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

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

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

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

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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.

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

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

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.

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

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

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

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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]).

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

-Conclusions

-References

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

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

-Tables and figures should be uploaded separately.

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

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

D. Literature Review

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

E. Editorial Commentary

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

F. Letters to the Editor

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

G. Surgery Videos on Urooncology (Video-urooncology)

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

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

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

Video-urooncology submission should include:

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

2) Title Page

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

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

6) "Acknowledgements From" should be uploaded separately.

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

6. Manuscript Preparation

Manuscripts should be prepared following sequence according to article type:

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

B. Title Page

The title page should include the following:

-Full title

-Running title

-Authors' names and institutions

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

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

C. Main Text (without authors' credentials)

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

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

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

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

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

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

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

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

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

Examples for writing references:

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

Example:

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

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

Example:

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

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

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

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

D. Tables and Figures

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

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

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

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

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

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

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

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

Submissions must include according to the following sequence:

A-Original Article

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

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

4) Table(s)

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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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Squamous Cell Carcinoma of Bladder

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Abstract

Squamous cell carcinoma (SCC) of the bladder is a malignant neoplasm of a pure squamous phenotype originating from the bladder urothelium. SCC of the bladder is a relatively rare tumor with no specific diagnostic test. The diagnosis is usually made at an advanced stage; therefore, the prognosis is poor and most cases result in mortality. Inflammation and infection leading to the metaplasia of epithelial cells are implicated in its etiology. SCC of the bladder is divided into two groups depending on whether it is due to bilharzial infections, and these two groups have different epidemiological, pathogenetic and clinicopathological features. SCC of the bladder accounts for the vast majority (approximately 75%) of bladder cancers in areas where Schistosoma haematobium infection is endemic. The European Association of Urology guidelines classify bladder cancer with any variant histology as high-risk bladder cancer. Because of the rarity and heterogeneity of non-urothelial tumors, treatments described are mostly based on retrospective series and small studies. Radical cystectomy is recommended as the first treatment in patients presenting with non-metastatic bladder SCC. Neoadjuvant radiation therapy (RT) is considered to play a role in schistosomal bladder cancer. However, there are not enough high-quality studies to indicate the role of RT or chemotherapy as adjuvant therapy. Due to the rarity of the disease, there are also no high-evidence guidelines for managing SCC. There is a need for further high-volume and prospective studies to review literature data and developments.

Keywords: Bladder tumor, squamous cell carcinoma, urothelial carcinoma

Introduction

In both men and women he most common genitourinary malignancy is bladder cancer. It is broadly classified as urothelial (98%) and non-urothelial (2%) (1). Although the pathogenesis of non-urothelial bladder cancer has not yet been fully elucidated, the main cause is deemed inflammation and infection leading to the metaplasia of epithelial cells. It constitutes less than 5% of all bladder tumors (1). Approximately 90% of non-urothelial bladder cancers are of epithelial origin, and epithelium-derived bladder cancer cases include small-cell carcinoma (1%), adenocarcinoma (2%) and squamous cell carcinoma (SCC) (3%) (2). Non-epithelial tumors include sarcoma, carcinosarcoma, paraganglioma, melanoma, and lymphoma (1).

Patients with non-urothelial bladder cancer typically present with painless hematuria (macroscopic or microscopic) to urothelial carcinoma, but irritative voiding symptoms (dysuria frequency and urgency) may also be the first sign (3). It has been reported that up to 93% of patients have a urinary tract infection (UTI) at the time of diagnosis (4). This may support the fact that non-urothelial bladder cancer develops in response to chronic infection. In all patients with suspected bladder neoplasms, cystoscopy is the gold standard diagnostic evaluation, and cystoscopic biopsy usually provides tissue for a definitive diagnosis.

Non-urothelial tumors are considered more likely to have invaded muscles at the time of diagnosis than urothelial cancers. Surgical pathological staging is usually an advanced stage at the time of diagnosis. Therefore, bladder cancer with variant histology is reported to have a worse prognosis and survival than the urothelial carcinoma of the bladder, which can be detected at a later stage (5,6,7,8,9). Most patients die within three years, and the five-year survival rate is 33-48% (10).

Pathological Characteristics

The pathogenesis of non-urothelial bladder cancer has not yet been fully elucidated. Both metaplasia and chronic infection are thought to play important roles in tumorigenesis. Another hypothesis includes the formation of non-urothelial bladder cancer from tumor-exposed and pre-developed urothelial carcinomas (transitional cell carcinomas) and metaplasia from multipotent stem cells in the bladder (11).

Non-urothelial bladder cancer develops in response to chronic infection and inflammation, which can lead to the development of tissue metaplasia, leukoplakia and squamous epithelium, or mucinous and glandular epithelium; however, factors leading to neoplastic transformation are unknown. SCC is often affiliated with squamous metaplasia and can be seen in 16-28% of patients with leukoplakia (12). Keratinized squamous metaplasia

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has been identified in most SCC cases, but it can also present as a normal histological variation in female patients. There is insufficient evidence concerning squamous metaplasia being a premalignant finding, and aggressive surgical treatment is not recommended (12,13,14).

Chronic UTIs are associated with both non-schistosomal and schistosomal bladder cancers. Infection may contribute to bladder cancer through multiple mechanisms. Predisposition to metaplasia constitutes the first step for carcinogenesis. Nitrosamines, which are the metabolites of Gram-negative bacteria, such as *Proteus mirabilis* and *Escherichia coli*, are highly carcinogenic for the bladder. Carcinogenesis occurs through DNA appendage formation and possibly other mechanisms. Reactive oxygen species produced by inflammatory cells responding to infection lead to DNA damage and activate other carcinogens (15,16,17,18,19,20).

SCC of the bladder originates from the urothelium and is characterized by a pure squamous cell phenotype. Concerning pathological findings, most SCCs are necrotic, bulky, polypoid, solid masses that fill the bladder lumen. The presence of necrotic material and keratin residues on the surface is typical. It usually involves the trigone region of the bladder, but it can occur in any region of the bladder, including the diverticula, as well as being locally observed in the ureter or urethra (21).

SCC is uncommonly non-muscle invasive, with early-stage (Ta and T1) tumors being rarely reported. In a case series of patients with SCC, T3 lesions (perivesical fat invasion) accounted for 60% of all cases, while only 2% were T1 (14). In the population-based Surveillance, Epidemiology, and End Results (SEER) program, which included 614 patients with SCC, 42.3% of the patients had T3 cancer and 42.5% had a high histological grade (22). In contrast, bilharzial SCCs are mostly well-differentiated tumors, although they are at advanced stages (23). SCC tumors also tend to show low rates of lymphovascular invasion (LVI) and lymph node (LN) metastases (24).

SCC of the bladder is morphologically indistinguishable from that of other regions. The invasive component may show good differentiation with keratinized squamous cell islands, minimal nuclear pleomorphism and prominent intercellular bridges. Poorly differentiated tumors are characterized by marked only focal squamous differentiation and nuclear pleomorphism. The presence of keratinized squamous metaplasia in the adjacent flat epithelium supports the presence of SCC (25).

Epidemiology and Risk Factors

SCC of the bladder is divided into two groups depending on whether it is due to bilharzial infections, and these two groups have different epidemiological, pathogenetic and clinicopathological features (21). SCC of the bladder accounts for the vast majority (approximately 75%) of bladder cancers in areas where Schistosoma haematobium infection is endemic, and it is usually diagnosed in the fifth decade of life in East Africa and the Middle East, where the disease is endemic. The incidence of bilharzial SCC due to the chronic Schistosoma haematobium infection has been reported as 58.8-80.7% in North African countries (26). Non-bilharzial SCC usually occurs in the seventh decade of life and constitutes 3 to 5% of bladder cancers in Europe and North America (4). The male/female ratio has been reported as 4-5:1 for the incidence of bilharzial SCC and 1.3-1.8:1 for that of non-bilharzial SCC (27).

In addition to the schistosomal infection, chronic or recurrent UTIs, previous intravesical Bacillus Calmette-Guerin therapy, pelvic radiation therapy (RT), bladder stones, and prolonged exposure to cyclophosphamide, especially when complicated by hemorrhagic cystitis, have been shown to be among the reported risk factors associated with the development of SCC (1,28,29,30).

In 1989, Brenner et al. (31) described a patient with the previously documented urothelial squamous dysplasia in whom an invasive SCC of the bladder without any transitional cell carcinomatous elements developed one and one-half years after successful eradication of carcinoma *in situ* with intravesical BCG. They drew particular attention to the need for careful evaluation before initiating BCG therapy in a patient with known squamous metaplasia dysplasia or other factors known to predispose to SCC of the bladder (31).

It has been reported that tobacco consumption is an important risk factor for bladder cancer in both SCC and urothelial carcinoma. (23). Although the risk of SCC has also been associated with smoking (32,33), an observational study with a long-term follow-up observed that the incidence of pure SCC was higher in females and had a lower rate of smoking history compared to those with urothelial carcinoma (34).

Several studies have reported that chronic indwelling catheters are associated with an increased risk of SCC, although this relationship remains controversial. Older studies indicate that the incidence of SCC is 10% in patients with indwelling catheters for over 10 years, and the risk of SCC increases 16 to 28 times in patients with paraplegia (35,36). A large study of 43,561 patients with spinal cord injuries (SCI) from Central Europe found no significant difference in bladder cancer risk between these patients and the general population. In this study, bladder cancer developed in 48 patients (0.11%). The data of 8 female and 29 male patients were complete and the mean age of the patients was 53.3 years. As bladder management, reflex voiding was used in 18 patients, intermittent catheterization in 12 patients, and indwelling catheters in 7 patients. They were suggested that the link to bladder cancer was primarily related to indwelling catheters, UTIs, and exposure to carcinogens (37). In another study conducted on 1334 patients with SCI, the age-standardized incidence of invasive bladder cancer was not statistically different from the general population. Also in this study, half of the patients were treated with a chronic indwelling urethral or suprapubic catheter, whereas 35% used intermittent self-catheterization and 15% used one of the alternative voiding methods: abdominal straining, reflex voiding, or urinary diversion (38). The planning of these investigations and the rates of SCC and adenocarcinoma in these individuals may have prevented statistically significant results. However, the incidence of muscle invasion was found to be high in individuals with neurogenic bladder, and researchers suggested that intermittent catheterization should be preferred instead of indwelling catheters in this patient group. Although periodic screening cystoscopy for individuals with spinal cord injury have been

recommended by some authors, no studies have demonstrated the advantage of screening, possibly because the incidence of cancer in these individuals is extremely low (38,39).

Most studies suggest that the human papillomavirus, which is associated with genitourinary cancer, plays a very limited and controversial role in the pathogenesis of the disease (25,26,40). There are publications reporting that there is usually a squamous differentiation in HPV-influenced bladder carcinomas. It has been reported that the virus may exhibit oncogenic activity in the bladder in cases such as persistent condylomatous infection (41). It has also been reported that bladder SCC developing from patients with persistent condylomas develop on the basis of a condyloma (42). It can also be considered that the presence of persistent chronic infection is an important factor in tumorigenesis.

Clinical Course and Treatment

The European Association of Urology guidelines classify bladder cancer with any variant histology as high-risk bladder cancer (43,44). However, the National Comprehensive Cancer Network guidelines provide more specific information depending on the presence of SCC, adenocarcinoma, and neuroendocrine carcinoma (45). Due to the rarity and heterogeneity of non-urothelial tumors, most described treatments are based on the results of retrospective series and small studies.

Radical cystectomy is recommended as the first treatment in patients presenting with non-metastatic bladder SCC (20). For patients with SCC, schistosomal bladder cancer (regardless of histology), or adenocarcinoma, this treatment is recommended to include LN dissection with radical cystectomy (14,46). However, no guidelines offer specific recommendations concerning potential early cystectomy in stage T1 SCC because to the lack of evidence. It has been observed that radical cystectomy increases cancer-specific survival in patients with stage T1 SCC and neuroendocrine carcinoma (43,14).

Observational and retrospective data support surgical treatment. The analysis of the SEER database including the data of 1,422 patients received between 1988 and 2003 showed that the two-year all-cause mortality rate following cystectomy ranged from 11% (in men with stage I disease) to 72% (in men with stage IV disease) (30). After the data were adjusted for age, sex, race, and baseline therapy, SCC histology was determined to be associated with worse outcomes compared to urothelial bladder cancer. However, a recent analysis of all stage III and stage IV bladder cancer cases in Ontario, Canada reported that SCC had a faster disease course than urothelial carcinoma, whereas the five-year overall survival of SCC was similar to urothelial carcinoma after the data were adjusted for covariates (47).

Preoperative or postoperative chemotherapy (CT) is not recommended for the non-urothelial carcinomas of the renal pelvis, ureter, or bladder since these tumors are less responsive to CT compared to urothelial carcinoma and are excluded in phase III studies (48). There are also no high-quality data reporting the role of CT and/or RT as adjuvant therapy.

In schistosomal bladder cancer, RT may play a role before cystectomy, but it is not part of the standard treatment for other bladder tumors (49,50). Preoperative RT can be considered especially in cases where complete resection cannot be performed owing to the suspicion of locally advanced disease. Approximately 90% of mortality in SCC is due to local pelvic recurrence (mostly bladder-urethral anastomosis or ureter). Distant metastasis is rarely observed, at a rate of 8-10% (21).

The tendency for locally high recurrence rates of SCC of the bladder following radical cystectomy suggests that postoperative or preoperative RT with or without radiosensitizing CT can be considered an option. Many retrospective case series have reported possible benefits of neoadjuvant RT or adjuvant (51,52,53,54). In a study conducted with patients with bilharzial SCC, it was determined that the disease-free survival rate was 48% in patients who received adjuvant RT compared with 29% in those that did not receive this therapy (55). However, these results may not be valid for non-schistosomal SCC (49).

Postoperative RT is a viable alternative for patients with persistent locally advanced SCC who are unsuitable or unwilling to undergo adjuvant CT after radical cystectomy. Recent data suggest that this can also be recommended for patients with positive surgical margins (56). The preliminary results of a randomized phase III study of 123 patients with locally advanced disease after radical cystectomy (51% with urothelial carcinoma and 49% with SCC or other carcinoma) indicated that postoperative RT improved local control compared to adjuvant CT (two-year recurrence-free survival: 69% vs 92%, hazard ratio: 0.28) (57). Distant metastasis-free survival, disease-free survival, and overall survival were similar between the two treatment groups. The subgroup analysis of the patients with urothelial carcinoma provided similar results (58).

In patients with unresectable locally advanced bladder SCC (as in head, neck, anus and cervix SCC), RT together with radiosensitizing CT is a treatment can be considered, particularly since the tumor has a locally aggressive course. However, there are only limited prospective data on disease management.

Information from the Phase III study BC2001 shows that mitomycin C and fluorouracil given concomitantly with RT are more effective in local control and survival in patients with muscle-invasive bladder cancer compared to RT alone (59). In that study, only 2.7% of the patients had adenocarcinoma or SCC, and no difference was found when the results were compared with urothelial cancer. A similar treatment regimen in SCC of the anus, which is not suitable for platinum-containing CT, presents as an effective and easily tolerated protocol (60,61). Therefore, it is also a possible treatment option in patients with bladder SCC.

Studies support the idea that SCC tends to be at a locally advanced or worse stage at the time of diagnosis and it is relatively resistant to CT regimens used for metastatic urothelial carcinoma (34,46,62,63). Considering these findings, there is a need for more prospective clinical studies.

The promising results of T-cell checkpoint immunotherapy treatments using pembrolizumab or atezolizumab in patients, who treated previously with platinum-based regimens for advanced urothelial carcinoma, as well as results obtained from immunotherapy in patients with lung, head, and neck SCC justify the inclusion of patients with SCC of the bladder in clinical trials (64). Atezolizumab, a PDL-1 (Programmed Death-

Ligand 1) agent, showed sustained activity and an objective response rate of 26% in platinum-resistant metastatic urothelial carcinoma (65). Although there are no data to support the use of immunotherapy in SCC of the bladder, it appears that clinical benefits may guide future treatment protocols.

The scarcity of clinical studies on metastatic diseases suggests that metastatic urothelial cancer treatment regimens can be considered. In a Phase II study, in which both 43 patients with urothelial cancer and 6 patients with bladder SCC were successfully treated with good outcomes, suggests that the combination of carboplatin, gemcitabine and paclitaxel can be preferred for treating these patients (66).

Some molecular biomarkers have also been investigated to predict oncological outcomes. Fibroblast growth factor 2 (FGF-2) overexpression has been reported to be associated with the aggressive pathological features of including LVI, LN involvement, and SCC, as well as worse overall outcomes following radical cystectomy. Additionally, it has been observed that changes in cyclooxygenase 2 (COX-2) can predict poor outcomes (23). It has also been suggested that a panel of five biomarkers, namely COX-2, p53, Bax, FGF-2, and epidermal growth factor receptor can predict outcomes after cystectomy (67). Lastly, the expression of the human epidermal growth factor receptor 2 oncoprotein has been reported to be at high levels in SCC tumors (68). It is considered that these biomarkers can guide the determination of optimal treatment approaches.

Conclusion

Due to the rarity of SCC of the bladder, there is a lack of level I evidence guidelines for managing the disease. There is a need for high-volume and prospective studies on all work and developments in this area. This will help develop more accurate and effective guidelines for multimodal treatment approaches.

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Original Article

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Comparison of Renal Cell Cancer Surgery During the COVID-19 Pandemic with Prepandemic Period, Turkey Multicenter Study

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Abstract

Objective: Coronavirus disease-2019 (COVID-19) pandemic changed various priorities in health area. Many elective surgeries for renal cell cancers (RCC) have been postponed. We examined the influence of the COVID-19 pandemic on the surgical treatment of RCC in Turkey.

Materials and Methods: Surgically treated 457 patients for kidney tumor, from March 1, 2019 to February 28, 2021 in 9 centers in Turkey were analyzed retrospectively.

Results: The number of surgical treatments for RCC during the COVID-19 pandemic has decreased significantly, in contrast to the same period before COVID-19. Admission symptoms were similar in these two periods (p=0.32). However, although not statistically significant, the rate of admission to hospital due to hematuria was higher during the pandemic period compared to the prepandemic period (14.4% vs 9.8%, respectively). The two study periods differed significantly in terms of the rate of metastatic RCC detected in preoperative imaging (13.1% vs 6.1%, during COVID-19 and pre-COVID-19, respectively) (p=0.01). Moreover, the study periods differed significantly in terms of time between imaging and operation [35 (2-240) vs 30 (1-210) days, during COVID-19 and pre-COVID-19, respectively] (p=0.01). However, these two periods were similar in terms of tumor size, type of surgery, and pathological stage (p≥0.05). Although the pathological stages were similar among the groups, nephrectomies due to the metastatic disease were significantly higher in the pandemic period (p=0.01).

Conclusion: The number of RCC-related surgeries were significantly decreased during the pandemic period. However, the rate of surgery for metastatic disease has significantly increased.

Keywords: COVID-19 pandemic, RCC, treatment

Introduction

The prevalence of renal cell cancer (RCC) is incrementally rising worldwide. With the increasing use of imaging methods such as ultrasonography (USG) and computed tomography (CT), more than 60% of RCC can often be detected in the early stages when patients are asymptomatic (1). RCC is the third most common urological cancer. Most of the cases are detected between the ages of 60-70. RCC is more common in men than in women (3:2). Only 10% of RCC patients present with characteristic clinical symptoms consisting of hematuria, palpable abdominal mass, and back or flank pain. Despite the increase in early

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diagnosis, metastatic RCC is detected in imaging methods in 20-30% of patients (2,3). Smoking, obesity, hypertension and/or medications have been implicated as risk factors, but the etiology of RCC is still unclear (4). RCC is divided into different histological types and the most common types are clear cell (70-90%) (5). Tumor-node-metastasis (TNM) classification can be used in RCC staging and surgery is the only viable option for non-metastatic RCC. Partial nephrectomy is the first choice for T1 tumors, while radical nephrectomy is the first choice for T2-4 tumors (6).

A viral syndrome-coronavirus-2 [coronavirus disease-2019 (COVID-19)] strain emerged in the Wuhan region of China in late 2019, initiating a pandemic that affected millions of people worldwide and caused a high number of deaths (7). Healthcare professionals were entrusted to deal with the pandemic, and intensive-care units were used to treat COVID-19 patients. A rapid working group has been formed by the European Association of Urology to establish convenient guidelines to deal with various circumstances and precedences following the COVID-19 outbreak. Within the scope of the COVID-19 pandemic, urological diseases were divided into 4 priority levels: low priority (can be delayed for 6 months), medium priority (can be delayed for 3-4 months), high priority (can't be delayed for more than 6 weeks), and emergency (can't be delayed for more than 24 h) (8).

In terms of RCC treatment, for Bosnian type III and IV cysts as well as T1 tumors it was recommended to postpone under monitoring and for T2 tumors to postpone and keep under close observation. It was suggested that surgery should be performed primarily for T3-T4 tumors. For metastatic RCC, it was recommended to be evaluated for surgery, follow-up, or chemotherapy, depending on the patient's condition (9).

In this study, we investigated whether there was a difference in the number of RCC operations, pathologies, and surgical preferences in 9 different centers in Turkey between the 1-year period before and during the COVID-19 pandemic. We also examined how the COVID-19 pandemic affected the diagnosis and treatment of RCC.

Materials and Methods

The study was conducted after approval from the Ethical Review Committee of Afyonkarahisar Health Science University, Afyonkarahisar, Turkey (date: 16.04.2021, reference code: 2011-KAEK-2 2021/292). Nine centers from various regions of Turkey were included in this study. The data of 457 patients who underwent surgery for kidney tumors between March 1, 2019 and February 28, 2021 were retrospectively analyzed. The period between March 1, 2019 and February 28, 2020 was defined as the 1-year period before COVID-19. The period between March 1, 2020 and February 28, 2021 was defined as a 1-year period during COVID-19. In the one-year period before COVID-19 and in the one-year period COVID-19, the number of operations for RCC, the age, gender of the patients, symptoms at presentation, tumor size and presence of distant metastases on imaging, time between imaging and operation, type of surgery, pathological tumor size and stages were evaluated and compared. 4 patients who were operated during the COVID-19 period and 8 patients who were operated during the pre-COVID-19 period, whose pre-operative images and Histopathology could not be reached, were excluded.

Statistical Analysis

All the data was analysed using the Statistical Package for the Social Sciences, version 15.0 (SPSS Inc. Chicago, Illinois). Any $p<0.05$ was accepted as significant. Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. Since the variables were non-normally distributed, Mann-Whitney U test for continuous and Pearson's chi-square for categorical variables were preferred for comparing these two groups.

Results

Of the 457 patients included in the study, 290 (63.5%) were male and 167 (36.5%) were female. The median age of the patients was 61 (19-86). Ages for the 25-50-75 percentiles were 52-61-69 respectively. A renal mass was detected incidentally in 221 (48.4%) patients. It was observed that 184 (40.2%) patients applied with the complaint of pain, 52 (11.4%) patients applied with the complaint of hematuria and were operated due to the detection of a mass in the kidney. The median tumor size in preoperative imaging methods was calculated 50 mm (10-180). Tumor sizes for the 25-50-75 percentiles were 35-50-72 respectively. Distant metastasis was detected in 39 (8.5%) patients. The time elapsed between imaging and operation median was 31 days (1-240). The time between imaging and operation for the 25-50-75 percentiles were 15-31-62, respectively. Open partial nephrectomy was performed in 135 (29.5%) patients, open radical nephrectomy in 157 (34.4%) patients, laparoscopic partial nephrectomy in 31 (6.8%) patients, and laparoscopic radical nephrectomy in 134 (29.3%) patients. Tumor pathologies were as following: clear cell RCC in 294 (64.3%) patients, papillary RCC in 56 (12.3%) patients, chromophobic RCCs in 39 (8.5%) patients, and other types in 68 (14.9%) patients. The median tumor size of the pathological specimens was 50 mm (10-200). Tumor size of pathological spesmen for the 25-50-75 percentiles were 35-50-72 respectively. Staging was as follows: 249 (54.5%) patients were diagnosed with stage 1,78 (17.1%) patients at stage 2,75 (16.4%) patients at stage 3, and 55 (12%) patients with stage 4 kidney tumors. Table 1 shows the socio-demographic characteristics of the patients included in the study.

Among all patients, 160 (35.01%) were in group 1 (operated during 1-year period amid COVID-19) and 297 (64.99%) were in group 2 (operated during period of 1-year before COVID-19). The number of surgeries was significantly lower in the COVID-19 period ($p<0.001$). Median age was statistically similar between the groups [60 (19-80) and 61 (21-86) respectively] ($p=0.31$). Twenty-three (14.4%) patients who applied with the complaint of hematuria were in group 1 and 29 (9.8%) were in group 2. Although there was no statistical difference, the percentage of applications due to hematuria during the COVID period increased compared with the pre-COVID period. In the preoperative imaging, tumor median size was 45 (10-180) mm in group 1 and 50 (12-180) mm in group 2, and the difference was not statistically significant ($p=0.21$). In the preoperative evaluation,

metastasis was significantly higher in group 1 [21 (13.1%) vs 18 (6.1%), p=0.01]. There was a significant difference among the groups in terms of time between imaging and operation [35 (2-240) days vs 30 (1-210) days, respectively] (p=0.01). However, the difference among these groups in terms of surgery type was not statistically significant (p=0.13). Moreover, no statistical difference was found between the groups in terms of the tumor median sizes measured in the pathology specimens [50 (10-200) mm vs 48 (12-200) mm, respectively] (p=0.73). Lastly, no significant difference was observed among the groups in terms of pathological stage (p=0.16). Metastasis was detected in preoperative imaging in 21 of 22 patients with stage 4 RCC during the period of COVID-19. In the pre-COVID-19 period, metastases were detected in 18 of 33 patients with stage 4 RCC on preoperative imaging. Although tumor size and stage did not change, an increase was observed in the number of surgeries for metastatic disease. Table 2 compares the data of operations performed for RCC in the 1-year period during and pre-COVID-19.

Table 1. Patients' socio-demographic characteristics

Gender	**Number %**	
Male Female	290 167	63.5 36.5
Group	Number %	
Group 1 (During COVID-19) Group 2 (Pre-COVID-19)	160 297	35.01 64.99
Median age	61 (19-86)	
Admission symptom	Number %	
Incidental	221	48.4
Pain	184	40.2
Hematuria	52	11.4
Median tumor size on imaging (mm)	50 (10-180)	
Distant metastasis	Number %	
Absent	418	91.5
Present	39	8.5
Median time between imaging and operation (day)	31 (1-240)	
Type of renal surgery	Number %	
Open partial nephrectomy	135	29.5
Open radical nephrectomy	157	34.4
Laparoscopic partial nephrectomy	31	6.8
Laparoscopic radical nephrectomy	134	29.3
Pathological tumor type	Number %	
Clear Cell RCC	294	64.3
Papillary RCC	56	12.3
Chromophobic RCC	39	8.5
Other pathological types	68	14.9
Median pathological tumor size (mm)	50 (10-200)	
Pathological stage	Number %	
Stage 1	249	54.5
Stage 2	78	17.1
Stage 3	75	16.4
Stage 4	55	12

COVID-19: Coronavirus disease-2019, RCC: Renal cell cancers

Discussion

In this article, we found that the number of surgeries for RCC decreased significantly during the COVID-19 period, but the number of surgeries for metastatic disease increased.

RCC is more common in males than in females (1). In our study, 63.5% of the patients were male and 36.5% were female, which was consistent with the literature. RCC is especially common among the 60-70 age group (3). The median age of our patients was 61 (19-86) years, which was similar to the literature.

More than 50-60% of RCCs are detected incidentally in USG evaluation for other reasons (2,3). Incidental RCCs were detected in 48.4% of the patients in our study. The rate of stage 1 RCC according to TNM staging Chang et al. (10) found 54.9%, while Chen et al. (11) they found it to be 69.8%. Because of the increased use of USG and CT over the years, it is expected that the incidence of incidental diagnosis will increase, which in turn increases the incidence of early-stage RCC. In our study, since the number of patients diagnosed incidentally (48.4%) was lower than expected, the rate of stage 1 RCC (54.5%) was also lower compared to other stages.

During the pandemic, active monitoring was recommended at 6-12 months intervals for kidney tumor masses below 4 cm. Patients with more advanced renal tumors, such as T2, T3, or

Table 2. Comparison of perioperative data between group 1 (during COVID-19) and group 2 (Pre-COVID-19)

	Group 1	**Group 2**	**p-value**
Number of patients	160	297	p<0.001
Median age	60 (19-80)	61 (21-86)	p=0.31
Admission symptom			
Incidental Pain Hematuria	76 (47.5%) 61 (38.1%) 23 (14.4%)	145 (48.8%) 123 (41.4%) 29 (9.8%)	p=0.32
Median tumor size on imaging (mm)	45 (10-180)	50 (12-180)	p=0.21
Metastasis	21 (13.1%)	18 (6.1%)	p=0.01
Median time between imaging and operation (day)	35 (2-240)	30 (1-210)	p=0.01
Type of renal surgery			
Open partial Open radical Laparoscopic partial Laparoscopic radical	49 (30.6%) 47 (29.4%) 16 (10%) 48 (30%)	86 (29%) 110 (37%) 15 (5.1%) 86 (29%)	p=0.13
Median pathological tumor size (mm)	50 (10-200)	48 (12-200)	p=0.73
Pathological stage			
Stage 1 Stage 2 Stage 3 Stage 4	76 (47.5%) 30 (18.8%) 32 (20%) 22 (13.7%)	173 (58.2%) 48 (16.2%) 43 (14.5%) 33 (11.1%)	p=0.16

COVID-19: Coronavirus disease-2019

T4 should be evaluated carefully as they are at risk of metastasis. Early treatment should be preferred if there are imaging findings showing aggressive features and if renal biopsy has been performed and aggressive features were detected (12). Lei et al. (13) reported 20% mortality after surgery, among the patients whose tests were positive for COVID-19 and without symptoms. However, in another study conducted during the COVID-19 pandemic, it was reported that surgical procedures can be performed safely without the development of COVID-19-related mortality if adequate precautions are taken (14).

RCC consists of a heterogeneous group of diseases. While treatment of some RCC tumors that do not show aggressive features can be safely postponed, treatment of RCC with aggressive features should be given a priority. Therefore, a risk-based approach should be made for patients with RCC during the pandemic (15). In our study, 297 (65%) patients were operated for RCC in the 1-year period before COVID-19, and 160 (35%) were operated in the 1-year period during COVID-19. The number of surgeries for RCC during the COVID-19 period have decreased drastically.

The classic symptom triad, which presents as gross hematuria, palpable abdominal mass, and flank pain, is rarely seen in RCC. However, hematuria is an important finding in terms of diagnosis and treatment (3). Lee et al. (16) reported that patients with symptomatic symptoms such as pain and hematuria showed aggressive histology and a poor prognosis. In our study, although there was no significant difference in terms of admission complaints between the two study periods, the rate of patients presenting with hematuria was found to be higher in the COVID-19 period compared in the pre-COVID-19 period (14.4% vs. 9.8%). Although patients can neglect or delay seeking medical help pain, hematuria is a finding that is noticed by the patient and urges them to seek medical attention. Therefore, we found that the rate of admission due to hematuria was observed more frequently throughout the pandemic.

In the study that they compared the prepandemic and COVID-19 period, Srivastava et al. (17) reported that postponing surgery for 3 or more months after diagnosis did not increase the risk of tumor progression and tumor size in localized RCC. In our study, the median time between diagnosis and surgery was 30 (1-210) days in the pre-pandemic, and 35 (2-240) days during the COVID-19 period, and the difference among these groups was significant. However, the pathological tumor size and tumor stage were statistically similar in these two periods.

In the review by de Simone et al. (18), they suggested that open surgery should be preferred instead of laparoscopy if adequate precautions cannot be taken in terms of the risk of airborne transmission throughout the COVID-19 period. To our knowledge, there are no studies comparing open surgery to laparoscopic surgery in terms of the possibility of transmission of a virus during the operation. The recommendation for open surgery over laparoscopy is solely based on expert opinion (19). In our study, there was no difference in open and laparoscopic surgery rates between the two study periods.

Although there is an increase in the early diagnosis of RCC, metastasis may be detected at first diagnosis in almost one-third of patients (20). It should be kept in mind that as the RCC tumor size increases, the possibilities of detecting metastases and the development of metastases in the future are higher (21). In localized RCC, after a surgical treatment, metastasis is detected in 30% of patients in the later stages (22). In our study, there was no significant difference between pre-COVID-19 period and the COVID-19 period in terms of tumor sizes in imaging. Metastasis was not detected in 418 (91.5%) patients in the imaging methods performed at the time of diagnosis. However, distant organ metastases were detected in 39 (8.5%) patients. There was a significant difference between the two study periods in terms of metastases detected in pre-operative imaging [21 (13.1%) vs 18 (6.1%) patients, in groups 1 and 2, respectively]. Although the number of metastatic patients was similar in both periods, the rate of metastatic patients was higher in the COVID-19 period due to the lower number of operated patients in that period. We think that this is due to the earlier admission due to metastatic disease symptoms.

In their study of RCCs smaller than 4 cm, Uzosike et al. (23) found that the mean tumor size increased by 0.09 cm per year during delayed treatment in RCC. They also reported that the increase was 0.54 cm in the group followed for less than 6 months, 0.07 cm in the group followed for more than 1 year. Moreover, no metastatic disease developed in any patient, no significant difference was found in growth rates, and the variability of tumor growth rates decreased over time (23). In Uzosike et al.'s (23) study, the tumor sizes increased more in the group of patients followed for less than 6 months, and therefore, earlier surgery was performed instead of follow-up in these rapidly growing tumors, therefore we believe that their grouping was not homogeneous. Daugherty et al. (24) found the rate of metastasis at the time of diagnosis to be 4% in RCC below 5 cm. They reported that tumor size is the main factor in decision making, but the risk of metastasis is different for each mass depending on the tumor histology. Kim et al. (25) compared waiting periods of less than 3 months and less than 1 month in RCC over 7 cm and concluded that there was no difference between the two groups in terms of overall survival and disease-related survival. Although it was not significant, they found the pathological upstage to be higher in the group with a longer waiting period. However, they excluded patients who waited longer than 3 months (25). In the literature, most studies were retrospective and clinicians seem to be more selective and turn to early surgery for RCC patients who appear to have more aggressive and fast-growing tumors. In our study, when the period between the COVID-19 period and the period before it is compared, there is an increase in the time between diagnosis and treatment, but it is seen that this increase is too short to increase tumor size and stage. This decrease in the number of surgeries for RCC is a situation that may increase the number of newly diagnosed patients, tumor sizes, advanced stage tumors and metastatic disease in the future.

Study Limitations

This study had some limitations. Due to the retrospective design of the study, all patients whose data were thought to be incomplete or inaccurate had to be excluded from this study. Another limitation is the unknown number of patients for whom follow-up is recommended because of low tumor size.

Conclusion

The COVID-19 pandemic has affected the practice of the diagnosis and management of RCC. There has been a decrease in the number of operations performed for RCC. The time between imaging and operation increased. There has been an increase in the rate of surgery for metastatic disease. An increase in the rate of advanced and metastatic diseases should be expected in the future.

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Ethics

Ethics Committee Approval: The study was conducted after approval from the Ethical Review Committee of Afyonkarahisar Health Science University, Afyonkarahisar, Turkey (date: 16.04.2021, reference code: 2011-KAEK-2 2021/292).

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The Effects of Metabolic Syndrome on the Prediction of Prostate Cancer in Patients with a PSA Value of 2.5-4 ng/mL

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Abstract

Objective: In this study, the aim was to evaluate the effect of metabolic syndrome (MetS) and criteria on the diagnosis of prostate cancer (PCa) in patients with a prostate-specific antigen (PSA) value of 2.5-4 ng/mL.
Materials and Methods: A total of 116 patients who underwent transrectal ultrasound-guided prostate biopsy between January 2016- June 2018 with a PSA value of 2.5-4 ng/mL were included in the study. Patient height, body weight, waist circumference (WC) and blood pressure were measured and body mass indexes were calculated. Blood samples were also collected and tested for fasting and postprandial blood glucose, along with lipid profiles. Patients were divided into two groups as those with and without PCa. The presence of MetS was evaluated according to the measurements and laboratory results.
Results: Patients were divided into two groups as those without PCa (n=101) and those with PCa (n=15). A significant difference was found between the groups in terms of the frequency of hypertension (p=0.024). There were no significant differences between the groups in terms of other demographic characteristics. There was a significant difference between the groups in terms of hypertension, a criterion for MetS. The presence of MetS and other MetS criteria (WC >102 cm, triglyceride ≥150 mg/dL, high density lipoprotein <40 mg/dL, fasting blood glucose ≥110 mg/dL or type 2 diabetes mellitus) was not associated with PCa in patients with PSA levels of 2.5-4 ng/mL.
Conclusions: Among the MetS criteria, there was only a positive relationship between hypertension and PCa in patients with PSA 2.5-4 ng/mL.
Keywords: Prostate biopsy, prostate cancer, prostate-specific antigen, metabolic syndrome

Introduction

Prostate cancer (PCa) is the fourth most common cancer in the world and the second most common cancer in men. Globally, nearly 1.4 million PCa diagnoses were made in 2020 and it comprises 14.1% of all cancers in men (1).

Men with prostate-specific antigen (PSA) values below 4 mg/mL are identified to have cancer at a rate of 15.2% (2). Another study found the cancer detection rate was 27.48% in the group with PSA value from 2.5-4.0 ng/mL, while it was 30.08% for the group with PSA value 4.0-10.0 ng/mL (3). According to the study results, it is necessary to lower the PSA threshold value to 2.5 ng/mL as an indication for prostate biopsy.

Metabolic syndrome (MetS) was first defined by Reaven in 1988 and is a systemic endocrinopathy that causes a group of diseases like glucose intolerance, type 2 diabetes mellitus (DM), abdominal obesity, dyslipidemia, hypertension and coronary artery diseases (4,5). A meta-analysis showed that the presence of MetS in men was associated with the liver, colorectal and bladder cancer, whereas it was associated with endometrial, pancreas, postmenopausal breast, rectal and colorectal cancer in women (6).

There are different results in the literature related to PCa development in the presence of MetS (7-9). In this study, the aim was to assess the effect of MetS and criteria and PSA on the prediction of PCa in patients with PSA value from 2.5-4.0 ng/mL with prostate biopsy performed accompanied by transrectal ultrasonography (TRUS-Bx).

Materials and Methods

After obtaining approval from the Ethics Committee of University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital (decision no: 3, date: 26/01/2015), the study was planned prospectively and included 116 patients with prostate biopsy performed from January 2016-June 2018 with/without

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lower urinary tract complaints, PSA value 2.5-4 ng/mL and age above 55 years. The patients did not have a history of urinary tract surgery, had no previous prostate biopsy history, had no PCa diagnosis, were not using 5-ARI, had no history of prostate abscess and acute prostatitis, no history of hypogonadism, no history of PCa in the family and no type 1 DM. All patients were given information with an informed consent form and signed consent was obtained from each patient.

All patients included in the study provided information about age, PSA, chronic diseases, medications used, smoking and alcohol use. Later, the patients' height, body mass (Wunder RA200), waist circumference (WC) and blood pressure values were measured. WC was measured on a horizontal plane at mid-level between the lowest level costa and iliac crest (10). Blood pressure measurements were taken on the right arm after 5 minute rest with a standard pressure device (Erka Perfect Aneroid) in the sitting position. Measurements were taken twice at 5 minute intervals and mean values were recorded. Body mass index (BMI) was calculated by dividing the body weight by the square of height and patients with values above 30 were assessed as obese. Blood samples were taken after 12 hour fasting with blood sugar, total cholesterol, triglyceride, low density lipoprotein (LDL), high density lipoprotein (HDL) and postprandial blood sugar tests (Beckman Coulter, Olympus AU 2700) examined 2 hour after eating.

All patients had prostate size measurements taken by digital rectal examination (DRE) and TRUS (BK Medical Flex Focus) before biopsy. Prostate sizes were calculated using the prolate ellipsoid formula: length x height x width x $\pi/6$ (11). The prostate biopsy procedure was performed after check-up urine culture showed no infection.

All patients with biopsy planned underwent 12 core systemic prostate biopsies via the transrectal route.

Patients were divided into two groups as those with and without PCa according to pathology results. Patients with benign prostate biopsy results but with repeat biopsy indications had re-biopsy performed and were added to the groups according to final pathology results. The presence of MetS was assessed with National Cholesterol Education Program - Adult Treatment Panel III (NCEP-ATP III) criteria (Table 1) (12). Patients with the presence of three or more criteria were diagnosed with MetS. In patients with PSA value from 2.5-4 ng/mL, the effect of MetS and components on PCa diagnosis was assessed.

Statistical Analysis

Analysis of data used the IBM SPSS Statistics 25.0 (Windows software) statistical program. Descriptive statistics for data used mean, standard deviation, minimum, maximum, frequency and percentage values. The normal distribution of numerical variables was assessed with the Kolmogorov-Smirnov ($n \geq 50$) or Shapiro-Wilk ($n < 59$) tests. Comparison of numerical variables in the two groups used the independent two-group t-test or the Mann-Whitney U test. Comparison of categoric variables used the chi-square or Fisher's Exact test. All tests of hypotheses were completed at $\alpha = 0.05$ significance level; in other words, $p < 0.05$ was accepted as statistically significant.

Table 1. NCEP: ATP III diagnostic criteria for metabolic syndrome

- The presence of three or more of these components:
- Abdominal obesity (waist circumference: >102 cm in men, >88 cm in women)
- Hypertriglyceridemia (≥150 mg/dL)
- Low HDL (<40 mg/dL in men, <50 mg/dL in women)
- Hypertension (blood pressure ≥130/85 mmHg)
- Hyperglycemia (fasting blood glucose ≥110 mg/dL)

NCEP: National Cholesterol Education Program, ATP: Adult Treatment Panel, HDL: High density lipoprotein

Results

The study included 116 patients with PSA value 2.5-4 ng/mL. Mean age of patients was 61.37±7.43 (44-79) years. Thirty-one patients (26.7%) had hypertension and 27 patients (23.3%) had type 2 DM. According to the BMI, 15 patients (12.9%) were assessed as obese. The mean WC of patients was 95.84±7.49 cm and fasting blood sugar was 92.81±15.03 mg/dL. The demographic characteristics, lipid and other laboratory values of patients are shown in Table 2.

According to the prostate biopsy results, 101 patients without PCa were included in group 1, while 15 patients with PCa were included in group 2. In group 2, 73.3% of the patients had a Gleason score of 3+3 (Table 3). In terms of demographic

Table 2. Demographic characteristics and laboratory values of patients

		n=116
Age (m ± SD) (min-max)		61.37±7.43 (44-79)
Height (cm) (m ± SD) (min-max)		172.84±6.67 (155-185)
Weight (kg) (m ± SD) (min-max)		80.2±10.47 (52-107)
BMI (kg/cm^2) (m ± SD) (min-max)		26.83±3.17 (18.9-37.9)
Obesity (n, %)		15 (12.1%)
Diagnosed with hypertension (n, %)		31 (26.7%)
Diagnosed with type 2 DM (n, %)		27 (23.3%)
Use of insulin (n, %)		5 (4.3%)
Use of metformin (n, %)		34 (29.3%)
Use of statin (n, %)		24 (20.7%)
Smoking (n, %)		36 (31%)
Use of alcohol (n, %)		27 (23.3%)
Waist circumference (cm) (m ± SD) (min-max)		95.84±7.49 (71-118)
Blood pressure (mm Hg) (m ± SD) (min-max)	Systolic	124.09±13.95 (100-180)
	Diastolic	78.97±7.62 (55-100)
Fasting blood sugar (mg/dL) (m ± SD) (min-max)		92.81±15.03 (72-163)
Postprandial blood sugar (mg/dL) (m ± SD) (min-max)		118.2±37.41 (53-300)
Cholesterol (mg/dL) (m ± SD) (min-max)		213.65±40.41 (114-374)
Triglycerides (mg/dL) (m ± SD) (min-max)		147.86±77.69 (50-500)
LDL (mg/dL) (m ± SD) (min-max)		139.13±47.26 (23-453)
HDL (mg/dL) (m ± SD) (min-max)		47.97±47.26 (21-90)

m: Mean, SD: Standard deviation, BMI: Body mass index, DM: Diabetes mellitus, LDL: Low density lipoprotein, HDL: High density lipoprotein, min-max: Minimum-maximum

Table 3. Pathology results of patients diagnosed with prostate cancer		
	Gleason score	n=15
Pathological staging of prostate cancer diagnoses (n, %)	3+3	11 (73.3%)
	3+4	2 (13.3%)
	4+3	1 (6.7%)
	4+4	1 (6.7%)

data, both groups had no differences identified in terms of age, BMI, smoking and alcohol habits. PCa patients had higher hypertension diagnoses compared to those without PCa and this difference was at statistically significant levels (53.5% vs. 22.8%, p=0.024). The other demographic data in both groups were similar (Table 4).

When measurements were compared between the two groups, there were no statistical differences found (Table 5).

In the non-PCa group, the number of MetS patients was 12 (11.9%), while there were 2 in the PCa group (13.3%) (p=1.000). The number of patients diagnosed with hypertension or with high blood pressure (>130/85 mmHg) when blood pressure is measured, alone among the MetS criteria, was found to be significantly high in those with PCa compared with those without PCa (53.3% vs. 27.7%, p=0.048). MetS and other MetS criteria on their own had no correlation with PCa in patients with PSA value 2.5-4 ng/mL (Table 6).

Discussion

The threshold value of 4 ng/mL began to be accepted from the beginning of the 1990s and this value was also assessed as the threshold for prostate biopsy indications in males with normal DRE for the diagnosis of PCa (13). Though high PSA values are more associated with malignancy, malignancy may be observed even at low PSA values (2). the prostate cancer prevention trial published in 2004 included 2,950 patients with PSA values below 4 ng/mL with normal DRE and identified PCa in 449 patients (15.2%) (2). A study of 36,316 patients by Gilbert et al. (3) found that the PCa rate was 21.8% with the PSA value interval from 2-2.5 ng/mL. For the intervals from 2.5-4 ng/mL and 4-10 ng/mL cancer identification rates were 27.4% and 30.0%, respectively, and were assessed as similar (3). Due to these results, it was proposed that a PSA of 2.5 ng/mL should be used as the threshold value.

In our study of 116 patients with PSA value from 2.5-4 ng/mL and prostate biopsy performed, 15 patients (12.1%) had PCa identified and this rate is low compared to data in the

Table 4. Comparison of patients' demographic data			
	Group 1 (n=101)	Group 2 (n=15)	p-value
Age (m ± SD)	61.10±7.28	63.20±8.42	0.309*
Height (cm) (m ± SD)	172.94±6.83	172.20±5.57	0.586**
Weight (kg) (m ± SD)	80.18±10.68	80.33±9.28	0.627**
BMI (kg/cm^2) (m ± SD)	26.78±3.18	27.13±3.28	0.961**
Obesity (n, %)	12 (11.9%)	3 (20%)	0.460***
Diagnosed with hypertension (n, %)	23 (22.8%)	8 (53.3%)	0.024***
Diagnosed with type 2 DM (n, %)	26 (25.7%)	1 (6.7%)	0.187***
Use of insulin (n, %)	5 (5%)	0 (0%)	1.000***
Use of metformin (n, %)	30 (29.7%)	4 (26.6%)	1.000***
Use of statin (n, %)	21 (20.8%)	3 (20%)	1.000***
Smoking (n, %)	31 (30.7%)	5 (33.3%)	1.000***
Use of alcohol (n, %)	23 (22.8%)	4 (26.7%)	0.748***
m: Mean, SD: Standard deviation, BMI: Body mass index, DM: Diabetes mellitus, *Student t-test, **Mann-Whitney U, ***Fisher's Exact test			

Table 5. Comparison of measurements and laboratory values between groups				
		Group 1 (n=101)	Group 2 (n=15)	p-value
Waist circumference (cm) (m ± SD)		95.78±7.61	96.20±6.88	0.990*
Blood pressure (mmHg) (m ± SD)	Systolic	123.96±14.38	125.00±11.02	0.440*
	Diastolic	78.91±7.83	79.33±6.23	0.587*
Fasting blood sugar (mg/dL) (m ± SD)		92.31±15.34	96.20±12.74	0.127*
Postprandial blood sugar (mg/dL) (m ± SD)		117.05±37.30	126.53±38.39	0.534*
Cholesterol (mg/dL) (m ± SD)		213.33±40.79	215.80±39.06	0.630*
Triglycerides (mg/dL) (m ± SD)		150.22±81.07	132.00±48.23	0.477*
LDL (mg/dL) (m ± SD)		138.34±49.04	144.47±33.76	0.226*
HDL (mg/dL) (m ± SD)		48.13±10.31	46.93±9.35	0.720*
m: Mean, SD: Standard deviation, LDL: Low density lipoprotein, HDL: High density lipoprotein, *Mann-Whitney U				

Table 6. Relationship of metabolic syndrome and criteria for prostate cancer				
		Group 1 (n=101)	Group 2 (n=15)	p-value
Abdominal obesity (waist circumference >102 cm) (n, %)		12 (11.9%)	3 (20%)	0.409*
Hypertriglyceridemia (≥150 mg/dL) (n, %)		31 (30.7%)	4 (26.7%)	1.000*
Low HDL (<40 mg/dL) (n, %)		16 (15.8%)	4 (26.7%)	0.289*
Hypertension (blood pressure ≥130/85 mmHg) or anti-hypertensive drug use (n, %)		28 (27.7%)	8 (53.3%)	0.048*
Hyperglycemia (fasting blood glucose ≥110 mg/dL) or presence of type 2 DM (n, %)		26 (25.2%)	2 (13.3%)	0.518*
Distribution of patients by MetS criteria (n, %)	0 1 2 3 4	36 (35.6%) 32 (31.7%) 21 (20.8%) 9 (8.9%) 3 (3%)	3 (20%) 6 (40%) 4 (26.7%) 1 (6.7%) 1 (6.7%)	0.730*
Number of MetS diagnostic criteria (m ± SD)		1.12±1.09	1.40±1.12	0.321**
Presence of MetS (n, %)		12 (11.9%)	2 (13.3%)	1.000*
m: Mean, SD: Standard deviation, HDL: High density lipoprotein, DM: Diabetes mellitus, MetS: Metabolic syndrome, *Fisher's Exact Test, **Mann-Whitney U				

international literature. The reason for this may be ethnic structure and differences in lifestyle. Additionally, the small number of patients in our study may have caused this difference.

MetS is a systemic endocrinopathy and according to one of the most comprehensive studies of the NCEP-ATP III, the MetS prevalence in the USA is 23.7% (14). A study in our country identified MetS in 28% of males (15). Another study in Turkey in 2010 determined the prevalence of MetS as 41.4% in men (16). In our study, 14 of the 116 patients included in the study (12.1%) had MetS diagnosis. When data from the world in general and from Turkey are examined in the literature, this rate is lower. The selection of the patient population may have caused this difference.

Hypertension and Prostate Cancer

In our study, the MetS criterion of hypertension on its own was found to be significantly high in those with PCa compared with those without PCa (p=0.048). When the literature is examined, a meta-analysis by Esposito et al. (17) showed that hypertension increased the PCa risk by 15%. A meta-analysis by Gacci et al. (7) in 2017 investigated 7 studies and showed that hypertension was the only MetS component significantly associated with PCa, causing a 10% increase in PCa risk.

In the literature, there are studies with contrary findings to our study. In Sweden, 336,159 men were monitored and 10,002 patients received PCa diagnosis with an inverse correlation was observed between high blood pressure and PCa risk (18). Again, a study in Sweden followed 289,866 patients for mean 12 years and there was no correlation found between high blood pressure and PCa incidence (9). Worldwide studies are needed to explain the correlation and physiopathology between hypertension and PCa, as these studies both reflect the Swedish population.

Waist Circumference and Prostate Cancer

One of the MetS criteria of WC is used as a marker of abdominal obesity. WC is a marker of visceral fat mass and this situation is considered to have occurred because of different visceral fat mass among those with similar BMI (19). Esposito et al. (17) investigated MetS and PCa in a meta-analysis and found that WC above 102 cm increased the risk of PCa by 56%. Research in Canada in 2015 assessed WC above and below 102 cm and observed no difference between the groups with and without PCa in terms of WC (20).

Boehm et al. (19) assessed subgroups according to BMI in 2015, and WC above 102 cm was shown to increase PCa risk by 23%. In our study, there was no significant correlation found between WC and PCa. In our study, the mean age of patients was higher compared to studies, which found a significant correlation and this may have caused this situation.

Obesity and Prostate Cancer

Obesity is defined as BMI >30 kg/m^2 and is among the MetS diagnostic criteria of the World Health Organization (21). A study with the ProtecT study group found no correlation between BMI and PCa. As the natural progression of PCa is long term, it is thought that obesity at early ages may increase the risk of PCa (22).

A systematic review investigating 56 studies and 68,753 patients by MacInnis et al. (23) found that every 5 kg/m^2 increase in BMI increased PCa risk by 5% and increased risk of advanced-stage PCa by 12%. However, the patient measurements assessed in this review were variable in terms of being performed before, during and after diagnosis.

The REDUCE study showed that obesity did not increase PCa risk; simultaneously, there were associations with reduced risk of low-grade PCa and increased risk of high-grade PCa. Obesity is stated to be a risk factor for high-grade disease independent of PSA levels (24). A 2015 study in Canada observed that those with PCa had significantly lower BMI (20). Again, a study in 2015 by Boehm et al. (19) showed that obese patients had significantly lower prostate risk. The different results obtained in studies were linked to differences in the study groups. Though people have similar BMI, the body fat distribution may be different between populations (19).

A 2017 study of the prostate, lung, colorectal and ovarian cohort compared those with BMI >30 kg/m^2 from 20 to 50 years of age with those with BMI from 18.5-25 kg/m^2 and observed a significant degree of reduction in PCa risk. This inverse correlation was explained by PSA hemodilution in obese cases reducing the diagnosis of PCa (25).

In our study, there was no difference between obese and non-obese patients in terms of PCa. The small total patient numbers and incidence of obesity may have affected our results.

Serum Lipids and Prostate Cancer

The role of serum lipids in PCa risk is unclear. The meta-analysis by Esposito et al. (17) investigated 7 studies, including 3,866 cases and found that high triglyceride levels increased PCa risk by 11% and low HDL levels (<40 mg/dL) increased PCa risk by 7%. However, these correlations were weak and not statistically significant. In 2015, a meta-analysis investigating 14 prospective studies in different populations did not find a correlation between total cholesterol, HDL and LDL with PCa risk (26). A meta-analysis study of MetS and PCa in 2017 investigated 8 studies on triglyceride and HDL and found no significant correlation with PCa risk. They explained this situation as due to the heterogeneity of the investigated studies (7).

In our study, there were no differences in terms of serum lipid levels between patients without PCa and those with PCa. Our study, being cross-sectional and including small patient numbers, may have prevented the investigation of this situation.

Hyperglycemia and Prostate Cancer

A meta-analysis by Esposito et al. (17) investigated 9 studies including 4,211 patients and did not show a correlation between hyperglycemia and DM with PCa. A meta-analysis by Gacci et al. (7) investigating 10 studies showed high fasting blood glucose (≥110 mg/dL) or DM diagnosis did not increase PCa. They explained this situation as due to not knowing the duration of DM disease and the efficacy of glycemic control of the treatment given (7).

A study by Dankner et al. (27) followed 1 million men for mean 11 years and showed that PCa risk increased in the first year following diagnosis in patients developing DM and reduced in later years. A study of the ProtecT patient group showed that the presence of DM reduced PCa risk by 22% (28).

When DM worsens, testosterone levels fall and this may result in low PSA (27). The low PCa incidence in men with DM may be explained by low PSA level and fewer biopsies being performed (27). Additionally, because of damage to pancreatic beta cells in long-term DM, insulin levels may fall below those of men without DM. This hypoinsulinemia may directly suppress prostate carcinogenesis or indirectly by reducing the levels or activity of insulin-like growth factor 1 (IGF-1), a risk factor for PCa (29).

In our study, there was no correlation between DM and PCa. The lack of knowledge about the duration of DM and the low number of patients with DM may be insufficient to explain this correlation.

Metabolic Syndromes and Prostate Cancer

When MetS and PCa risk is assessed, there are different outcomes have in the literature. A study including 6,429 people with 385 PCa patients reported 23% fewer patients with MetS developed PCa. This situation was associated with low androgen levels in MetS (30). Blanc-Lapierre et al. (20) found that patients with MetS had PCa risk reduced significantly by 30%. The cause was predicted to be low insulin, IGF-1 and testosterone levels (20).

Bhindi et al. (31) found that the components of MetS on their own did not increase PCa risk, while the PCa risk significantly increased as the number of components increased and those with 3 or more components had 54% greater PCa risk compared with those without any component. The reason for this increase was thought to be the greater number of biopsies and increased diagnostic frequency (31).

However, another study including 1,880 patients with mean 13-year follow-up found that PCa development was 1.9 times greater in MetS patients and associated this with IGF-1 metabolism, sex hormones and SHBG disorder. This was the first study in the literature showing that MetS increased the PCa risk (32).

Esposito et al. (17) found that patients with MetS had 12% increase in PCa risk. They stated that correlations between MetS and PCa may be different between races and PCa detection rates may display differences between countries (17). Gacci et al. (7) reported MetS increased PCa risk by 17%. Simultaneously, high-grade PCa (GS ≥8) risk was significantly increased. MetS criteria alone are not effective, but the combination of these criteria was correlated with PCa (7).

Another meta-analysis by Hammarsten et al. (8) revealed a reduction in low-grade PCa risk and an increase in high-grade PCa risk. They explained that the diagnostic frequency of low-grade PCa reduced due to reasons such as low PSA levels due to low testosterone levels leading to small numbers of patients with biopsy, and reduced sensitivity of biopsy due to large prostate volume in MetS patients. Because of PSA-focused diagnostic procedures, diagnosis was made at high-grade due to progression of PCa in MetS (8).

In our study, only the MetS component of hypertension was found to have a significant correlation with PCa. The other criteria on their own or the presence of MetS diagnosis were not correlated with PCa.

Study Limitations

The most important limitation of this study was the limited number of patients. Additionally, the low diagnostic frequency of MetS may have prevented the determination of a significant correlation between PCa and MetS.

Conclusions

MetS and PCa are two common situations related to the aging population around the world. In our study, only the MetS component of hypertension was found to correlate positively with PCa. Though some factors associated with MetS appear to be related to PCa, the definite relationship between these two will remain uncertain until all these factors are researched in detail.

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Ethics

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Authorship Contributions

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Original Article

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Fluoroquinolone Resistance Level in Rectal Swab Taken Before Transrectal Ultrasound Prostate Biopsy

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Abstract

Objective: It has been shown that antibiotic prophylaxis before transrectal ultrasound prostate biopsy (TRUS-Bx) reduces the incidence of post-biopsy infectious complications. Without the superiority of a particular antibiotic regimen, there are differences in the antibiotic regimens used by clinics. However, recently, there have been serious concerns about TRUS-Bx-related infectious complications due to the increase in fluoroquinolone (FQ)-resistant bacterial strains. To overcome this global problem, alternative antibiotic prophylaxis should be investigated and appropriate antibiotic management should be applied in patients who will undergo TRUS-Bx. This study aimed to determine the antibiotic susceptibility of the rectal flora based on rectal cultures before TRUS-Bx, to systematically determine the basic prevalence of FQ resistance, to investigate the relationship between FQ resistance and the risk of infection after TRUS-Bx, and to determine the susceptibility of Fosfomycin and trimethoprim-sulfamethoxazole (TMP-SMX) as an alternative to the FQ group.

Materials and Methods: Rectal swab cultures were taken from each patient to undergo TRUS-Bx two days before the procedure. Two daily doses of 500 mg ciprofloxacin were given orally for one week, starting one hour before the procedure. All patients underwent 12 core biopsies.

Results: Antibiograms obtained from rectal swabs showed sensitivity to FQ in 78 patients (89.7%), to Fosfomycin in 85 patients (97.7%), to TMP-SMX in 78 patients (89.7%).

Conclusion: Although different antibiotic prophylaxis methods are discussed due to FQ resistance in today's medical practices, FQ sensitivity continues at a high rate of 89.7% in our region and still seems to be a viable prophylaxis method.

Keywords: Antibiotic prophylaxis, antibiotic resistance, fluoroquinolones, image-guided biopsy, prostate

Introduction

Prostate cancer is the most common cancer in men over 50 years of age in Europe and the USA and is responsible for 225,000 new cases in Europe and 240,000 in the USA each year (1). Transrectal ultrasound prostate biopsy (TRUS-Bx) is the most commonly used method for the histological diagnosis of prostate cancer. Besides being a procedure that can be performed safely without hospitalization and is easily tolerated by patients, TRUS-Bx may have complications such as hematuria, rectal bleeding, acute urinary retention, prostatitis, urinary system infection, and sepsis (2).

Antibiotic prophylaxis reduces the incidence of infectious complications after TRUS-Bx (3). There are differences in the antibiotic regimens used by clinics, without the predominance of a particular regimen (4). Among these antibiotic regimens, the fluoroquinolone (FQ) group is the most commonly used prophylactic agent and is recommended by the North American, European, and other international urology societies (5,6,7).

However, recently, there have been serious concerns about TRUS-Bx-related infectious complications due to the increase in bacterial strains resistant to FQ (8,9). In a population-based study of 75,190 men undergoing TRUS-Bx in Canada, hospital readmission rates within 30 days increased from 1.0% (1996) to 4.1% (2005). More than 70% of readmissions in this study were due to infection-related complications (10). In addition to the TRUS-Bx-related morbidity experienced by patients, post-TRUS-Bx infection also has significant negative economic consequences on healthcare systems (11).

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FQs are traditionally used for antibiotic prophylaxis, but overuse and misuse of FQs have increased FQ resistance. The European Medicines Agency has implemented strict regulatory requirements for the use of FQ, resulting in the suspension of the indication for perioperative antibiotic prophylaxis, including TRUS-Bx (12).

Alternative prophylaxis methods that can be used instead of traditional FQ prophylaxis before TRUS-Bx, which is also mentioned in the European urology guideline, can be examined under three procedures. The first procedure was targeted prophylaxis. It is the initiation of appropriate antibiotic prophylaxis with a rectal swab or stool culture to be made before TRUS-Bx. The second procedure is the application of extended antibiotic prophylaxis by adding aminoglycoside or cephalosporin group antibiotics to the FQ group to be administered with two or more antibiotic groups. The last procedure is the use of fosfomycin, cephalosporin, or aminoglycoside antibiotics instead of the FQ group (13).

The increasing rate of FQ resistance and infective complications following TRUS-Bx pose a significant challenge for urologists. To overcome this global problem, alternative antibiotic prophylaxis should be investigated and appropriate antibiotic management should be applied in patients who will undergo TRUS-Bx.

It has been reported that prophylaxis with antimicrobial agents, based on the rectal culture results obtained before the biopsy, reduces infections and morbidity after TRUS-Bx and reduces hospital readmission (14,15).

In this study, infective complications and antibiotic susceptibility of rectal flora were prospectively investigated in patients who underwent empirical FQ treatment before TRUS-Bx in the urology clinic of Sivas Cumhuriyet University approximately 2019-2021. This study aimed to determine the antibiotic susceptibility of the rectal flora based on rectal cultures before TRUS-Bx, to systematically determine the basic prevalence of FQ resistance, to investigate the relationship between FQ resistance and the risk of infection after TRUS-Bx, and to determine the susceptibility of fosfomycin and trimethoprim-sulfamethoxazole (TMP-SMX) as an alternative to the FQ group.

Materials and Methods

Patients who underwent TRUS-Bx in the urology clinic of Sivas Cumhuriyet University between March 2019 and March 2021 were included in this prospective study. Patients who underwent urological surgery in the last three months had significant growth in the last urine culture, had a history of acute or chronic prostatitis in the three last months and had a history of antibiotic use in the three last weeks were excluded from the study. Secondary biopsies were excluded from the study. TRUS-Bx indication was elevated serum prostate-specific antigen (PSA) and/or rectal digital examination positivity. Two days before the procedure, cultures were obtained from each patient with a rectal swab. Informed consent was obtained from each patient. A 135 cc rectal enema was applied to all patients for rectal cleansing two hours before the procedure. 500 mg ciprofloxacin was given orally in two daily doses for one week, starting one hour before the procedure.

The procedure was performed in the left lateral decubitus position. A Viking 2400 model (B-K Medical, Herlev, Denmark) ultrasonography device and a biplanar transrectal ultrasonography (TRUS) probe were used for imaging. The TRUS probe was covered with a latex condom and ultrasound gel was used to eliminate the rectal air artifact. No povidine iodine was used as a rectal preparation. Only enema was used. Local anesthesia was provided with lidocaine gel applied rectally before the biopsy. Then, periprostatic local anesthesia was performed with a 22-G Chiba needle inserted through the disposable biopsy needle guide channel attached to the TRUS probe. Prostate volume (cc) was calculated by measuring prostate dimensions (length x width x height x 0.5236). A biopsy gun and 18-G biopsy needles (GTA Medical Product and Service, Quistello, Italy) were used for the biopsies. All patients underwent 12 core biopsies. After the procedure, the patients were informed that they should reapply to the hospital in case of possible signs of infection. Age, serum PSA levels, prostate volume, presence of diabetes, biopsy pathology results, rectal swab culture results, and antibiogram sensitivity of the cases were analyzed.

Statistical Analysis

The data obtained from the study were evaluated with the SPSS 23.0 program. Mean and standard deviation parameters were used as descriptive statistics. Analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) were used to determine the normal distribution of the variables. Parametric tests were used for normally distributed data, and non-parametric tests were used for non-normally distributed data. The student's t-test was used to compare normally distributed data, and the Kruskal-Wallis test was used for non-normally distributed data. The chi-square test was used to compare categorical values. The error level was taken as 0.05.

All subjects gave their informed consent for inclusion before participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Cumhuriyet University ethics committee (decision no: 2019-03/02, date: 19.03.2019).

Results

The mean age of 87 patients included in the study was 64.4 (±7.7). The mean PSA value was 12.31 (±11.6). Mean prostate volume was 59.46ccs (±21.7). Twelve of the patients (13.8%) had previously undergone TRUS-Bx. 22 patients (25.3%) were diagnosed with diabetes mellitus. The pathological result of 22 patients (25.3%) was malignant (Table 1).

In rectal swab cultures, *Escherichia coli* in 77 patients (88.5%), *Staphilococcus epidermidis* in 6 patients (6.8%), *Klebsiella pneumoniae* in 1 patient (1.1%), *Enterobacter cloacae* in 1 patient (1.1%), *Corynebacterium* in 1 patient (1.1%), *Enterococcus faecalis* in 1 patient (1.1%) were grown (Table 2).

Antibiogram susceptibilities of rectal swabs were evaluated according to FQ, TMP-SMX, and fosfomycin. FQ susceptibility was observed in 78 (89.7%) patients, fosfomycin susceptibility was observed in 85 (97.7%) patients, and TMP-SMX sensitivity was observed in 78 (89.7%) patients (Table 3).

Table 1. Mean age, PSA, and prostate volumes and percentage of diagnosis of diabetes mellitus, and malignant pathology	
	Number (± standard deviation), (%)
Age	64.4 (±7.7)
PSA	12.31 (±11.6)
Prostat volume (cc)	59.46 (±21.7)
Diabetes mellitus	22 (25.3%)
Malignant pathology	22 (25.3%)
PSA: Prostate-spesific antigen	

Table 2. Bacteria growth in rectal swab culture		
	Number	**%**
Escherichia coli	77	88.5
Staphilococcus epidermidis	6	6.8
Klebsiella pneumoniae	1	1.1
Enterobacter cloacae	1	1.1
Corynebacterium	1	1.1
Enterococcus faecalis	1	1.1

Table 3. Antibiogram susceptibilities		
	Sensitive patient (n)	**%**
Fluoroquinolone	78	89.7
Trimethoprim - sulfamethoxazole	78	89.7
Fosfomycin	85	97.7

No statistically significant relationship was found between FQ resistance and patients' age, diagnosis of diabetes, and malignancy of pathology ($p>0.05$). Of 9 patients with FQ resistance, 8 were Fosfomycin sensitive and 6 were TMP-SMX sensitive.

Urinary system infection, sepsis, severe hematuria, and rectal bleeding were not observed in any patient.

Discussion

TRUS-Bx is a method that is frequently used in the urology outpatient clinic for the diagnosis of prostate cancer and is considered safe. Despite bowel cleansing and antibiotics used, it can cause complications such as asymptomatic bacteriuria, urinary tract infections, and sepsis.

With the increasing use of antibiotics, multi-drug resistant (MDR) infections have become an important health problem. Recently, the number of infective complications after TRUS-Bx has been increasing worldwide. It has been observed that 50% resistance has developed in some regions to FQs used for prophylactic purposes (14). It is recommended to perform transperineal biopsies after surgical cleaning of the perineal skin due to the lower risk of infection (15).

To prevent urinary infections from developing after TRUS-Bx due to MDR infections, giving antibiotic prophylaxis according to the results of rectal swab culture taken before the procedure will reduce the morbidity and mortality rates that may occur due to urinary infections, as well as reduce the treatment costs resulting from infectious complications.

In the study of Cook et al. (16), infectious complications were seen at a rate of 0.41% in the group of 244 patients who were given appropriate antibiotics according to the swab, whereas infectious complications were observed at a rate of 2.65% in the control group of 264 patients, and the difference was significant between the two groups ($p<0.05$). In this study, many bacteria, especially *Escherichia coli*, were produced in rectal swab cultures examined before TRUS-Bx. In the antibiotic susceptibility tests, FQ sensitivity was 89.7%, fosfomycin sensitivity was 97.7%, and TMP-SMX sensitivity was 89.7%. None of the 87 patients who underwent TRUS-Bx had complications, such as urinary tract infection, fever, and sepsis. This may be due to the success of prophylactic antibiotics applied in our clinic and the low level of antibiotic resistance in the region.

Antibiotic prophylaxis by performing a rectal swab culture before the procedure is an ideal method for widespread antibiotic resistance. In the study of Knaapila et al. (17), the rate of antibiotic-resistant bacteria in rectal swab culture was 11%, while the rate of infectious complications was 0.7%. While Fosfomycin resistance was not found in the study, FQ resistance was detected in 12% of the patients (17). In our study, 10.3% resistance to the antibiotic used was observed according to the rectal swab culture, but no infectious complications were observed. In our study, fosfomycin resistance was seen as 2.3%, and although fosfomycin is a good option for prophylaxis, it has also been shown that fosfomycin resistance may occur.

In the study by Taylor et al. (15) on 457 male patients, infectious complications were observed at a significantly lower rate ($p=0.12$) in the group that received targeted antimicrobial prophylaxis by taking rectal swab compared with the group that received empirical prophylaxis (16). Because of the cost of infectious complications caused by FQ-resistant organisms, the targeted antibiotic prophylaxis group was found to be more cost-effective than the empirical prophylaxis group. In our study, all prophylaxis were empirical FQ and no infection was observed. The use of empirical FQ seems to be cost-effective, but the small sample size of our study with 87 patients should also be considered.

Although different antibiotic prophylaxis methods are discussed in today's medical practice due to FQ resistance, rectal swab removal from patients before TRUS-Bx is a method that prolongs the procedure and involves difficulties in applying for the patient. Although FQ sensitivity is as high as 89.7% in our region, it is still a cost-effective prophylaxis method.

Study Limitations

There are several limitations to this study. The most important one is the limited number of patients.

Another limiting factor is that direct quinolone prophylaxis was used, not prophylaxis for the culture results obtained before biopsy. Although prophylaxis was not changed according to the culture results, no infective complications were observed after biopsy.

Conclusion

Although different antibiotic prophylaxis methods are discussed due to FQ resistance in today's medical practices, FQ sensitivity

continues at a high rate of 89.7% in our region and still seems to be a viable prophylaxis method.

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Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Cumhuriyet University ethics committee (decision no: 2019-03/02, date: 19.03.2019).

Informed Consent: Informed consent was obtained from each patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.A., İ.E.E., C.Ö., S.A.B., Design: A.A., A.F.V., Supervision: A.A., İ.E.E., E.K., Data Collection or Processing: A.Ö., A.F.V., Analysis-Interpretation: A.A., İ.E.E., Literature Review: H.S., M.H., S.A.B., Writing: H.S., A.A., C.Ö., S.A.B., Critical Review: H.S., A.A., M.H., E.Ko., Funding: A.Ö., E.K., E.Ko.

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The Effect of Delay in Diagnosis and Treatment Process on Recurrence and Progression of Patients with Non-Muscle-Invasive Bladder Cancer During The COVID-19 Pandemic

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Abstract

Objective: The coronavirus disease-2019 (COVID-19) pandemic caused significant delays in the diagnosis and treatment of non-muscle invasive bladder cancer (NMIBC), like many diseases. We investigated the effect of delays due to the COVID-19 pandemic on oncological outcomes in NMIBC.

Materials and Methods: The patients diagnosed and followed up with primary bladder cancer between October 2017 and August 2022 were analyzed retrospectively. Patients were divided into groups the pre-COVID-19 and COVID-19 periods.

Results: A total of 93 patients were included, 54 (58.1%) in the pre-COVID-19 and 39 (41.9%) in the COVID-19 group. The median time from symptoms to diagnosis (p=0.002), time from diagnosis to transurethral resection of the bladder tumor (TUR-BT) (p=0.001), the time to re-TUR-BT (p<0.001) and time to adjuvant therapy (p=0.004) were significantly longer in the COVID-19 period. The maintenance bladder instillation rates were significantly lower in the COVID-19 period (p=0.028). The progression rates were similar in both periods (p=0.347), and the recurrence rate was significantly higher in the COVID-19 period (p=0.041). Recurrence-free survival (RFS) was significantly lower in the pre-COVID-19 period (p=0.024). In multivariate analysis, time from symptoms to diagnosis (p=0.030) and time to adjuvant therapy (p=0.010) were independent predictors of recurrence.

Conclusion: NMIBC patients in the COVID-19 era had worse RFS outcomes. Especially with a delay of >7.5 weeks from symptoms to diagnosis and a delay of >3.5 weeks to adjuvant therapy, recurrence rates increase significantly.

Keywords: Bladder cancer, COVID-19, delay, recurrence, progression

Introduction

Bladder cancer (BC) is the sixth most frequent cancer in men globally. Almost 75% of BC patients have non-muscle invasive bladder cancer (NMIBC) at diagnosis (1). Although it has better oncologic outcomes than muscle-invasive bladder cancer (MIBC), recurrence rates of up to 60% and progression rates of 10-20% have been reported in the first year (2). Therefore, following transurethral resection of the bladder tumor (TUR-BT), appropriate risk groups should be determined together with histopathological confirmation and a risk group-specific follow-up and treatment scheme should be applied (3).

It has been shown that delays in diagnosis and initiation of treatment in many fast-growing cancer types adversely affect the prognosis (4). In MIBC, a delay of more than three months without neoadjuvant chemotherapy between TUR-BT and radical cystectomy adversely affects survival (5). Additionally, in very high-risk (HR) NMIBC patients, early radical cystectomy significantly improved oncological outcomes (6). In some retrospective studies, it has been shown that the prolongation of the time from symptoms to diagnosis adversely affects oncological outcomes (7).

In early 2020, the coronavirus disease of 2019 (COVID-19) emerged and the World Health Organization declared it a pandemic on March 11, 2020. The pandemic process has adversely affected the functioning of healthcare systems around the world. Many clinicians have been assigned to the management processes of COVID-19 patients outside their speciality. Due to both patients' fear of possible transmission of COVID-19 and the lack of adequate clinicians in outpatient clinics

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other than COVID-19, delays occurred in the management of numerous diseases except COVID-19, especially among malign diseases. Similarly, delays occurred in the diagnosis and treatment processes of many BC patients.

The current study evaluated the impact of COVID-19 pandemic-related delays in NMIBC diagnosis and treatment on oncological outcomes.

Materials and Methods

After the Ethics Committee of Siirt University approval (decision no: 2022/04.14, date: 26.04.2022), patients diagnosed with BC in our clinic were analyzed retrospectively. The patients diagnosed with primary BC between March 2020 and August 2022 and followed up during this period were determined as the COVID-19 group. To provide a symmetrical working time interval, patients diagnosed with primary BC between October 2017 and March 2020 and followed up during this period were determined as the pre-COVID-19 group. We established 23, 2020, as the threshold date, when the first COVID-19 case was seen in Turkey. Patients with non-urothelial cancer, less than the one-year follow-up, variant histology, and missing data were excluded. Additionally, patients with MIBC were excluded from the survival analysis.

After the diagnosis of the bladder tumor by imaging or cystoscopy, TUR-BT operations were performed by specialist urologists and the tissues taken from the bladder were analyzed by specialist pathologists. All patients with pT1 underwent re-TUR-BT as to the recommendation (8). Due to the lack of intravesical chemotherapy drugs in our region, intravesical chemotherapy is not applied for both early postoperative and intermediate risk (IR) patients. Intravesical Bacilli Calmette-Guerin (BCG) therapy is administered to patients with intermediate and HR-NMIBC. In HR-NMIBC, intravesical BCG included an induction course (six instillations per week) followed by full dose maintenance (three instillations per week at 3, 6, 12, 18, 24, 30, and 36 months). In IR-NMIBC, maintenance therapy is administered for up to one year following induction. The follow-up was conducted with cystoscopy and urine cytology at 3 and 6 months, then every 3-6 months for 2 years, and afterwards according to management modified for the risk of recurrence.

The primary endpoint was to reveal the delays caused by the COVID-19 pandemic in the diagnosis and treatment of BC. The secondary endpoint was the impact of delays in diagnosis and treatment on recurrence-free survival (RFS) and progression-free survival (PFS) of NMIBC patients. Recurrence was defined as a histologically confirmed tumor on follow-up cystoscopy. During the follow-up, the histopathological elevation of any grade (low to high) or grade (Ta to T1 or any T2) was considered progression.

Statistical Analysis

The IBM SPSS Statistics Version 20.0 statistical software package was used. The normality of continuous variable distribution was confirmed with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were expressed as numbers and percentages, and continuous variables were summarized as median and interquartile ranges. χ^2-test or Fisher's Exact was used to compare categorical variables between the groups. The Mann-Whitney U test was used to compare continuous variables between the two groups. RFS and PFS analyses were performed using the Kaplan-Meier method and a log-rank test. Multivariable Cox proportional-hazards models were used to determine whether parameters related to delay in diagnosis and treatment during the COVID-19 period are possible predictive factors for RFS. The receiver operator characteristic (ROC) curve analysis was used to determine the optimal threshold via the area under the curve (AUC). Youden's curve index was used to determine an optimum cut-off value of time from symptoms to diagnosis and time to adjuvant therapy for predicting RFS. The statistical level of significance for all tests was considered 0.05.

Results

Patients' Characteristics

Perioperative characteristics of patients diagnosed with primary BC in the entire study cohort are divided by the COVID-19 period. Accordingly, the number of patients who underwent primary TUR-BT was 54 (58.1%) in pre-COVID-19 and 39 (41.9%) in COVID-19. The median age of the patients in both periods was similar (68.0 vs 67.0 years, p=0.128). Patients in both groups were similar in terms of gender distribution (p=0.539), smoking status (p=0.969), Charlson Comorbidity Index (p=0.978), and presenting symptoms (p=0.923) (Table 1).

As tumor-specific parameters; T-stage (p=0.355), grade (p=0.272) and size (p=0.697) were similar in both groups. According to the European Association of Urology (EAU) NMIBC prognostic factor risk grouping, in the pre-COVID-19 period, 5 (9.8%) patients were in the low-risk, 11 (21.6%) patients in the IR, and 35 (68.6%) patients in the HR group, similarly, in the COVID-19 period, 2 (5.9%) patients were in the low risk, 9 (26.5%) patients in the IR, and 23 (67.6%) patients in the HR group (p=0.744). The median time from symptom to diagnosis was significantly longer in the COVID-19 period (5.0 vs 7.0 weeks, p=0.002). Also, the median time from diagnosis to TURBT was significantly longer during the COVID-19 period (2.0 vs 3.0 weeks, p=0.001). Although re-TURBT rates were similar in both periods (55.6% vs 38.5%, p=0.104), the time to re-TURBT was significantly longer in the COVID-19 period (3.0 vs 5.0 weeks, p<0.001). Adjuvant bladder instillation rates were similar in both periods (75.9% vs 61.5%, p=0.136), but the median time to adjuvant therapy was significantly longer in the COVID-19 period (3.0 vs 3.5 weeks, p=0.004). The maintenance bladder instillation rates were significantly lower in COVID-19 period (56.5% vs 31.5%, p=0.028) (Table 1).

Oncological Results and Survival Analysis

There were eight pathological ≥T2 patients, three in the pre-COVID-19 period and five in the COVID-19 period. These eight patients were excluded from the oncological outcomes and survival analyses. Even though the progression rates were similar in both periods (5.9% vs 11.8%, p=0.347), the recurrence rate was significantly higher in the COVID-19 period (13.3% vs 33.3%, p=0.041) (Table 1). RFS was significantly lower for the pre-COVID-19 period (p=0.024; Figure 1A). PFS was similar between pre-COVID-19 and COVID-19 periods (p=0.147; Figure 1B).

Table 1. Demographic, clinical and oncological data of pre-COVID 19 and COVID-19 NMIBC patients				
	Pre-COVID 19 (n=54)	**COVID-19 (n=39)**	**Test statistic**	**p-value**
Age (years), median (IQR)	68.0 (7.0)	67.0 (9.25)	Z=-1.524	0.128
Gender Female Male	 11 (20.4) 43 (79.6)	 6 (15.4) 33 (84.6)	X^2=0.377	0.539
Smoking status Never Active Former	 14 (25.9) 26 (48.2) 14 (25.9)	 11 (28.2) 18 (46.2) 10 (25.6)	X^2=0.064	0.969
CCI score 0-2 ≥3	 22 (40.7) 32 (59.3)	 16 (41.0) 23 (59.0)	X^2=0.001	0.978
Symptoms Hematuria Other	 42 (77.8) 12 (22.2)	 30 (76.9) 9 (23.1)	X^2=0.009	0.923
Tumor focality Unifocal Multifocal	 44 (81.5) 10 (18.5)	 30 (76.9) 9 (23.1)	X^2=0.289	0.591
Tumor T-stage Ta T1 ≥T2	 19 (35.2) 32 (59.3) 3 (5.6)	 10 (25.6) 24 (61.5) 5 (12.8)	X^2=2.070	0.355
Tumor grade Grade 1 Grade 2 Grade 3	 5 (9.3) 16 (29.6) 33 (61.1)	 7 (17.9) 7 (17.9) 25 (64.1)	X^2=2.607	0.272
Tumor size <3 cm ≥3 cm	 34 (63.0) 20 (37.0)	 23 (59.0) 16 (41.0)	X^2=0.152	0.697
Concomitant cis	5 (9.3)	5 (12.8)	X^2=0.299	0.584
EAU risk stratification Low Intermediate High	 5 (9.8) 11 (21.6) 35 (68.6)	 2 (5.9) 9 (26.5) 23 (67.6)	X^2=0.592	0.744
Time from symptoms to diagnosis (wk), median (IQR)	5.0 (2.5)	7.0 (4.0)	Z=-3.165	0.002
Time from diagnosis to TURBT (wk), median (IQR)	2.0 (1.0)	3.0 (2.0)	Z=-3.391	0.001
Re-TURBT	30 (55.6)	15 (38.5)	X^2=2.650	0.104
Time to Re-TURBT (wk), median (IQR)	3.0 (1.0)	5.0 (2.0)	Z=-4.512	<0.001
Adjuvant bladder instillation	41 (75.9)	24 (61.5)	X^2=2.228	0.136
Time to adjuvant therapy (wk), median (IQR)	3.0 (1.0)	3.5 (3.0)	Z=-3.676	0.004
Maintenance installations	26 (56.5)	10 (31.3)	X^2=4.850	0.028
Follow-up period (wk), median (IQR)	61.0 (22.5)	60.0 (11.0)	Z=-1.767	0.077
Recurrence	7 (13.7)	10 (33.3)	X^2=4.241	0.039
Progression	3 (5.9)	3 (8.8)	X^2=0.934	0.334

COVID-19: Coronavirus disease-2019, NMIBC: Non-muscle invasive bladder cancer, IQR: Interquartile range, TURBT: Transurethral resection of the bladder, CCI: Charlson Comorbidity Index, EAU: European Association of Urology

A Cox proportional hazards model was used to assess delays in diagnosis and treatment due to the COVID-19 era as possible predictors of RFS and PFS. In multivariate analysis, time from symptoms to diagnosis [HR: 2.238, 95% confidence interval (CI): 1.083-4.622; p=0.030] and time to adjuvant therapy (HR: 4.048, 95% CI: 1.390-11.793; p=0.010) were independent predictors of RFS (Table 2).

In the ROC curve analysis for RFS, the optimal cut-off values for the time from symptoms to diagnosis and time to adjuvant therapy were 7.5 weeks and 3.5 weeks, respectively. The AUC were 0.879 (95% CI: 0.783-0.974) and 0.864 (95% CI: 0.738-0.991) for the time from symptoms to diagnosis and time to adjuvant therapy, respectively. The highest sensitivity and specificity were 0.875 and 0.735 for the time from symptom to diagnosis, 0.813 and 0.796 for the time to adjuvant therapy (Figure 2).

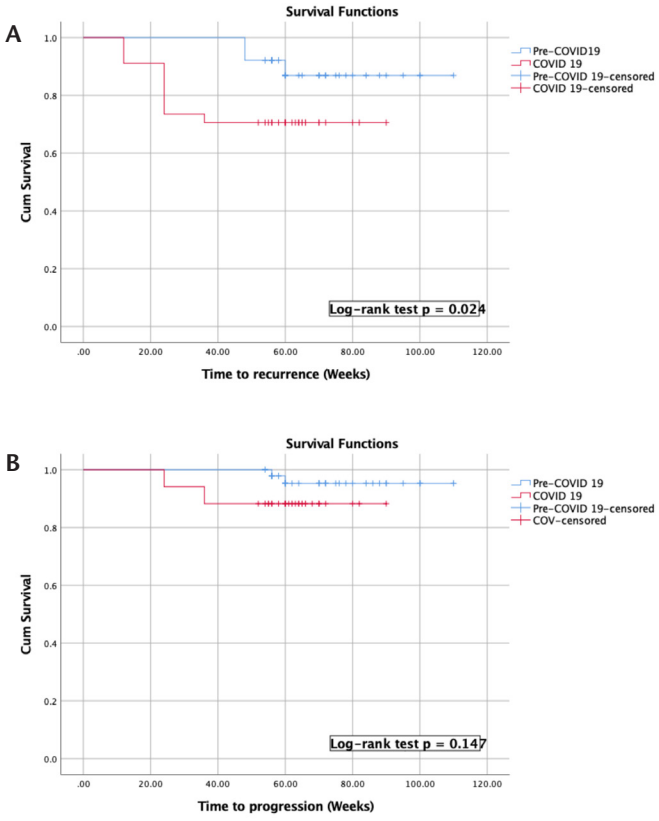

Figure 1. (A) Kaplan-Meier curve of RFS for NMIBC patients pre-COVID-19 and COVID-19 period. (B) Kaplan-Meier curve of PFS for NMIBC patients pre-COVID 19 and COVID-19 period

RFS: Recurrence free-survival, NMIBC: Non-muscle invasive bladder cancer, COVID-19: Coronavirus disease-2019, PFS: Progression free-survival

Table 2. Multivariable Cox regression analysis predicting RFS in patients with NMIBC

	RFS		p-value
Variables	Adjusted* hazard ratio	95% CI	
EAU risk group Intermediate High	 Reference 1.661	 0.480-5.743	 **0.423**
Time from symptoms to diagnosis	2.238	1.083-4.622	**0.030**
Time from diagnosis to TURBT	1.207	0.254-5.743	**0.813**
Time to Re-TURBT	0.538	0.145-2.002	**0.355**
Time to adjuvant therapy	4.048	1.390-11.793	**0.010**
Maintance instillations	0.241	0.018-3.251	0.284

*Adjusted for age, gender and Charlson Comorbidity Index, EAU: European Association of Urology, TURBT: Transurethral resection of the bladder, RFS: Recurrence free-survival, CI: Confidence interval, PFS: Progression free-survival
There was no recurrence in the EAU low risk group, so only IR and HR groups were used in the cox regression analysis. No analysis was performed for progression because of the low number of events

RFS was significantly lower for the time from symptoms to diagnosis >7.5 weeks (p<0.001; Figure 3A) and time to adjuvant therapy >3.5 weeks (p<0.001; Figure 3B).

Discussion

Study data reveal that the COVID-19 pandemic has negative impacts on the results of RFS by causing delays in the time from symptoms to diagnosis and time to adjuvant therapy of NMIBC patients. A delay of >7.5 weeks for the time from symptoms to diagnosis was associated with worse RFS outcomes. Similarly, >3.5-week delay of time to adjuvant bladder instillation had worse RFS results.

As seen in our study, the COVID-19 pandemic has caused significant delays in diagnosis and treatment processes. The EAU has suggested supplementary guidelines to assist clinicians in daily practice to reduce the potential impact of pandemic-related delays (9). EAU divided NMIBC patients into four priority groups based on clinical status: low priority group (small papillary recurrences <1 cm and/or Ta/1 history of low-grade BC) that should be delayed for 6 months; intermediate priority group (BC >1 cm), which should not be delayed for more than 3-4 months; high priority group (HR-BC or macroscopic hematuria) that should not be delayed for more than 6 weeks. Additionally, cases such as very HR-NMIBC or BCG failure are in the emergency priority group and interventions that cannot be postponed, such as emergency radical cystectomy, have been recommended (9).

Notably fewer BC diagnoses were made in our study cohort during the COVID-19 pandemic than before the pandemic in a similar period (54 vs 39 patients). In parallel, there were significant delays in time from symptoms to diagnosis (5.0 vs 7.0 weeks), time from diagnosis to TURBT (2.0 vs 3.0 weeks), time to Re-TURBT (3.0 vs 5.0 weeks) and time to adjuvant therapy (3.0 vs 3.5 weeks) during the pandemic period. Additionally, a significant reduction was observed in maintenance bladder instillation of BCG (56.5% vs 31.3%). In a study conducted with 2,591 patients from 27 different centres in Italy, fewer patients were diagnosed with BC by primary TUR-BT during the pandemic period compared with the pre-COVID-19 period (59.2% vs 40.8%) (10). Additionally, they reported that the time of diagnosis to TURBT (65 vs 52 days) and the median time to secondary resection (55 vs 48 days) were significantly longer during the COVID-19 period (10). They also revealed that the rate of maintenance treatment decreased significantly during the pandemic period (79.5% vs 60.4%) (10). The declining activity of clinicians in small or medium-capacity cities like our region, may have further contributed to these delays. As our hospital is the only well-equipped health centre in the city, the vast majority of inpatients during the pandemic were COVID-19 cases for a long time. As demonstrated by Naspro and Da Pozzo (11), the appointment of health personnel in newly opened COVID-19 units and the resulting decrease in effective staff caused serious disruptions in ordinary clinical and surgical applications. Apart from the changes in the health system related to the pandemic, low education and socioeconomic condition, and deficiency of knowledge about symptoms such as cancer-related hematuria or denial of the patient, although alarming, may cause delays in the diagnostic process (7).

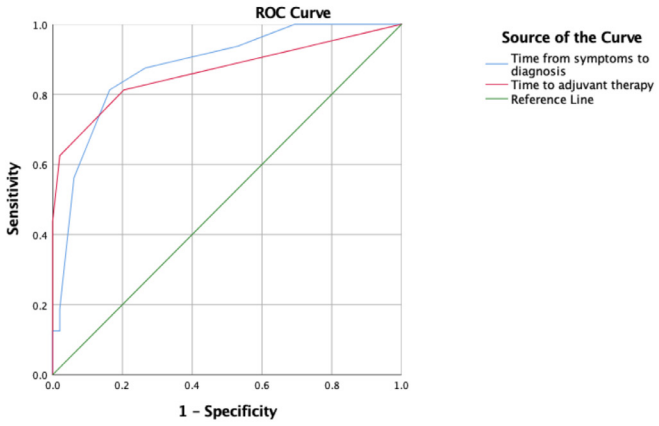

Figure 2. The ROC curve analysis of the time from symptoms to diagnosis and time to adjuvant therapy for recurrence-free survival

ROC: Receiver operating characteristic

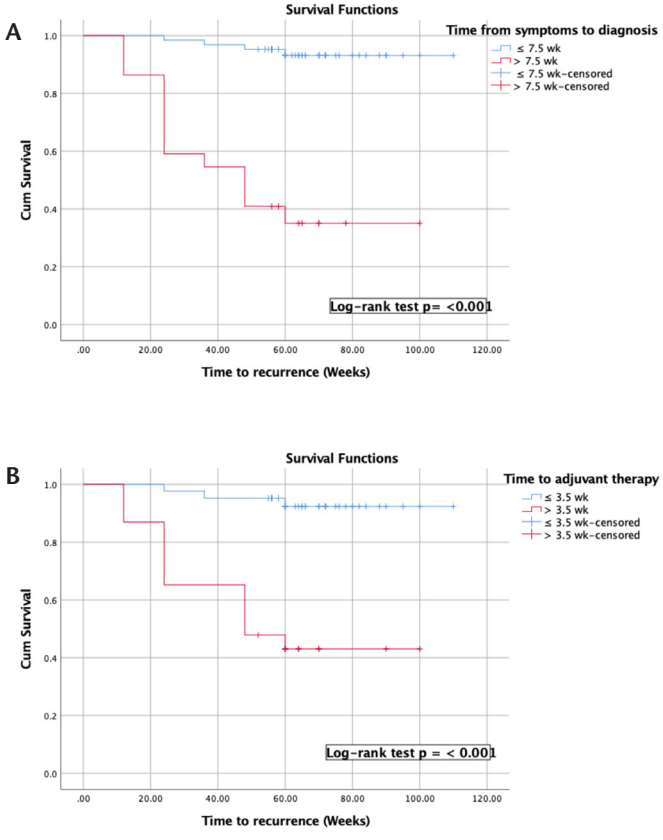

Figure 3. (A) Kaplan-Meier curve of recurrence-free survival probability according to time from symptom to diagnosis in NMIBC patients. (B) Kaplan-Meier curve of recurrence-free survival probability according to time to adjuvant therapy in NMIBC patients

NMIBC: Non-muscle invasive bladder cancer

It has been shown that shortening the duration of the initiation of symptoms and the first examination in BC improves disease-specific survival (7). In their study of 1,537 BC patients, Wallace et al. (12) reported a mean delay of 68 days in transitioning from a general practitioner (GP) to TUR-BT. They reported that solely the delay from symptom onset to GP was associated with poor survival; but, all pathological stages of BC (pTa, pT1, ≥ pT2) were included (12). In a large literature review, Fahmy et al. (13), associated delays in BC treatment with worse outcomes. In a study by Ourfali et al. (7), which examined 434 NMIBC patients, delays of >6 weeks to the first TUR-BT in IR and HR patients, and more than 7 weeks to the first instillation in IR patients are associated with increases in the risk of recurrence. They also found that time to re-TUR-BT of more than 7 weeks is also associated with a higher risk of progression (7). In our study, time from symptoms to diagnosis (HR: 2.238) and time to adjuvant therapy (HR: 4.048) were determined as independent predictive factors for RFS. Since the number of events was not sufficient, further survival analyses related to progression could not be performed. We found that a delay of >7.5 weeks for the time from symptoms to diagnosis and >3.5 weeks from time to adjuvant intravesical BCG therapy was associated with worse RFS outcomes. However, Ourfali et al. (7) found EAU risk classification as an independent predictive value for recurrence in multivariate analysis (HR: 1.32), but it did not reach a significant level in our cohort. The lower rate of IR patients in our cohort (23.5% vs 38.7%) and the fact that we used BCG as an intravesical treatment in the IR group may explain this result.

When 3-year maintenance of intravesical BCG therapy was compared with 1-year maintenance, it was reported that there was no effect on progression or death, but a significant difference in the recurrence rate (14). In our study, we observed that there is a significant decrease in the rate of maintenance treatment during the pandemic process (56.5% vs 32.5%). There were disruptions in maintenance treatments due to the limitation in outpatient practices due to the pandemic and the BCG shortage. However, maintenance BCG therapy could not be an independent predictive value for RFS, probably because of the short follow-up period of our study.

Study Limitations

To our knowledge, this is the first research to examine the impact of delays due to the COVID-19 pandemic in the diagnosis and treatment of NMIBC on recurrence and progression. However, some of the limitations are noteworthy. Firstly, this was a retrospective study with a limited number of patients in a single centre. Because of the insufficient number of patients, we could not perform subgroup analyzes within the EAU risk groups. Secondly, the effect of delay in diagnosis and treatment of NMIBC on specific survival could not be evaluated because of insufficient follow-up and the small number of patients experiencing disease progression. Additionally, due to the lack of intravesical chemotherapy agents in our institution, the use of only BCG therapy in IR patients and the inability to give a single dose instillation in the low-risk group may be another limitation. To better grasp the act of these disruptions in the diagnosis and treatment of NMIBC, we believe that long-term follow-up of these patients will yield more accurate results.

Conclusion

The COVID-19 pandemic has caused significant delays in the diagnosis and treatment process of NMIBC, in many cancer types. Due to these delays, NMIBC patients in the COVID-19 era had worse RFS outcomes. Especially with a delay of >7.5 weeks from symptoms to diagnosis and a delay of >3.5 weeks to adjuvant therapy, recurrence rates increase significantly. To prove our findings multicenter studies with longer follow-ups are necessary.

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Ethics

Ethics Committee Approval: After the Ethics Committee of Siirt University approval (decision no: 2022/04.14, date: 26.04.2022), patients diagnosed with BC in our clinic were analyzed retrospectively.

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: F.O., E.D., Concept: F.O., Design: F.O., Data Collection or Processing: E.D., Analysis-Interpretation: F.O., Literature Search: F.O., E.D., Writing: F.O.

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Case Report

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Bladder Explosion, a Serious Complication Occurred During Transurethral Resection of Prostate

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Abstract

A case of bladder explosion with three wide ruptures that occurred during transurethral resection of prostate (TURP) is being reported. Immediate open surgical primary repair of bladder rupture can be obtained without any complication. On the review of the literature, it was found that a limited number of cases have been reported. The main mechanism has been reported as the explosion of the gases, which was produced during electro cauterization and mixed with air oxygen from the atmosphere. A bladder explosion is a rare complication, which can occur during a very common surgical procedure in urological practice. Urologist should alert of the sounds that can be heard during TURP and organ rupture possibility should always be kept in mind as immediate surgical repair is critical for the patient and surgeon.

Keywords: TURP, bladder explosion, bladder injury

Introduction

Bladder eruption is a very rare complication during transurethral resection of prostate (TURP) procedure. There are very few case reports in the literature. However, although it is a rare complication, it can be an important life-threatening situation. Urologists should always be very careful and eliminate the possible complication urgently.

Case Report

This is a retrospectively evaluated case report of a 68-year-old male patient who was operated because of recurrent urinary bleeding and pronounced difficulty in urinating. TURP operation was applied to the patient without any obvious pathology that could cause bleeding in his bladder on cystoscopy. When approaching the termination of the operation after about half an hour period, a sudden booming sound was heard simultaneously by the coagulation procedure for a small bleeding focus at 11 o'clock and we observed that the endoscopic image suddenly disappeared. The patient was considered as having a bladder perforation and was immediately under general anesthesia open surgical exploration through a suprapubic "Pfannenstiel" incision was performed. We observed that the bladder had been burst by tearing a full floor from 3 different regions and the peritoneum was opened, with luck there was no pathology of the intestines. The bladder and peritoneum ruptures were primary repaired. During the postoperative follow-up, the patient was discharged from the clinic without any problem.

Discussion

The first bladder eruption was reported by Cassuto in 1926 after TURP (1). Bladder injuries that may occur can range from mild mucosal tears to severe tears such as extraperitoneal or intraperitoneal bladder ruptures.

In all reported cases, an explosive sound was reported to be heard almost at the end of surgery and mostly when cauterizing particularly the anterior prostatic fossa. One of the important points is that nearly in all cases intraperitoneal injury (2).

In the etiology of the explosion, it is emphasized that the gases that released during the diathermic surgery in human tissue and accumulated in the bladder dome come into contact with oxygen that is present in the ambient air. Especially the combination of hydrogen and oxygen is critical. It is anticipated that the electric current formed in the cutting loop during diathermy triggered the explosion of the existing gas accumulation (3).

With *in vitro* experiments, Ning et al. (1) has shown that basically 40-50% of hydrogen is released during electrocautery. It has been proved that the contact of the exposed hydrogen with the outer oxygen reveals the explosive potential (4). Hansen and Iversen (5) showed that in *in vitro* and *in vivo* TURP processes, 65% hydrogen, 19% oxygen and to other residual

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hydrocarbons (methane, ethylene, ethane, propylene, propane and butane) were released, and the mixture with the outdoor air increased the probability of explosion. We emphasized that the operation time is parallel to the explosion probability of the accumulated gas (5). Viville et al. (6) also emphasized that the risk is higher in the use of continuous current resectoscope and in surgeries using high energy.

As mentioned in the previous studies, exploration and bladder repair was performed immediately in most cases with open surgery. Just in two cases, laparoscopic surgery was preferred (2). There was no significant difference in the outcome between the two approaches (2).

Conclusion

Various degrees of bladder injuries can be encountered in all TURP surgeries.

In TURP surgery, it is important to keep the operation time short, not to allow gas accumulation inside the bladder as much as possible, to pay attention not to give air into the bladder during the use of evaporator and to avoid high energy.

Observing the above rules in operating practice may decrease the likelihood of complications. Even though, it is critical for the urologists to be careful about the explosion sounds and be aware of the possible complications.

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Ethics

Informed Consent: Retrospective study.

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Case Report

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Xanthogranulomatous Cystitis: A Rare Clinical Case

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Abstract

Xanthogranulomatous cystitis is a rare benign chronic inflammatory disease of unknown etiology. We report a 77-year-old male whose treatment is complete endoscopic resection. Patient was asymptomatic at three months follow-up after treatment.
Keywords: Cystitis, macrophages, urinary bladder neoplasms

Introduction

Xanthogranulomatous changes have been reported at multiple sites in the urinary system (1), with the kidney being the most common organ. Histologically, there are multinucleated giant cells, lipid-laden macrophages, and cholesterol clefts. Although, xanthogranulomatous cystitis (XC) is an uncommon, chronic, benign inflammatory disease of unknown etiology and was first defined in 1932 (2). It is usually diagnosed as a papillary lesion in the bladder, but lateral wall enrolment is very rare. In this case report, we want to present a patient who had XC because of the pathology of the transurethral resection performed for the papillary lesion on the lateral and posterior bladder wall.

Case Report

A 77-year-old male hospitalized with urgency, frequency, dysuria, hematuria symptoms for nine months period. He has been with urethral catheterized for 6 months due to lower urinary tract obstructive symptoms. The patient was immobile because of paraplegia for 3 years. Hematological and biochemical examinations were normal. Urinalysis showed 23 leukocytes and 580 erythrocytes per high power field. Urine culture was sterile. Urinary ultrasonography revealed diffuse bladder wall thickness (13 mm) and echogenic foci in the posterior wall. Abdomen computed tomography revealed diffuse of the bladder wall thickening, papillary lesions on the right lateral and posterior wall of the bladder and a giant fecaloma in the rectum (Figure 1).

During the cystoscopy, multiple polypoid formations with a cotton-like appearance were observed on the bladder posterior and right lateral wall (Figure 2) .Complete endoscopic resection was performed; the postoperative course was uneventful.

Inpathological assesment xanthogranulatous macrophage cells were positive for periodic acid schiff mark for calcospherules (Michaelis - Guttman bodies). Acid fast bacteriathe mark was negative. CD68 immunohistochemically stained strongly, however, cytokeratin was negative (Figure 3). According to these findings, the patient was diagnosed with XC. That findings did not support malignancy. The patient was given antibiotic prophylaxis for 3 months. At a follow-up after three months there was no recurrence. Patient consent was obtained for this case report.

Discussion

XC is an extremely rare benign chronic inflammatory disease. The first case was published by Wassiljew in 1932 (2). There are 28 XC cases in the literature and most of the cases were urachal remnants and cysts. There are no specific signs of the disease rather than cystitis like symptoms, abdominal pain, occasional hematuria and umbilical discharge. The importance of XC in the bladder is that these symptoms can be confused with bladder cancer. Also, XC in the bladder with papillary lesions can mimic bladder cancer. Accordingly, it is very important to accurately evaluate the pathological results and diagnose the disease.

The XC etiology has not been clarified yet. There are many theories highlighting immunological disorders (3,4), unusual lipid metabolism (5) and urothelial metaplasia resulting from chronic infection (6). Here, the lesions on the right lateral and posterior wall of the bladder showed that they were not caused

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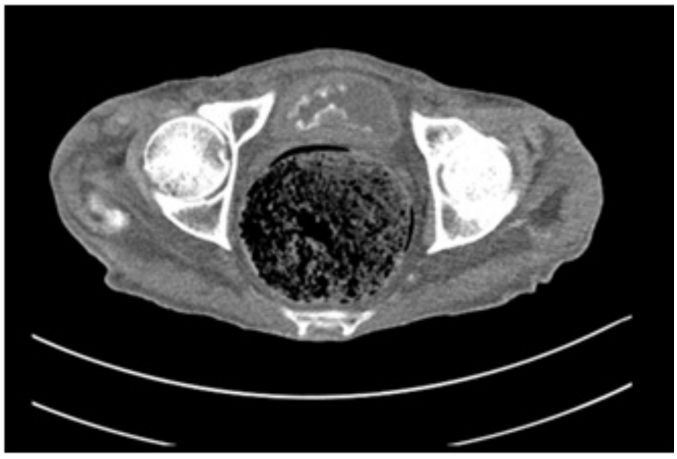

Figure 1. Polypoid masses on bladder right and inferior wall in computerized tomography

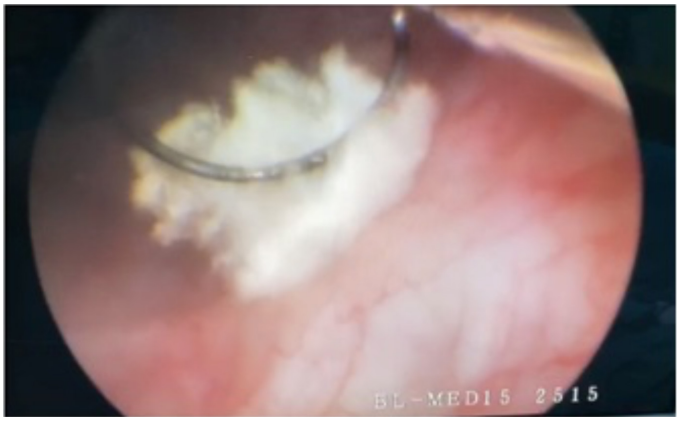

Figure 2. Cystoscopy reveals cotton-like appearance on the floor amd right wall of bladder

by the urachus anomaly. As the patient had a urethral catheter for 6 months, chronic irritation of the catheter may have be in this case.

Conclusion

In the XC of the bladder, medical treatment is unsuccessful therefore conservative treatment is uncommon. Although partial resection was performed 22 cases in the literature, the most effective treatment for small lesions is complete endoscopic resection. The etiology of XC is unclear. Although the urine culture was negatif, give antibiotic may be helpful for preventing the disease.

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

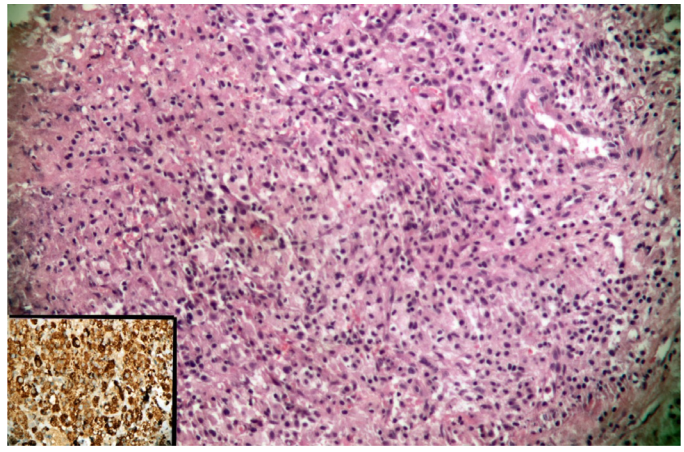

Figure 3. Histological examination of the resection specimen revealed abundant histiocytes and other chonic inflammatory cells consisted of xanthogranulomatous cytitis (H and E stains 200x magnification). Additionally CD68 were diffuse positive in histiocytes (inset-x400 magnification)

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

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

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Ethics

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Authorship Contributions

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Case Report

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Paratesticular Leiomyoma; A Rare Case Report

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Abstract

Paratesticular leiomyomas are rare tumors and originated from the subcutaneous smooth muscles and tunica dartos. Patients usually present with the complaint of a long-standing palpable painless mass and it is important to differentiate it from testicular masses. A 35-year-old male patient presented to our clinic with a palpabl mass, which he has realized since 15 year-old in scrotum that it growth 3-4 times over the last month. Physical examination revealed a palpable solid mass of approximately 3 cm, regular bordered, painless and localized inferiorly in the scrotum. Scrotal Doppler ultrasonography scan showed a 3x2.5 cm solid mass localized inferiorly in the scrotum, which has an internal blood supply. The inguinal exploration was planned due to malignancy risk. When the inguinal exploration was performed, we observed that the paratesticular mass was not connected with the testis. The mass, which was adherent to the scrotal skin, was excised together with the scrotal skin tissue with a safe surgical margin. In the pathology report, it was diagnosed as leiomyoma. The treatment for the vast majority of scrotal masses is radical inguinal orchiectomy. Testis preserving surgical procedures performing is critical for protecting both the fertility and the hormonal level of patients who have benign scrotal masses. Although physical examination suggests malignant neoplasms in patients presenting with a paratesticular mass, it should be kept in mind that benign neoplasms may also be present.

Keywords: Leiomyoma, scrotum, testicular neoplasms

Introduction

Leiomyomas are regular capsulled smooth muscle tumors that grow from the mesenchymal cells (1,2). Scrotal leiomyomas are usually localizated in testis, epididymis, spermatic cord and scrotal skin (2,3). Generally, clinic presentation is an asymptomatic, painless palpable mass in the scrotum (4). we describe in this study the diagnostic and treatment process of a patient who presented with an isolated paratesticular mass, which is rarely seen.

Case Report

A 35-year-old male patient presented to our clinic with a palpabl mass, which he has realized since 15 year-old in scrotum that it growth 3-4 times over the last month. In the patient's history, he is married and he has 4 children. Physical examination revealed a palpable solid mass of approximately 3 cm, regular bordered, painless and localized inferiorly in the scrotum. On palpation that mass is unrelated on testis (Figure 1). The bilateral testes, epidydimes, ductus deferenses and right scrotum skin were normal on physical examination. Scrotal Doppler ultrasonography scan showed a 3x2.5 cm solid mass localized inferiorly in the scrotum, which has an internal blood supply. Serum tumor markers (beta-human chronic gonadotropin, lactate dehydrogenase, alpha-fetoprotein) were within the normal range. The inguinal exploration was planned due to malignancy risk. We performed inguinal oblique incision and dissection; left testis and scrotal mass was found (Figure 2). We observed that the paratesticular mass was not connected with the testis. The mass, which was adherent to the scrotal skin, was

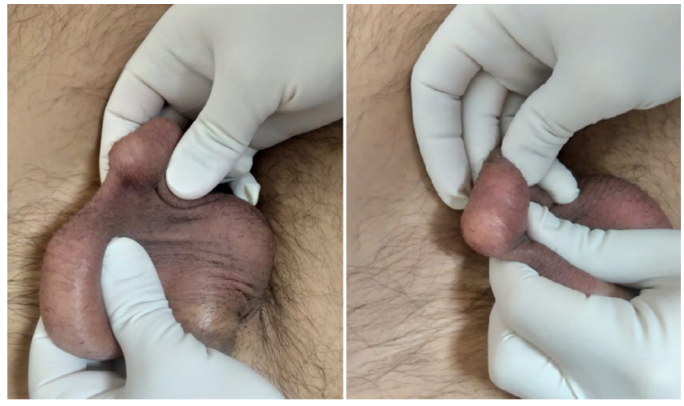

Figure 1. Testis and paratesticuler mass observed on physical examination

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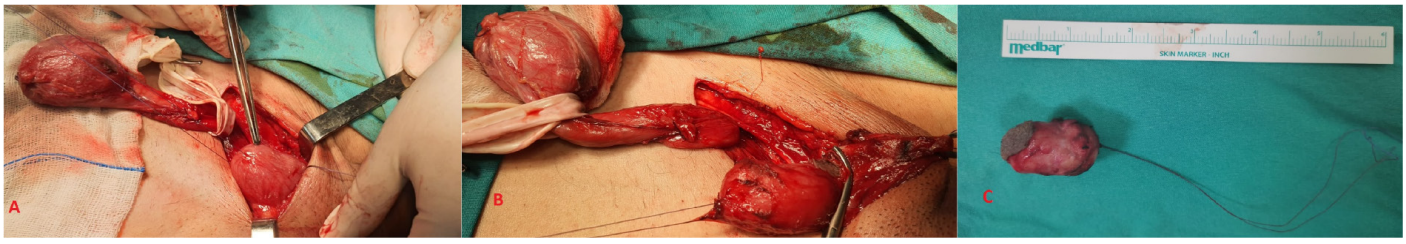

Figure 2. (A-B) Testis and scin-fixed paratesticular mass is seen seperately each other. (A) Mass shown with forceps. (B) Pulled with suture. (C) Paratesticular mass specimen

excised together with the scrotal skin tissue with a safe surgical margin. (Figure 2). The postoperative period was unevenful, and the patient day. In the pathology report there were seen desmin (+), SMA (+), CD34 (-), CD117 (-), Ki67 proliferative index 1% and diagnosed leiomyoma (Figure 3).

Discussion

Paratesticular masses constitute 2% of intrascrotal tumors and these 70% are benign, slow-growth tumors (5). The remaining 30% are malign tumors and the majority are sarcomas. The most common malignant tumor is rhabdomyosarcoma. Benign tumors are; lipoma, adenomatoid tumors, leiomyoma and neurofibroma (4).

As in our case, paratesticular leiomyomas are painless with palpation and long existing scrotal masses. However, it can be seen at all ages, most commonly observed in the fourth and 5th decades (6). In scrotal pathologies; ultrasonography is used as the first-line imaging method in diagnosis cause of it has high sensitivity. Also, it is cost-effective and reachable (7). But in paratesticuler masses, ultrasonography images may be variable and not be specific. Magnetic resonance imaging (MRI) can recognize cysts, lipomas and it can reveal invasion to the surrounding structures, and internal seatures of the lesion (8). MRI is a more sensitive and accurate imaging modality for the detection and localization of leiomyomas (9).

Leiomyomas originated from subcutaneous smooth muscles and tunica dartos. As in our case it can appear a mass that isolated in the paratesticular region, independent of the testis, solitary, growing over the years. According our literature review; there are eight paratesticular leiomyoma cases have been reported and our case is one of the that rarely clinical condition (1,3,7,8,10,11,12,13).

A total excision of the mass should be performed for diagnosis and treatment. If the risk of malignancy is high, it can intraoperative frozen examination applied. Thus situation of malignancy retraction, can perform organ-preserving surgery.

Leiomyomas are macroscopicly encapsulled and regular-bordered masses, as in this study. In Microscopic there are fibrous, hyalinized connective tissues, smooth muscle spindles arranged in bundles to be seen (4). Leiomyomas have characteristic features, which can be recognized than the other paratesticuler masses in immunohistochemical investigations. As our case's pathological evaluation; positive staining for SMA and desmin was important to confirm the diagnosis of leiomyoma. To exclude neurofibroma and schwannoma, S-100 negativity

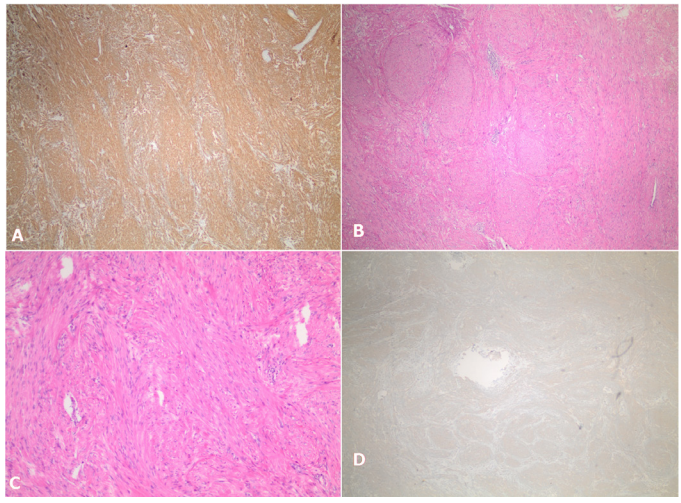

Figure 3. (A) Diffuse desmin (+) cells (x4). (B) Mesenchymal smooth muscle cells composed of spindle cells in Hematoxin-Eosin staining (x4). (C) Mesenchymal smooth muscle cells composed of spindle cells in Hematoxin-Eosin staining (x40). (D) Diffuse SMA (+) cells (x4)

is necessary. Also, low mitotic activity Ki67 (Ki67 proliferation index) is related to leiomyoma (8).

Consequently, in the differential diagnosis of paratesticular leiomyomas, there are both intratesticular and extratesticular benign, malignant tumors. Paratesticular leiomyomas are non-invasive slow-growing rarely observed tumors (5). A differential diagnosis of malignant tumors should be carefully made. MRI and intraoperative frozen examination should be performed if there is in case doubt.

Conclusion

The treatment for the vast majority of scrotal masses is radical inguinal orchiectomy. Testis preserving surgical procedures performing is critical for protecting both the fertility and the hormonal level of patients who have benign scrotal masses. Although physical examination suggests malignant neoplasms in patients presenting with a paratesticular mass, it should be kept in mind that benign neoplasms may also be present.

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Ethics

Ethics Committee Approval: The University of Health Sciences Turkey, Diskapi Yildirim Beyazit Training and Research Hospital Clinical Research Ethics Committee approved the study protocol (decision number: 130/12, date: 07.02.2022).

Informed Consent: Informed consent was obtained from the patient.

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Authorship Contributions

Concept: B.Y.E., Design: B.Y.E., H.M.D., A.E.D., Supervision: H.S., F.Y., Data Collection, or Processing: A.K., Literature Review: A.K., H.S., Writing: B.Y.E., H.M.D., A.E.D., H.S., Critical Review: F.Y.

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