilateral) tumor is observed in approximately 35% of these patients, and metachronous (second contralateral) tumor is seen in 65% (5).

In general, although it is known that synchronous tumors are seen at more advanced stages and survival rates are lower than metachronous tumors, our knowledge about epidemiological and clinicopathological features and treatment strategies of bilateral TGCT is limited (1). Therefore, we aimed to evaluate the prognostic factors that might affect oncological outcomes in patients with bilateral TGCT by examining the clinical and pathological features of patients diagnosed as having bilateral or unilateral TGCT in our clinic.

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Materials and Methods

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. Each patient was informed before the surgery that the demographic, clinical, pathological and oncological data of the patients could be used in various oncological studies to be performed in the clinic without specifying the patient names and identity information, and the data of the patients who did not consent was not used in this study.

Pathological findings of 99 patients who underwent radical orchiectomy with a pre-diagnosis of testicular tumor between January 2010 and July 2016 were evaluated retrospectively. The patients of whom pathological examination of orchiectomy specimens showed paratesticular sarcoma (n=5), epidermoid cyst (n=1), inflammatory myofibroblastic tumor (n=1), benign cystic teratoma (n=2), benign leydig cell tumor (n=1), paratesticular fibroma (n=1) and non-Hodgkin lymphoma (n=1) were excluded from the study, and the data of 87 patients with TGCT were evaluated.

Demographic data, histopathological tumor subtypes, clinical tumor stage, tumor localization, tumor size, expression of serum tumor markers (alpha-fetoprotein, beta human chorionic gonadotropin, lactate dehydrogenase), serum hemogram parameters [(neutrophil/lymphocyte ratio (NLR)], monocyte/lymphocyte ratio (MLR), platelet/lymphocyte ratio (PLR), mean platelet volume, red cell distribution width], prognostic factors of tumor in pathology samples, follow-up time after orchiectomy, local recurrence, distant metastasis and overall mortality rates of the patients were noted. Family history, the presence of undescended testis, hypospadias or semen parameter disorder (the presence of any disorder in terms of number, motility, morphology or vitality in semen parameters), presence of atrophic testis (testicular volume <12 mL), and the status of microlithiasis in preoperative ultrasonographic examination were also recorded by scanning patient files. Seventy eight patients with TGCT who could be reached were included.

Clinical tumor stages were evaluated according to the 2009 tumor-node-metastasis classification. While early stage tumors consisted of stage IA and IB; advanced stage tumors included stage IS, IIA/IIB/IIC and IIIA/IIIB/IIIC. Histological tumor subtypes were evaluated according to the World Health Organization's classification. According to the European Association of Urology (EAU) 2020 guidelines, for stage I seminoma, presence of rete testicular involvement and tumor size greater than 4 cm; for stage I non-seminoma, the presence of lymphovascular invasion, embryonal carcinoma rate over 50% and proliferation index over 70% were evaluated as pathological prognostic risk factors (3).

The definition of TDS includes the presence of at least two of undescended testicles, hypospadias, decreased spermatogenesis or TGCT (6). Since all patients in our study had TGCT, we classified the patients as having TDS due to whether having at least one of undescended testis, hypospadias or semen parameters disorder. Patients were divided into two groups without randomization. Group I included patients with bilateral TCHT (n=10), group II with unilateral TGCT (n=68). Both groups were compared in terms of demographic and clinical data, prognostic risk factors, serum hemogram parameters and oncological results. Patients with bilateral TGCT were also evaluated by dividing them into two subgroups as synchronous (n=4) and metachronous (n=6).

Statistical Analysis

After evaluating the normality status with the Kolmogorov-Smirnov and Shapiro-Wilk tests, when comparing the differences between the two groups, Mann-Whitney U test was used for continuous variables that did not show normal distribution. Pearson chi-square analysis or Fisher's Exact test was used for categorical variables. Kaplan-Meier method was used for the analysis of disease-free survival (DFS), progression-free survival (PFS) and overall survival (OS), while differences between patient groups were evaluated using the log rank test. Logistic regression analysis was used to determine prognostic factors that may affect contralateral tumor development in the follow-up of patients with unilateral tumors at the time of initial diagnosis. Receiver operating characteristic analysis could not be performed to determine the threshold value for serum hemogram parameters due to the small sample size. Instead, the median values of all 78 patients included in the study were taken as threshold values and included in univariate and multivariate models in logistic regression analysis. Analyzes were performed using IBM SPSS Statistics 21 (IBM, Armonk, NY USA) software. Values of $p<0.05$ were considered statistically significant.

Results

Patient Population and General Characteristics

Bilateral tumors were detected in 10 (11.4%) of 87 patients who were diagnosed as having TGCT after radical orchiectomy between January 2010 and July 2016. Four (40%) of them had synchronous tumors and six (60%) had metachronous tumors. Since the data were fully available, the median age of 78 patients included in the study was 31 and during a median of 57.50 (minimum= 6- maximum= 106) months follow-up, 15 (19.2%) developed local recurrence, 17 (21.8%) developed distant metastasis, and 16 (20.5%) cancer-related death was observed. Distant metastases were detected in the lung in 8 patients, liver in 4 patients, and non-regional lymph nodes in 5 patients. Demographic, pathological, clinical data and oncological results of the patients are shown in Tables 1 and 2.

Synchronous Tumors

The median age at diagnosis was 33 (24-42) in 4 patients with bilateral synchronous TGCT. Two of the patients had a history of undescended testis, 1 had a history of hypospadias, 2 had a defect in semen parameters, 1 had atrophic testis, and 2 had testicular microlithiasis. Two patients were determined to be suitable for the TDS definition. Increased tumor markers were found in 3 (75%) patients, while tumor histopathology was found as pure seminoma on both sides in all patients. After clinical staging, it was determined that one of the patients had

Table 1. Demographic and pathologic data of all patients				
Parameters	**Group I (bilateral TGCT) (n=10)**	**Group II (unilateral TGCT) (n=68)**	**Total (n=78)**	**p-value**
Age Median (25.-75. percentiles)	27.00 (24.75-36.00)	31.00 (25.25-41.00)	31.00 (25.00-39.50)	†0.342
**Tumor size (cm) Median (25.-75. percentiles)	4.80 (3.45-7.62)	4.00 (2.50-6.40)	4.15 (2.57-6.55)	†0.282
Tumor side (n, %)				
-Left	0 (0.0)	25 (36.8)	25 (32.1)	‡<0.001*
-Right	0 (0.0)	43 (63.2)	43 (55.1)	
-Bilateral	10 (100.0)	0 (0.0)	10 (12.8)	
Histopathologic subtype (n, %)				
-Seminoma	6 (60.0)	35 (51.5)	41 (52.6)	‡0.877
-Non-seminoma	3 (30.0)	24 (35.3)	27 (34.6)	
-Mixed type	1 (10.0)	9 (13.2)	10 (12.8)	
AFP (ng/mL) Median (25.-75. percentiles)	4.35 (2.07-82.02)	6.15 (2.15-76.06)	5.60 (2.17-72.68)	†0.864
β-hCG (mIU/mL) Median (25.-75. percentiles)	5.00 (1.75-370.00)	17.95 (2.55-114.00)	12.45 (2.50-124.00)	†0.899
LDH (U/L) Median (25.-75. percentiles)	608.50 (230.00-1090.75)	308.50 (187.75-717.00)	309.00 (201.35-784.50)	†0.145
Tumor stage				
-I	5 (50.0)	38 (55.9)	43 (55.1)	§0.455
-II	0 (0.0)	8 (11.8)	8 (10.3)	
-III	5 (50.0)	22 (32.4)	27 (34.6)	
ITGCN (n, %)				
Yes	8 (80.0)	30 (44.1)	38 (48.7)	‡0.034*
No	2 (20.0)	38 (55.9)	40 (51.3)	
Rete testis invasion (n, %)				
Yes	2 (20.0)	16 (23.5)	18 (23.1)	§0.582
No	8 (80.0)	52 (76.5)	60 (76.9)	
Tumor diameter >4 cm (n, %)				
Yes	7 (70.0)	33 (48.5)	40 (51.3)	§0.312
No	3 (30.0)	35 (51.5)	38 (48.7)	
Lymphovascular invasion (n, %)				
Yes	4 (40.0)	23 (33.8)	27 (34.6)	§0.478
No	6 (60.0)	45 (66.2)	51 (65.4)	
Embryonal carcinoma rate >50% (n, %)				
Yes	1 (10.0)	18 (26.5)	19 (24.4)	§0.436
No	9 (90.0)	50 (73.5)	59 (75.6)	
Proliferation rate >70% (n, %)				
Yes	1 (10.0)	1 (1.5)	2 (2.6)	§0.241
No	9 (90.0)	67 (98.5)	76 (97.4)	

*p<0.05 Asterisk (*) indicates statistical significance.
**In patients with bilateral tumors, the size of the tumor with the largest diameter is given in the table.
AFP: Alpha-fetoprotein, β-hCG: Beta human chorionic gonadotropin, ITGCN: Intratubular germ cell neoplasia, LDH: Lactate dehydrogenase, TGCT: Testicular germ cell tumor
†: Mann-Whitney U test, ‡: Chi-square test, §: Fisher's Exact test

stage I disease and the other 3 had stage III disease. At a median follow-up of 31.50 (29-37) months, local recurrence, distant metastasis and death were observed in 2 patients with stage III disease (Tables 3 and 4).

Table 2. Clinical data and oncologic results of all patients				
Parameters	**Group I (bilateral TGCT) (n=10)**	**Group II (unilateral TGCT) (n=68)**	**Total (n=78)**	**p-value**
Undescended testis (n, %)				
Yes	4 (40.0)	8 (11.8)	12 (15.4)	§0.042*
No	6 (60.0)	60 (88.2)	66 (84.6)	
Semen parameter disorders (n, %)				
Yes	4 (40.0)	7 (10.3)	11 (14.1)	§0.030*
No	6 (60.0)	61 (89.7)	67 (85.9)	
Hypospadias (n, %)				
Yes	2 (20.0)	1 (1.5)	3 (3.8)	§0.042*
No	8 (80.0)	67 (98.5)	75 (96.2)	
Atrophic testis (n, %)				
Yes	1 (10.0)	4 (5.9)	5 (6.4)	§0.506
No	9 (90.0)	64 (94.1)	73 (93.6)	
Testicular microlithiasis (n, %)				
Yes	5 (50.0)	14 (20.6)	19 (24.4)	‡0.043*
No	5 (50.0)	54 (79.4)	59 (75.6)	
Presence of TDS (n, %)				
Yes	5 (50.0)	12 (17.6)	17 (21.8)	§0.035*
No	5 (50.0)	56 (82.4)	61 (78.2)	
Family history of TGCT (n, %)				
Yes	4 (40.0)	9 (13.2)	13 (16.7)	‡0.034*
No	6 (60.0)	59 (86.8)	65 (83.3)	
Neutrophil/lymphocyte ratio	5.34 (4.33-7.45)	2.76 (1.80-4.42)	3.23 (2.09-4.58)	†0.001*
Monocyte/lymphocyte ratio	0.38 (0.33-0.49)	0.27 (0.18-0.37)	0.31 (0.19-0.38)	†0.006*
Platelet/lymphocyte ratio	190.34 (169.05-248.76)	142.69 (98.16-197.48)	150.01 (107.48-207.86)	†0.013*
Mean platelet volume (fL)	4.29 (3.63-6.04)	5.20 (3.72-7.13)	5.08 (3.74-6.86)	†0.424
Red blood cell distribution width (fL)	14.75 (13.57-15.37)	13.90 (12.72-14.67)	13.90 (12.87-14.80)	†0.081
Follow-up time [median (minimim-maximum), months]	49.50 (29-69)	60.50 (6-106)	57.50 (6-106)	†0.313
Local recurrence rate (n, %)	2 (20.0)	13 (19.1)	15 (19.2)	§0.616
Distant metastasis rate (n, %)	3 (30.0)	14 (20.6)	17 (21.8)	§0.376
Total mortality rate (n, %)	3 (30.0)	13 (19.1)	16 (20.5)	§0.420

*p<0.05 Asterisk (*) indicates statistical significance.
TDS: Testicular dysgenesis syndrome, TGCT: Testicular germ cell tumor
†: Mann-Whitney U test, ‡: Chi-square test, §: Fisher's Exact test

Metachronous Tumors

In 6 patients with bilateral metachronous TGCT, the median age at diagnosis was 26 (20-35) when the first tumor was detected, and 29.5 (22-37) when the contralateral second tumor was detected. Two of the patients had a history of undescended testis, one had a history of hypospadias, 2 had a defect in semen parameters, and 3 had testicular microlithiasis. Three patients were consistent with the TDS definition. During the first tumor diagnosis, elevation in tumor markers was detected in 5 (83.3%) patients, while tumor histopathology was determined as pure seminoma in 2 patients, pure non-seminoma in 3 patients, and mixed type TGCT in one patient. In this subgroup, where 4 patients had stage I disease and 2 patients had stage III disease, no recurrence or metastasis was observed at a median follow-up of 33 (24-50) months until the contralateral tumor developed (Tables 3 and 4).

When the contralateral second testicular tumor was detected, tumor markers were elevated in 3 (50%) patients, while tumor histopathology was determined as pure seminoma in 4 patients and pure non-seminoma in 2 patients. Although the first tumor was not seminoma in 2 patients, it was observed that the contralateral tumor was seminoma. No significant difference was found in terms of initial tumor size, and contralateral tumor size developed at follow-up [4.75 (3-8) cm vs 4.35 (3.1-6.1) cm, p=0.699]. Unlike the initial tumor staging, stage III contralateral tumor was observed in only one patient and stage I contralateral

Table 3. Demographic and pathologic data of patients with bilateral testicular germ cell tumor				
Parameters	**Synchronous tumors (n=4)**	**Metachronous tumors (n=6)**	**Total (n=10)**	**p-value**
Age Median (25.-75. percentiles)	33.00 (24.75-41.25)	26.00 (23.75-33.50)	27.00 (24.75-36.00)	†0.334
**Tumor size (cm) Median (25.-75. percentiles)	5.50 (2.40-7.37)	4.75 (3.45-7.77)	4.80 (3.45-7.62)	†0.831
Histopathologic subtype (n, %)				
-Seminoma	4 (100.0)	2 (33.3)	6 (60.0)	‡0.035*
-Non-seminoma	0 (0.0)	3 (50.0)	3 (30.0)	
-Mixed type	0 (0.0)	1 (16.7)	1 (10.0)	
AFP (ng/mL) Median (25.-75. percentiles)	4.10 (1.92-54.50)	33.00 (2.07-430.62)	4.35 (2.07-82.02)	†0.522
β-hCG (mIU/mL) Median (25.-75. percentiles)	1.50 (0.25-120.50)	71.40 (4.27-279.00)	5.00 (1.75-370.00)	†0.088
LDH (U/L) Median (25.-75. percentiles)	1159.00 (407.75-2304.25)	408.00 (230.00-880.00)	608.50 (230.00-1090.75)	†0.394
Tumor stage				
-I	1 (25.0)	4 (66.7)	5 (50.0)	‡0.197
-II	0 (0.0)	0 (0.0)	0 (0.0)	
-III	3 (75.0)	2 (33.3)	5 (50.0)	
ITGCN (n, %)				
Yes	4 (100.0)	4 (66.7)	8 (80.0)	§0.333
No	0 (0.0)	2 (33.3)	2 (20.0)	
Rete testis invasion (n, %)				
Yes	1 (25.0)	1 (16.7)	2 (20.0)	§0.667
No	3 (75.0)	5 (83.3)	8 (80.0)	
Tumor diameter >4 cm (n, %)				
Yes	3 (75.0)	4 (66.7)	7 (70.0)	§0.667
No	1 (25.0)	2 (33.3)	3 (30.0)	
Lymphovascular invasion (n, %)				
Yes	3 (75.0)	1 (16.7)	4 (40.0)	§0.119
No	1 (25.0)	5 (83.3)	6 (60.0)	
Embryonal carcinoma rate >50% (n, %)				
Yes	0 (0.0)	1 (16.7)	1 (10.0)	§0.389
No	4 (100.0)	5 (83.3)	9 (90.0)	
Proliferation rate >70% (n, %)				
Yes	0 (0.0)	1 (16.7)	1 (10.0)	§0.389
No	4 (100.0)	5 (83.3)	9 (90.0)	

*p<0.05 Asterisk (*) indicates statistical significance.
**In patients with bilateral tumors, the size of the tumor with the largest diameter is given in the table.
AFP: Alpha-fetoprotein, β-hCG: Beta human chorionic gonadotropin, ITGCN: Intratubular germ cell neoplasia
LDH: Lactate dehydrogenase, TGCT: Testicular germ cell tumor
†: Mann-Whitney U test, ‡: Chi-square test, §: Fisher's Exact test

tumor in the other 5 patients. At a median follow-up of 25 (11-39) months after the development of the contralateral tumor; local recurrence, distant metastasis and death were observed in one patient with stage III disease. It was noteworthy that the first tumor of this patient was also a stage III tumor. The total follow-up period of 6 patients with metachronous tumors after the first tumor was detected was 64 (48-69) months.

Clinical Differences Between Bilateral and Unilateral Tumors

While ITGCN (p=0.034) was found with a significantly higher rate in bilateral patients compared to unilateral patients (Table 1), again in these patients undescended testis (p=0.042), semen parameter disorder (p=0.030), hypospadias (p=0.042), the incidence of testicular microlithiasis (p=0.043) and TDS

(p=0.035) were higher (Table 2). When we divided bilateral patients into two subgroups as patients having synchronous or metachronous tumors, no significant difference was observed between groups in terms of both ITGCN rates (Table 3) and other parameters mentioned (Table 4).

When the rates of local recurrence, distant metastasis and overall mortality were compared, statistical similarity was observed between both bilateral and unilateral patients, and bilateral synchronous-metachronous subgroups (Tables 2 and 4).

While NLR (p=0.001), MLR (p=0.006) and PLR (p=0.013) were found to be significantly higher in bilateral patient; when we divided bilateral patients into subgroups within themselves, no difference was found between synchronous-metachronous subgroups (Tables 2 and 4).

In the median follow-up of 57.5 months for all bilateral and unilateral patients, there was no significant difference in terms of DFS, PFS and OS durations (Figure 1-3). It was observed that PFS and OS durations were significantly shorter in bilateral synchronous tumors compared to bilateral metachronous tumors (Figure 4-6).

Prognostic factors affecting contralateral tumor development in the follow-up of 68 patients with unilateral tumors at the time of diagnosis are shown in Table 5. In multivariate analysis, family history [Odds ratio (OR): 6.556, p=0.035)], presence of TDS (OR: 3.876, p=0.031), impairment in semen parameters (OR: 2.879, p=0.037), history of undescended testis (OR: 2.561, p=0.026), MLO >0.31 (OR: 2.234, p=0.022), presence of testicular microlithiasis (OR: 2.015, p=0.015), and NLR >3.23 (OR: 1.348, p=0.025) were found to be independent variables that increased the risk of contralateral tumor development.

Table 4. Clinical data and oncologic results of patients with bilateral testicular germ cell tumor

Parameters	Synchronous tumors (n=4)	Metachronous tumors (n=6)	Total (n=10)	p-value
Undescended testis (n, %)				
Yes	2 (50.0)	2 (33.3)	4 (40.0)	§0.548
No	2 (50.0)	4 (66.7)	6 (60.0)	
Semen parameter disorders (n, %)				
Yes	2 (50.0)	2 (33.3)	4 (40.0)	§0.548
No	2 (50.0)	4 (66.7)	6 (60.0)	
Hypospadias (n, %)				
Yes	1 (25.0)	1 (16.7)	2 (20.0)	§0.667
No	3 (75.0)	5 (83.3)	8 (80.0)	
Atrophic testis (n, %)				
Yes	1 (25.0)	0 (0.0)	1 (10.0)	§0.400
No	3 (75.0)	6 (100.0)	9 (90.0)	
Testicular microlithiasis (n, %)				
Yes	2 (50.0)	3 (50.0)	5 (50.0)	§0.738
No	2 (50.0)	3 (50.0)	5 (50.0)	
Presence of TDS (n, %)				
Yes	2 (50.0)	3 (50.0)	5 (50.0)	§0.738
No	2 (50.0)	3 (50.0)	5 (50.0)	
Family history of TGCT (n, %)				
Yes	1 (25.0)	3 (50.0)	4 (40.0)	§0.452
No	3 (75.0)	3 (50.0)	6 (60.0)	
Neutrophil/lymphocyte ratio	6.13 (4.90-7.83)	4.66 (3.62-7.45)	5.34 (4.33-7.45)	†0.394
Monocyte/lymphocyte ratio	0.35 (0.33-0.45)	0.40 (0.33-0.54)	0.38 (0.33-0.49)	†0.522
Platelet/lymphocyte ratio	210.17 (170.64-277.13)	189.67 (166.30-248.76)	190.34 (169.05-248.76)	†0.670
Mean platelet volume (fL)	3.84 (2.95-5.59)	4.65 (3.82-8.66)	4.29 (3.63-6.04)	†0.286
Red blood cell distribution width (fL)	14.75 (13.80-15.10)	14.55 (13.32-16.40)	14.75 (13.57-15.37)	†0.670
Follow-up time [median (minimim-maximum), months]	2 (50.0)	0 (0.0)	2 (20.0)	§0.133
Local recurrence rate (n, %)	2 (50.0)	1 (16.7)	3 (30.0)	§0.333
Distant metastasis rate (n, %)	2 (50.0)	1 (16.7)	3 (30.0)	§0.333

*p<0.05 Asterisk (*) indicates statistical significance.
TDS: Testicular dysgenesis syndrome, TGCT: Testicular germ cell tumor
†: Mann-Whitney U test, ‡: Chi-square test, §: Fisher's Exact test

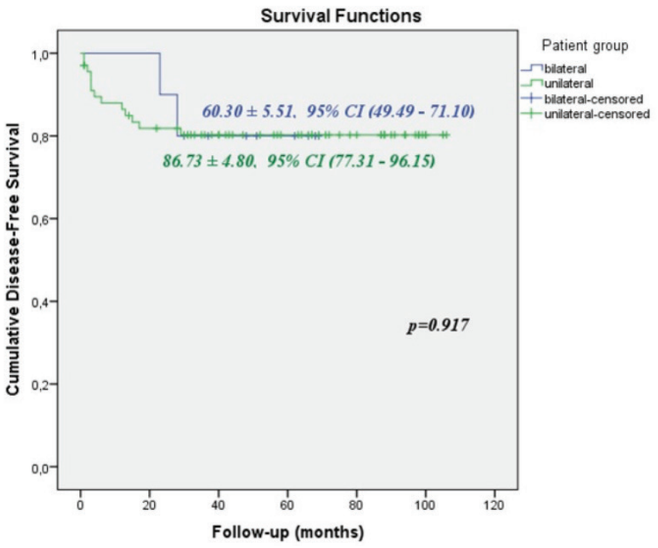

Figure 1. Plot of disease-free survival of bilateral - unilateral testicular germ cell tumors

CI: Confidence interval

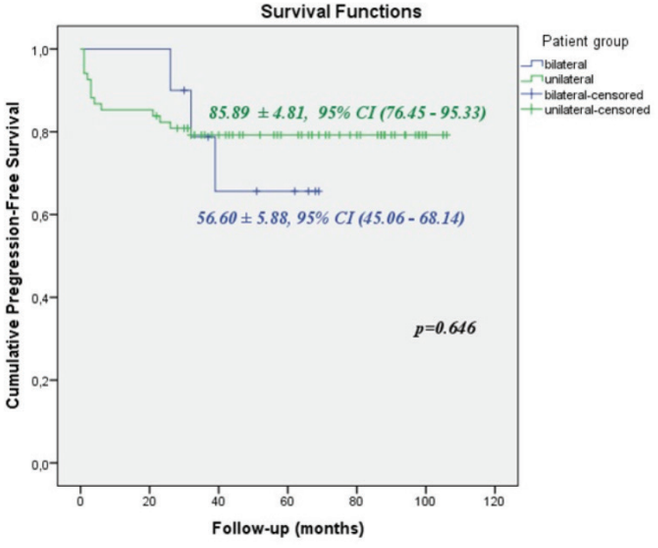

Figure 2. Plot of progression-free survival of bilateral - unilateral testicular germ cell tumors

CI: Confidence interval

Discussion

Since bilateral TGCT was reported for the first time in 1805, patient survival rates and durations have increased thanks to the developments in adjuvant treatment strategies (7). In parallel with the increasing survival durations, a significant increase is observed especially in metachronous tumor development rates (8). Bilateral TGCT is seen at a rate of approximately 2% (0.5-7%) (7). Of those tumors 64.7-88.9% are metachronous and 6.8-35.3% are synchronous tumors (9). Approximately half of metachronous tumors have the same histopathology with the first tumor detected and the most common histological type is

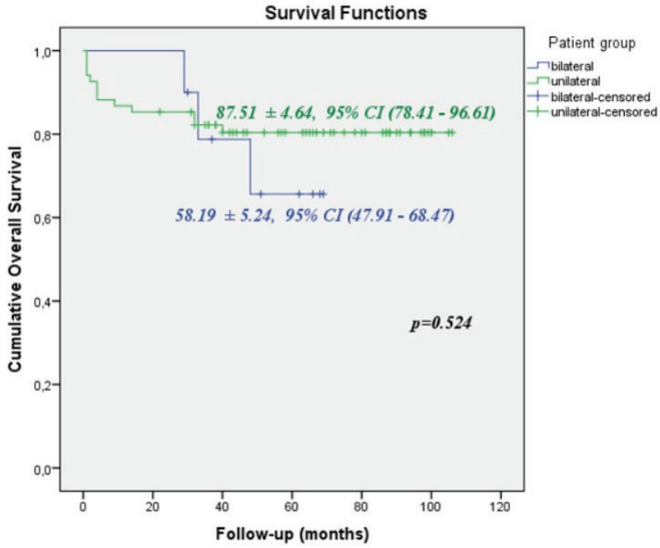

Figure 3. Plot of overall survival of bilateral - unilateral testicular germ cell tumors

CI: Confidence interval

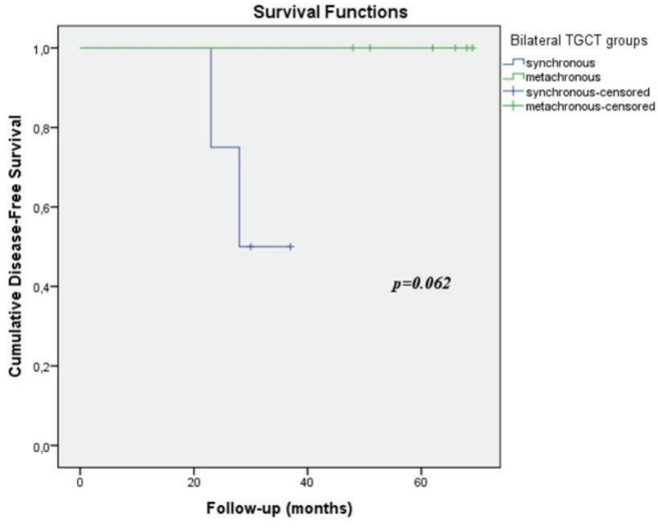

Figure 4. Plot of disease-free survival of bilateral synchronous - metachronous testicular germ cell tumors

CI: Confidence interval, TGCT: Testicular germ cell tumours

seminoma (7). In synchronous tumors, different histopathological types are less common in both testicles and the histology seen in most of them is also seminoma (1). It has been reported that contralateral tumors develop more in patients with seminoma (1.8% vs 0.6%) compared to patients with non-seminomas (10,11). However, in two studies conducted with limited patient data, it was stated that more contralateral tumors could develop in patients with non-seminoma than patients with seminoma (12,13), and tumor histopathology was reported to have no effect on bilateral tumor development in a case series of 6 patients (14).

In our current study, although we had a small number of patients with bilateral TGCT, we found the rate of bilateral tumors to

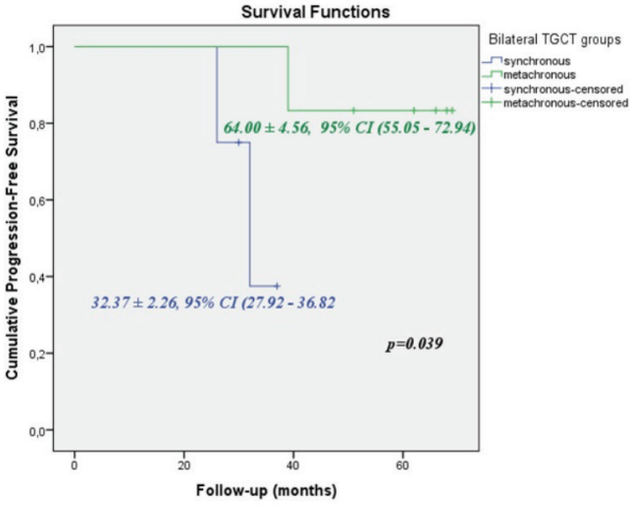

Figure 5. Plot of progression-free survival of bilateral synchronous - metachronous testicular germ cell tumors

CI: Confidence interval, TGCT: Testicular germ cell tumours

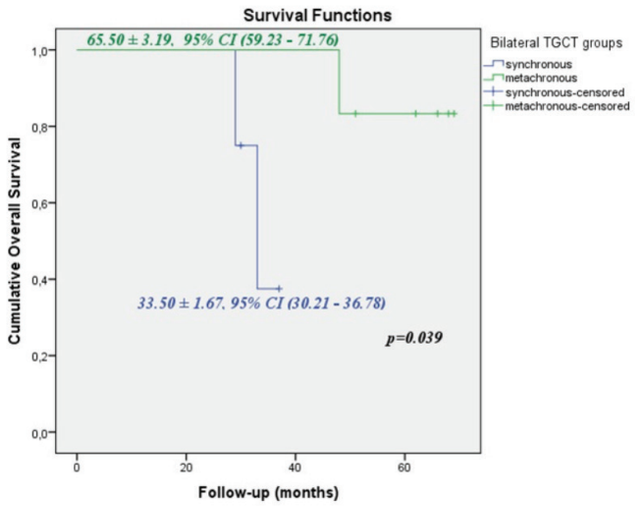

Figure 6. Plot of overall survival of bilateral synchronous - metachronous testicular germ cell tumors

CI: Confidence interval, TGCT: Testicular germ cell tumours

Table 5. Prognostic factors affecting contralateral tumor development in the follow-up of unilateral testicular germ cell tumors

	Univariate Model				Multivariate Model			
	OR	95% Confidence interval		p	OR	95% Confidence interval		p
		Lower	Upper			Lower	Upper	
Age	1.054	0.966	1.152	**0.233**				
Tumor size	1.058	0.823	1.361	**0.659**				
Histopathologic subtype	1.497	0.490	4.578	**0.479**				
Tumor side (Left vs Right)	1.910	0.533	2.381	**0.162**				
AFP	1.001	0.988	1.004	**0.681**				
β-hCG	1.012	0.895	1.058	**0.828**				
LDH	1.014	0.912	1.095	**0.835**				
Tumor stage	1.128	0.440	2.890	**0.801**				
ITGCN (Yes vs No)	2.533	0.434	14.778	**0.032***				
Rete testis invasion (Yes vs No)	1.538	0.167	14.084	**0.704**				
Lymphovascular invasion (Yes vs No)	2.557	0.281	23.255	**0.404**				
Embryonal carcinoma rate >50%	1.798	0.196	16.393	**0.603**				
Proliferation rate >70%	3.400	0.725	7.694	**0.081**				
Undescended testis (Yes vs No)	3.750	0.589	23.867	**0.042***	2.561	1.243	13.456	**0.026***
Semen parameter disorders (Yes vs No)	4.357	0.672	28.240	**0.023***	2.879	1.457	15.457	**0.037***
Hypospadias (Yes vs No)	2.400	0.725	7.694	**0.041***				
Atrophic testis (Yes vs No)	1.001	0.456	1.965	**0.789**				
Testicular microlithiasis (Yes vs No)	3.857	0.701	21.216	**0.021***	2.015	1.127	9.420	**0.015***
Testicular Dysgenesis Syndrome (Yes vs No)	5.182	0.923	29.100	**0.042***	3.876	1.523	10.123	**0.031***
Family history of TGCT (Yes vs. No)	6.556	1.142	37.621	**0.035***	6.556	1.142	37.621	**0.035***
NLR >3.23	1.433	1.002	2.052	**0.041***	1.348	0.859	3.145	**0.025***
MLR >0.31	4.312	2.091	14.177	**0.027***	2.234	1.158	7.815	**0.022***
PLR >150.01	1.101	0.595	2.017	**0.044***				
MPV >5.08	1.084	0.847	1.386	**0.522**				
RDW >13.90	1.282	0.867	1.896	**0.213**				

*p<0.05 Asterisk (*) indicates statistical significance.
AFP: Alpha-fetoprotein, β-hCG: Beta human chorionic gonadotropin, ITGCN: Intratubular germ cell neoplasia
LDH: Lactate dehydrogenase, MLO: Monocyte/lymphocyte ratio, MPV: Mean platelet volume,
NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, RDW: Red blood cell distribution width,
TGCT: Testicular germ cell tumor, OR: Odds ratio

be 11.4%, above the rates reported in the literature, since we were a selected center where oncology patients were referred. Consistent with the literature, 40% of these patients had synchronous and 60% had metachronous tumors. While pure seminoma was present on both sides of all synchronous tumors; in 2 (33.3%) patients with metachronous tumors, contralateral tumor was observed to be seminoma, unlike the first non-seminoma tumor. When we examined a total of 68 patients with unilateral tumors at the time of diagnosis, contrary to most publications reported in the literature and similar to the studies of Osterlind et al. (13) and Colls et al. (12); we found that more contralateral metachronous tumors developed in patients with non-seminoma (10.8% vs 5.4%) than patients with seminoma.

Survival and remission rates in bilateral patients were found to be similar to unilateral patients in some studies (7). When bilateral patients were compared within themselves, it was observed that the clinical stage was higher in synchronous tumors, and the DFS and OS rates were found to be lower (1). It was observed that DFS and OS rates of metachronous tumors decreased when he clinical stage was higher, when the time until the second tumor development was >60 months, and when the histopathology of the first tumor was seminoma (1). Unlike these findings, Holzbeierlein et al. (15) observed that most of the bilateral synchronous and metachronous tumors were at low stage. Klatte et al. (16), on the other hand, reported that, although bilateral synchronous tumors were diagnosed at a higher stage, if an effective treatment was applied, oncologically similar results could be obtained in synchronous and metachronous tumors compared with unilateral tumors. We also observed similar rates among bilateral and unilateral patients and between bilateral synchronous and bilateral metachronous subgroups in terms of local recurrence, distant metastasis and overall mortality rates in our patients. However, we found that the PFS and OS durations were significantly shorter in bilateral synchronous tumors than in bilateral metachronous tumors, and that stage III disease developed more in synchronous tumors (75% vs 33.3%).

According to the common interpretation of most studies in the literature; since seminomas are thought to be less aggressive than non-seminomas, active surveillance is used more frequently than adjuvant therapy in patients with bilateral synchronous seminomas. It has been suggested that this may be the reason for the greater decrease in DFS and OS durations of synchronous seminomas compared to synchronous non-seminomas (1,17,18). A similar decrease in survival rates was observed in patients with metachronous tumors in whom seminoma developed in the contralateral testicle after the first seminoma compared to metachronous tumors with non-seminoma histopathology, and this situation was attributed to the same cause (1). Zequi et al. (1) observed that seminoma developed at a higher rate in patients who developed tumor in the contralateral testis during a follow-up period longer than 60 months. Depending on the above-mentioned interpretation, they stated that the DFS and OS rates decreased in relation to this situation, since more seminomas were seen when the time until the second tumor development was >60 months. As is known in most solid tumors, the prolongation of the time between the onset of the primary lesion and the recurrence or metastasis is a good prognostic indicator. However, metachronous testicular tumors were not metastases, and according to Zequi et al.'s argument (1), the prolongation of the time until the detection of metachronous tumors increased the likelihood of development of seminoma and, on the contrary, it was found to be associated with a poor prognosis. Nevertheless, there is no accepted clear consensus to explain this situation and both the findings of Holzbeierlein et al. (15) and Klatte et al. (16) and our findings do not support the mentioned relationship.

It was found that the frequency of metachronous tumor development was lower in patients who underwent adjuvant CT. In addition, it was observed that more seminoma was observed in metachronous tumors developing in patients who underwent CT compared to metachronous tumors developing in the follow-up of patients who did not undergo CT, regardless of the initial tumor histology (1). Although there were publications predicting that adjuvant CT would reduce the risk of contralateral tumor development (16,19), there were also studies in which this relationship was not observed (1,20). We realized that adjuvant radiotherapy (RT) was applied to patients who were diagnosed as having stage I seminoma and were treated between 2010 and 2013 in our study, as part of the treatment protocol of that period. However, adjuvant RT has been replaced by single-dose carboplatine in the treatment of these patients in the EAU guidelines since 2014 (3). Of our 68 patients with unilateral tumors at the time of diagnosis, contralateral tumors were observed in 20% of those who were under active follow-up because they had stage I disease and did not have a risk factor for occult metastasis development, while the rate of contralateral tumor development after adjuvant CT or RT was lower (6.25%). In our 2 patients who developed contralateral tumors after active follow-up, we observed that the rate of development of seminoma was higher, consistent with the findings of Zequi et al. (1).

While the incidence of TGCT development is 0.005% in the general population, the rate of tumor development in the contralateral testicle in individuals with a history of TGCT is up to 5% (1). Despite this increased risk, it was observed that the tumor detected in the contralateral testis in patients with metachronous tumors was mostly (95.2%) stage I tumor and the developing second tumor was smaller than the first tumor (10,11). Therefore, it has been emphasized that self-examination and early diagnosis are important in patients with a history of TGCT (10). The time until the second tumor development has been reported as a median of 39-47 months (4 months-32 years) in different studies (1,7,16,17). Among our 68 patients with unilateral tumors at the time of diagnosis, contralateral tumors were detected in 8.1% of them during a follow-up of a median 57.5 months, and a second tumor emerged within 5 years, after the first tumor was detected in all metachronous tumors. But we did not observe a significant difference in the size of the second tumors in our patients.

ITGCN is defined as a precursor lesion in the development of TGCT (1). There are still controversies about the application of biopsy to confirm the presence of ITGCN in the contralateral testis during orchiectomy, since the incidence of ITGCN and tumor development in the contralateral testis is low, the developing metachronous tumors are mostly at low stage, and side effects such as infertility and testosterone production

disorders due to local RT to be applied in case of detection of ITGCN, can be observed (16,21). However, it is known that the risk of developing ITGCN in the contralateral testis is >35% in patients with unilateral tumors under the age of 40 with testicular volumes of <12 mL (22). Therefore, contralateral testis biopsy is recommended during orchiectomy in patients under 40 years of age with risk factors for the development of TGCT (testicular volume <12 mL, history of undescended testis or impaired spermatogenesis) (3). In our study, ITGCN was detected in 34 of 68 patients who had unilateral tumors at the time of diagnosis, and 15 of these 68 patients (20.2%) who had the above risk factors did not undergo contralateral testicular biopsy, because none of them accepted it. We observed that 4 (26.6%) of 15 patients with risk factors developed contralateral metachronous tumors. Of these 4 patients, 2 (50%) had a history of undescended testis, 2 (50%) had abnormal semen parameters, while all were under the age of 40, but none of them had atrophic testis. Since our findings are consistent with the data in the literature, we continue to present testicular biopsy as a recommendation to patients with these risks in our clinical practice.

Although the gold standard approach is bilateral orchiectomy in cases of bilateral TGCT, the most important problems related to this are infertility, the need for lifelong androgen maintenance, and the psychological effects observed due to the young age of the patients (7,10). Therefore, if preoperative serum testosterone levels are normal in small-sized (<2 cm in size or tumor volume is less than 30% of testicular volume) synchronous bilateral and metachronous contralateral tumors, testis-sparing surgery (partial orchiectomy) can be used as an alternative approach (3). However, if ITGCN is detected histologically in the remaining testicular tissue, it is recommended to give adjuvant RT to the testis on that side (3). Therefore, patients who want to have children should be given detailed information about this situation. Partial orchiectomy was not performed in any patient among 10 patients with bilateral tumors in our study considering that there would not be enough testicular parenchyma to be preserved, because tumor size was not less than 2 cm or the estimated tumor volume/testicular volume ratio was not less than 30%.

Individuals with a family history are at higher risk for developing TGCT, and the rate of bilateral tumor development is higher in these individuals compared to sporadic patients (10). In our patients with bilateral tumors, family history was significantly higher than in patients with unilateral tumors (40% vs 13.2%). When bilateral tumors were examined within themselves, we found that although no significant difference was found between synchronous and metachronous tumors in terms of family history, family history was the risk factor that increased tumor development 6.5 times in the contralateral testicle.

Recently, the effects of inflammation markers and hemogram parameters on oncological outcomes have been more popularly investigated, and it has been reported that high NLR and platelet levels in TGCT may cause development of metastasis and a decrease in disease-specific survival (23,24). When we examined the effects of serum hemogram parameters on our patients, it was found that NLR, MLR, PLR values at the time of diagnosis were higher in bilateral tumors compared to unilateral tumors. We found that high NLR (>3.23) and MLR (>0.31) values increased the risk of contralateral TGCT by 1.3 and 2.2 times, respectively.

The effects of molecular and genetic risk factors on the development of TGCT have not been fully elucidated yet. Recently, there are publications defending that c-kit mutations are more common in bilateral patients than unilateral patients (25), and also opposite results have been encountered (26,27). Although no genetic and biomolecular markers were examined in our study, we observed that the development of TGCT in the contralateral testis significantly increased in the presence of family history, testicular microlithiasis, undescended testis with increased NLR, MLR, TDS and TDS components, and impairment in semen parameters. Although it is known that metachronous contralateral TGCT develops within the first five years in 60% of the patients, it has been reported in the literature that metachronous contralateral TGCT may develop even after 32 years and long-term follow-up is required in all patients, especially in individuals with the risk factors mentioned above (16).

Study Limitations

The retrospective design of our study, the limited power of the statistical analysis performed due to the small number of patients, lack of randomization while determining the groups, short follow-up periods, and the fact that the follow-up results belonging to a single center, were the main limiting factors. In addition, since our hospital was a center where oncology patients were referred, the patients we included in the study mostly represented a selected group with advanced stage disease. For this reason, bilateral TGCT detection, recurrence, progression and death rates in our study were higher than the rates reported in the literature. We think that these rates may not reflect the real population incidence.

Conclusion

According to our findings, although bilateral synchronous tumors were detected at a more advanced stage at the time of diagnosis, we showed that the survival rates of bilateral tumors were similar to unilateral tumors thanks to appropriate treatments, although a significant decrease in PFS and OS times was observed. Nevertheless, we observed that patients with unilateral tumors at the time of diagnosis increased the risk of development of contralateral tumors in cases of family history, TDS, impaired semen parameters, undescended testicular history, presence of testicular microlithiasis, NLR >3.23 and MLR >0.31. If patients with a history of TGCT carry these risk factors, it is important to follow-up the contralateral testis regularly, as the possibility of development of bilateral metachronous tumors in long-term follow-up increases.

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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.

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Authorship Contributions

Surgical and Medical Practise: A.İ.A., M.S.B., H.B., Concept: A.İ.A., M.S.B., Design: İ.S., H.B., Data Collection or Processing: İ.S., Analysis or Interpretation: İ.S., A.İ.A., Literature Search: İ.S., Writing: İ.S.

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Case Report

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Acute Ischemic Stroke Following Chemotherapy for Malignant Mixed Testicular Germ Cell Tumour: Does Cisplatin Play a Role?

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Abstract

Among males aged between 15 and 35 years, testicular cancer is the most commonly diagnosed cancer. Testicular germ cell tumours are generally considered curable and respond dramatically to adjuvant treatment. Cisplatin-based chemotherapy regimens are used ubiquitously, inevitably leading to iatrogenic morbidity. Herein, we represent a case of a patient diagnosed with a non-seminomatous germ cell tumour, who underwent adjuvant cisplatin-based chemotherapy treatment and subsequently developed an acute ischemic stroke. In cancer patients, a malignancy-induced hypercoagulability state can cause thromboembolic events. Nonetheless, anti-cancer therapy may dramatically increase the risk of thromboembolic events, by analogue mechanisms, such as the release of pro-coagulant mediators, direct endothelial injury or stimulation of tissue factor production by host cells. Among various chemotherapy agents correlated with thromboembolism, cisplatin is expected to carry a higher risk for thromboembolic complications. Acute cerebrovascular events secondary to anti-neoplastic agents require an interdisciplinary approach, including referral to more experienced centres when needed.

Keywords: Germ cell testicular cancer, chemotherapy, cisplatin, stroke, thromboembolism

Introduction

Testicular cancer accounts for only 1%-2% of male cancers. However, is the most commonly diagnosed cancer in young males aged between 15 and 35 (1). Testicular germ cell tumours are considered to be one of the most curable cancers (2). The wide use of cisplatin-based chemotherapy regimens is correlated with improved outcomes. In contrast, therapy-related morbidity remains a serious concern (3). While adverse effects such as nephrotoxicity, peripheral neuropathy, ototoxicity or pulmonary toxicity are routinely considered, vascular toxicity seems to receive less frequent attention yet remains a confronting challenge. A recent study suggests that early vascular endothelial changes in patients who underwent cisplatin-based chemotherapy may contribute to long-term cardiovascular morbidity in survivors (4). Herein, we present a case of a patient diagnosed with non-seminomatous germ cell tumour (NSGCT), who underwent adjuvant cisplatin-based chemotherapy treatment and subsequently developed an acute ischemic stroke. We present the management of this adverse effect and discuss the possible causes of this situation. We suggest that his cisplatin-based chemotherapy regimen played a role in this case.

Case Presentation

A 34-year-old male; without significant medical history or previous cardiovascular events, presented with a right-sided testicular mass. Testicular ultrasound showed a 90×65×55 mm solid mass in the right testicle. The patient's tumour markers were as follows: β-human chorionic gonadotropin (β-hCG) of 37.42 mIU/mL, α-fetoprotein (AFP) of 17.5 ng/mL and lactic dehydrogenase (LDH) of 275 U/L. Radical inguinal orchiectomy was performed, and the pathologist reported a malignant mixed germ cell tumour, composed of seminoma (90%), yolk sac tumour (5%) and teratoma (5%). The pathological staging was determined as pT2. A computed tomography (CT) of the abdomen and thorax showed no signs of metastasis.

A single cycle of bleomycin-etoposide-cisplatin (BEP) chemotherapy protocol was initiated three weeks after the surgery. Tumour markers at the beginning of the chemotherapy were regressed to 1.2 mIU/mL (β-hCG), 2.46 ng/mL (AFP) and

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168 U/L (LDH). The patient received his chemotherapy and was discharged without any problem. Four days following his discharge, he developed fever, left-sided paralysis of the upper and lower extremities, and difficulty speaking. He also suffered from malaise and fatigue. He was admitted to the emergency department, and a cranial CT scan showed no signs of acute lesions. His neurological examination (NE) upon admission showed mild motor weakness in his upper (4/5) and lower (4/5) extremities, with no sensory deficit, and an apparent loss of the left nasolabial fold. He had no aphasia, and the NE was otherwise healthy. He was admitted to the urology ward. A cranial magnetic resonance imaging (MRI) was performed, along with a biochemical examination of his blood and a complete blood count. The MRI showed sub-acute infarction areas in the right middle cerebral artery shed area (Figure 1). Later, CT angiography of the head and neck was performed, which revealed a floating thrombus in the right internal carotid artery (ICA) (Figure 2). Neither open surgical nor minimal-invasive intervention was advised. Anti-coagulant treatment with 4000 IU of low molecular weight heparin (LMWH) every 12 h was ordered instead.

Several tests were done to decipher the factor underlying the arterial thrombotic event seen in this patient. An electrocardiogram at admission revealed a normal sinus rhythm. In contrast, trans-thoracic echocardiography and a 24-h Holter monitoring showed no signs of arrhythmia, patent foramen ovale or an intracardiac thrombus, excluding a cardiac cause. His HbA1c value was 5.8%. A lipid profile showed no dyslipidaemia symptoms; low-density lipoprotein of 122 mg/dL, high-density lipoprotein of 36 mg/dL and a total cholesterol level of 175 mg/dL. Anti-nuclear antibodies and lupus anti-coagulant tests, which were ordered to rule out the rheumatological disorders that could contribute to the patient's condition, were within healthy limits. C1 esterase inhibitor and C3 complement levels were normal, ruling out a disorder of the complement system. Gene mutations in factor V Leiden, prothrombin, C677T and A1298C polymorphisms of methylenetetrahydrofolate reductase (MTHFR), and 4G/5G polymorphism of the plasminogen activator inhibitor type 1 *(PAI-1)* gene were assessed by real-time polymerase chain reaction. Heterozygote mutations in prothrombin and MTHFR C677T and a homozygote 4G/4G polymorphism of PAI-1 were determined. Protein C and Protein S deficiencies are other important causes of inherited thrombophilia cases. However, tests revealed that the activities of Protein C and Protein S were normal. His homocysteine level was found to be moderately elevated (21.2 µmol/L). His folic acid level was healthy, although his B12 level was low; therefore, he was administered intramuscular (IM) vitamin B12 injections. Von Willebrand factor antigen level was measured and was found to be elevated to 199.5%. The serum magnesium level was within healthy limits.

The patient was prescribed with 4000 IU of LMWH every 12 h, 40 mg atorvastatin every 12 h and a vitamin B12 supplementation regimen with IM injections were initiated. Physical therapy was also advised, which he received regularly. He was encouraged to quit smoking.

One month after his initial presentation, he was seen for a follow-up examination. His NE showed only mild paraesthesia of the left foot, with no other symptoms persisting.

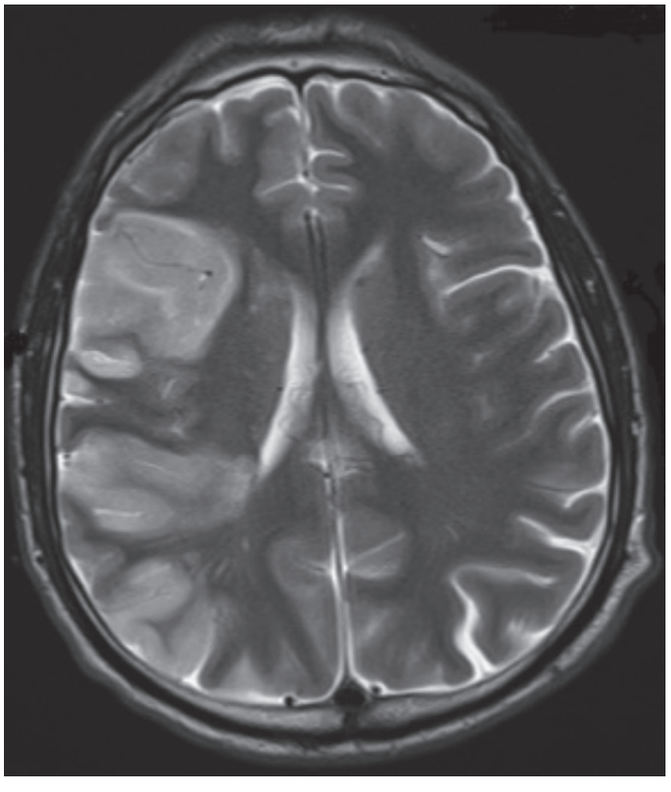

Figure 1. Magnetic resonance image of sub-acute infarction in the right middle cerebral artery shed area

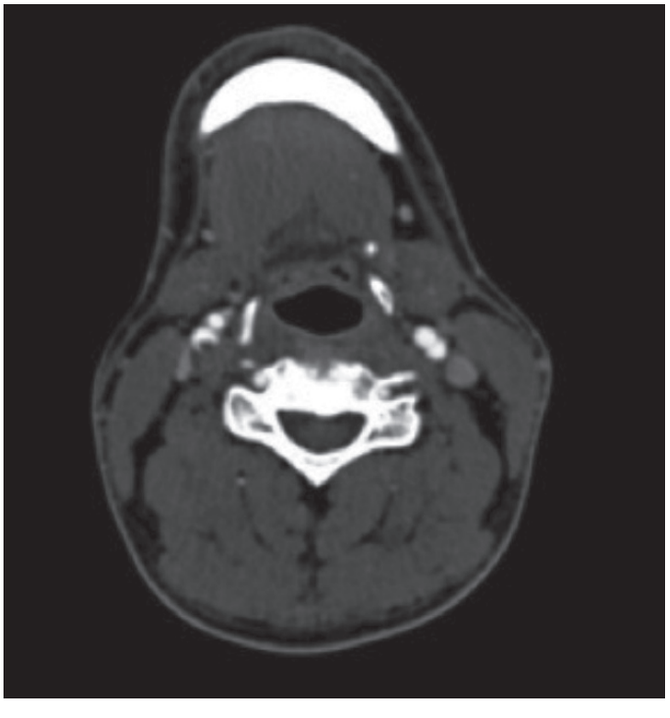

Figure 2. Computed tomography showing floating thrombus in the right internal carotid artery

Discussion

Our patient was diagnosed with Stage IA disease, according to the tumor node metastasis classification (5). Treatment options for Stage IA NSGCT following orchiectomy include retroperitoneal lymph node dissection (RPLND), intensive follow-up with frequent CT scans, or one course of BEP for individuals who are considered at high risk of relapse (6). RPLND was not offered to the patient because of procedure-related morbidity and possible ejaculatory dysfunction. Due to socio-economic reasons, our patient was found non-suitable for an intensive follow-up program. Hence, considering the absence of lymphovascular involvement and histologic type of the tumour, he was offered one cycle of BEP treatment.

In cancer patients, a malignancy-induced hypercoagulability state can cause thromboembolic events (7). Nonetheless, anti-cancer therapy may dramatically increase the risk of thromboembolic events by analogue mechanisms, such as the release of pro-coagulant mediators, direct endothelial injury or stimulation of tissue factor production by host cells (7). Among various chemotherapy agents that are correlated with thromboembolism, cisplatin is expected to carry a higher risk for thromboembolic complications (8). It is associated with a greater likelihood of venous thromboembolic events in daily practice. Acute arterial thromboembolic complications due to cisplatin-based chemotherapy are rare when compared with venous events (9).

Several tests and examinations were conducted to explain the pathogenesis of the ischemic stroke in our case. The patient had a history of smoking 11 cigarette packs/year. His history was negative for cerebrovascular disease and common conditions, such as diabetes mellitus or hypertension. The patient's smoking history and hyperhomocysteinemia may have made him susceptible to vascular events (10). In addition to this, the MTHFR (677) gene mutation present in our patient, can be a predisposing factor for thrombosis (11,12).

Nonetheless, considering the patient's age and his rapid onset of stroke a few days after chemotherapy makes cisplatin a plausible cause. Following the vascular, metabolic and cardiac evaluation, we suggest that cisplatin-based chemotherapy was a significant etiological factor for stroke in our patient. There are case reports and a few literature reviews that indicate cisplatin-induced vascular toxicity (13). The exact pathophysiological mechanism of acute injury of cisplatin remains uncertain. Cytotoxic agents, such as cisplatin, can affect coagulation protease levels and may directly injure the endothelium (14). Owing to hypomagnesemia, cisplatin seems to be associated with serious vascular complications involving increased thrombogenicity and vascular spasm (15). Also, cisplatin has been identified as causing cardiac arrhythmias, owing to both direct drug-induced myocardial toxicity and alterations in electrolyte balance (4).

In our case, the von Willebrand factor antigen level was found to be elevated to 199.5%. Previous studies also reported elevated von Willebrand factor antigen levels in patients receiving cisplatin-based chemotherapy (4). The clinical value of this finding for patients, before the administration of chemotherapy, remains unclear. High levels of von Willebrand factor antigen may have impacted on the patient's clinical condition.

Cisplatin-induced hypomagnesemia is also blamed for fatal cardiac arrhythmias (15). For this reason, the serum magnesium level of the patient was assessed but was observed to be within healthy limits.

There are multiple pathways proposed linking cisplatin therapy to vascular toxicity and thromboembolic events. It is hard to predict which patients will experience this adverse effect. Patients with known risk factors such as smoking history, older age, history of thromboembolic events and known medical conditions predisposing to thromboembolism may be under higher risk of vascular toxicity and should be monitored carefully after therapy. Prophylactic anti-thrombotic agents have been utilised in several solid cancers and showed a decrease in vascular complications (16). However, we believe that further studies are needed to justify this approach. If possible, scoring systems should be developed to risk-stratify patients and determine which patients will benefit from prophylactic anti-coagulation.

Testicular cancer cure rates are high, owing to cisplatin-based chemotherapy. Cisplatin remains an indisputable choice for oncologists and urologists worldwide. However, clinicians should be aware of less common adverse effects. When unrecognised, these side effects may result in dramatic outcomes. The decision about chemotherapy should be based on individual needs, with consideration of treatment-related risks. Acute cerebrovascular events secondary to anti-neoplastic agents require an interdisciplinary approach, including referral to more experienced centres when needed. Early cerebrovascular monitoring is of vital importance. We emphasise the correlation between the time of onset of neurological symptoms and the beginning of the thrombolytic treatment, as there is a chance of complete recovery of neurological deficits. The need and rationale for routinely screening for hypercoagulability conditions before cisplatin therapy remains unclear. Prophylactic anti-coagulant therapy should be kept in mind in high-risk patients. The pros and cons of the continuation of chemotherapy or a chemotherapy regimen change should be considered for patients who develop thrombosis.

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Authorship Contributions

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

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Video Article

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Key Steps in Robotic Simple Prostatectomy for Benign Prostatic Hyperplasia

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Abstract

Open prostatectomy is still an option for the surgical treatment of benign prostate hyperplasia (BPH). In this video, key steps in robotic simple prostatectomy are summarised. Robotic surgery provides a reasonable alternative for BPH management when open surgery is indicated.
Keywords: Benign prostatic hyperplasia, robotic surgery, robotic assisted laparoscopic prostatectomy

Under general anaesthesia, urethral catheter and orogastric tube are inserted to keep the bladder and stomach empty before accessing the abdomen. Five or six port technique can be used for robotic assisted laparoscopic simple prostatectomy. After access and port placement in the supine position, docking of the robot between the legs is done in the Trendelenburg position. The monopolar scissors is positioned on the right hand and the prograsp and fenestrated bipolar forceps are on the left.

The bladder is dropped starting from lateral to the medial umblical ligaments down to the level of vasa deferens using a blunt and sharp dissection, and the space of retzius is developed. Removal of the periprostatic and perivesical fat provided a clean surgical field.

Access to the prostatic adenoma can be achieved transvesically or by direct incision to the prostatic pseudocapsule. As shown in this video, a vertical cystotomy can be used, which can be extended to the proximal 1-2 cm of the prostate when necessary. Vertical cystotomy provides a good exposure to the trigone and ureteric orifices and facilitates bladder stone removal.

Using a monopolar scissors, mucosal incision was made at 6-position of the bladder neck. A stay suture is placed on the median lobe and held up by fourth arm for upper traction to achieve a better exposure. Dissection plane between adenoma and surgical capsule is developed. Care is taken not do dissect too deep in the posterior plane to avoid capsular laceration. Dissection plane is also developed circumferentially to the anterior commissure and proceeds distally toward the apex. The fourth arm is very helpful for traction and exposure during dissection. "The apical shoulders" is an important landmark for distal limit of dissection and approaching the urethral sphincter. Thermal energy should be kept at minimum and avoided at the apex and urethra. Adenoma is divided proximal to the urethral sphincter, freed and removed and put in a specimen bag. Urethral Foley catheter acts as a guide for better identification of the urethra at this level. Prostatic fossa should be inspected carefully for bleeders and remaining small adenoma tissues that be cleaned. Haemostatic sutures are placed at 5- and 7-position to control the main arteries.

Trigonization is a key step of the operation. Mucosal edges of the bladder trigone and the urethra are approximated with 3/0 absorbable barbed suture. Occasionally the gap between two edges may be too long to establish a tension-free approximation. Three rows of sutures through the posterior surgical capsule between the bladder neck and urethral edge will fascilitate a tension-free reconstruction.

Cystotomy incision is closed using 2/0 or 3/0 barbed suture in continuous full-thickness sutures. Seromuscular Lembert sutures are also used as a second layer. The bladder is filled with 100 cc saline to confirm water-tight closure. A 22 Fr 3-way Foley catheter is inserted with the balloon filled with 35 cc and kept in continuous irrigation for the first 24 hours. A pelvic drain is placed and removed usually on the first postoperative day.

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