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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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Editorial Office of Bulletin of Urooncology

Nihat Karakoyunlu, MD

Editor in Chief

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

E-mail: bulten@uroonkolojibulteni.com

Tel: +90 (216) 594 52 85

Fax: +90 (216) 594 57 99

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Galenos Yayınevi

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

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1. General Information

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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.

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

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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.

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

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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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

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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.

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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,

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

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

-Abbreviations:

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

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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.

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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.

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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.

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-Introduction

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

-Conclusions

-References

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

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

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-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:

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

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B. Case Reports

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

4) Table(s)

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

4) Table(s)

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6) Acknowledgements Form

D. Literature Review

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

4) Table(s)

5) Figure(s)

6) Acknowledgements Form

E. Editorial Commentary

1) Copyright Transfer and Author Declaration Statement Form

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3) Main text (Text, References)

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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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Bulletin of Urooncology

Editor in Chief

Nihat Karakoyunlu, M.D.
Dışkapı Training and Research Hospital, Department of Urology, Ankara, Turkey

Editor

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Editor

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Editorial Office

Şerif Ali Mevkii, Pakdil Sokak, No: 5, 34775, Yukarı Dudullu, Ümraniye, İstanbul, Turkey
+90 216 594 52 85
+90 216 594 57 99
bulten@uroonkolojibulteni.com

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Testicular and Paratesticular Tumors in Children

Doğancan Dörücü, Çağrı Akın Şekerci, Selçuk Yücel

Marmara University Faculty of Medicine, Department of Urology, İstanbul, Turkey

Abstract

Testicular and paratesticular tumors are rare in the prepubertal age group as compared with the postpubertal period and adulthood. Testicular tumors are separated mainly into two groups; germ cell tumors (teratoma, yolk sac tumors, epidermoid cyst) and gonadal stromal tumors (Juvenile granulosa cell, Leydig cell, and Sertoli cell tumors). Paratesticular tumors can either be lipomas, leiomyomas, hemangiomas, or rhabdomyosarcomas. Physical examination, serum markers, and the scrotal ultrasound have an important role in their diagnosis. Testes-sparing surgery is gaining more grounds in children owing to the dominancy of benign tumors. In malignant tumors, radical orchiectomy and selective chemotherapy are standard approaches. Radiotherapy and retroperitoneal lymph node dissection have a minimal role in treatment.

Keywords: Testis tumors, children, radical inguinal orchiectomy, testis-sparing surgery, yolk sac tumor, paratesticular rhabdomyosarcoma

Introduction

Testicular tumors (TT) are rarely seen in the prepubertal period, and benign lesions are more common in childhood. These tumors are approximately 1% of all pediatric solid tumors and their incidence ranges from 0.5 to 2 per 100,000 (1). Germ cell tumors (GCT) constitute 95% of TT in adulthood, but this rate is only 60-75% in children (2). However, the fact that the TT in children is more benign compared to adults affects management strategies (3). Although radical inguinal orchiectomy (RIO) is the gold standard, testis-sparing surgery (TSS) may also be a standard of choice in children (4,5).

Paratesticular tumors originate from tunica vaginalis, epididymis, or spermatic cord, and appear as rhabdomyosarcoma [(RMS) representing 40%]. Approximately 15-20% of RMS is of genitourinary origin and it is more benign compared to the other forms (6).

Diagnosing and treating testicular and paratesticular tumors remarkably different with different age groups. Thus, the aim of this article is to review the characteristics and treatment modalities of testicular and paratesticular tumors in children under the light of the current literature.

Epidemiology

Relevant data about TT in children was obtained from the prepubertal testis tumor registry (PTTR). TT peaks twice; before the age of 3 and after puberty (1). According to PTTR data, yolk sac tumor (YST) is the most common type with 62% prevalence, followed by teratomas with 23% (Table 1) (3,7). Similarly, a recent study from the National Cancer Database reported that YSTs are the most common pathology; however, this registry does not record benign lesions such as teratoma (8). Some studies have reported findings that differ from the PTTR. In a multicenter study involving 98 patients, the most common types were teratoma (48%), YST (15%), and epidermoid cyst (14%). In the same study, gonadal stromal tumors were detected in 13% of all patients (9). In another study involving 51 patients, the incidence of mature teratoma, RMS, epidermoid cyst, YST, and others were reported as 47%, 27%, 10%, 8%, and 8%, respectively (4). The most common paratesticular tumors were RMS. Paratesticular RMS accounts for 75% of all RMS (6,10) and

Table 1. Incidence of pediatric TT according to prepubertal testis tumor registry (3)

Tumor type	Percent (%)
Germ cell tumors	
Yolk sac tumor	62
Teratoma	23
Epidermoid cyst	3
Gonadal stromal tumors	
Juvenile granulosa cell	3
Sertoli cell	3
Leydig cell	1
Non-specified	4
Gonadoblastoma	1

TT: Testicular tumor

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Address for Correspondence: Selçuk Yücel, Marmara University Faculty of Medicine, Department of Urology, İstanbul, Turkey
Phone: +90 216 657 06 06 **E-mail:** drsyucel@yahoo.com **ORCID-ID:** orcid.org/0000-0002-2168-7468
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peaks in the first 3-4 months and at the age of 16 (11). The most common benign paratesticular tumor at all ages is lipomas (12).

Etiology

Causes of GCT include cryptorchidism, disorders of sexual development, in-utero estrogen exposure, neonatal jaundice, low or high-birth weight (13-16). Cryptorchidism is one of the most important risk factors for GCT and is associated with 10% of all cases. Cryptorchidism increases the life-long risk of GCT by four times (17,18). Cancer rate also increases with delay in the orchiopexy (19). Increased incidence of GCT has been observed in patients with disorders of sexual development -particularly hypovirililization and gonadal dysgenesis. The presence of a Y-chromosome in gonadal dysgenesis further increases the risk of tumor, there by raising the incidence to 10% at the age of 20 (20). YST is non-diploid, but pediatric GCT is usually diploid. It is characterized by 1p deletion, loss of chromosome 6q, chromosome 2, and 3p anomalies (21).

Diagnosis and Staging

TT presents with a painless mass in children. However, it can be detected incidentally in cases such as torsion, scrotal pain, and hydrocele. Physical examination has an important role in the diagnosis of TT. The mass can often be palpated as a painless, solid testicular lesion (4). However, physical examination may be unremarkable. Differential diagnoses include epididymo-orchitis, hydrocele, inguinal hernia, and testicular torsion.

Serum tumor markers play an important role in the diagnosis and follow-up. For example, human chorionic gonadotropin -ß (ß-hCG) and alpha feto protein (AFP) are used as serum markers in TT. AFP is produced in the fetal yolk sac, liver, and gastrointestinal tract and has a half-life of five days. It is the most important tumor marker in prepubertal TT and increases in 90% of YST. However, in children under 1-year-old, the increase in AFP can be physiological and it may take 6-8 months to reach its normal level (4,22). ß-hCG rarely increases in prepubertal tumors, making it not very useful in the diagnosis (23).

Scrotal ultrasonography (US) is the first-choice method for imaging in TT. Doppler US is more beneficial in diagnosis than conventional US (24). Although the US has close to 100% sensitivity in the diagnosis, its reliability is low in distinguishing malignant from benign lesions. However, the US is useful to distinguish between the testicular and paratesticular tumors and recognize some specific lesions (5). Benign tumors are generally characterized by properly limited lesions with low blood flow. In the US, epidermoid cysts appear as a properly limited cyst containing echogenic debris, YST as a solid mass, and teratomas as a heterogeneous complex lesion with cystic and solid contents (5). Disseminated disease in children is rare. In the case of malignant appearance with elevated AFP values, abdominal CT is advised. It is worthy to note that the most common site of metastasis is the lungs.

The staging described by children's oncology group (COG) is used in the prepubertal period and it is based on the localization of the disease, the presence of metastasis, and the change in the level of the postoperative tumor marker (Table 2). Staging is done between 1 and 4 (25). Postpubertal TT is evaluated according to TNM staging system just as in adults.

Table 2. Testicular GCT staging from the COG

Stage	Description
I	Local disease, markers normalize after complete resection
II	Transscrotal orchiectomy, microscopic disease in scrotum or high cord (less than 5 cm from proximal end), less than 2 cm retroperitoneal lymph node or persistently increased tumor markers
III	Greater than 2 cm retroperitoneal lymph nodes
IV	Distant metastases

Adapted from Wu and Snyder (24), GCT: Germ cell tumors, COG: Children's oncology group

Treatment

The treatment strategy in the pediatric age group should be chosen carefully because most of them are benign. TSS is gaining grounds as it prevents overtreatment of benign lesions. It should be considered in tumors without a high level of serum AFP and have benign features in the US (4,5). The intraoperative frozen examination has an important role in TSS. Many studies have shown that frozen examination has high sensitivity and specificity (26,27). In case of malignant features with frozen section examination, RIO should be performed. If the final pathology of the excised tumor is benign, further treatment is not required. In adolescents and adults, the standard approach is RIO, since the tumor is more likely to be malignant. Surgical approaches for TT in children are displayed in Table 3.

GCT

1. YST

YST is the most common malignant TT in the prepubertal period (4,9,28). It occurs especially before the age of 2 and is also called endodermal sinus tumor or juvenile embryonal carcinoma. It is usually characterized by a solid mass and a high level of AFP (2). It is seen as a well-limited, heterogeneous mass in the scrotal US. Schiller Duval bodies, which show a variable histological pattern and appear as two layers of tumor cells surrounding the vessel, are pathognomonic findings in the histological examination of specimens (29).

Although the management of YST is more aggressive in adults, a more conservative approach is upheld in children. The reason for the conservative approach is that it can be recognized at an early stage, AFP can be used as a reliable biomarker, and has pure histology. While 85% of YST are diagnosed at stage 1 in the prepubertal period, only 35% are diagnosed in the postpubertal period (30). In the prepubertal period, 40% hematogenous, 28% lymphatic, and 20% mixed (hematogenous and lymphatic) spread have been observed for YST, with the lung as the most common site of metastasis (31). If the tumor is limited to the testicle (stage 1) and AFP decreases after orchiectomy, chemotherapy is not indicated (just follow-up is required) (32). The algorithm for the management of YST is displayed in Figure 1.

The overall recurrence is 20%, therefore serum AFP, PA chest X-ray, and abdominal MRI/CT should be performed every 3 months for the first year. The controls then follow every six

Table 3. Surgical approaches for testicular tumors in children		
	Radical inguinal orchiectomy	**Testis-sparing surgery with frozen section examination**
AFP	**Elevated**	**Normal**
Scrotal USG	Malignant appearance	Benign appearance
Clinical signs	Not enough testicular tissue for sufficient testosterone production	
	Accompanying disorders of sex development	Early puberty symptoms particularly under the age of 5
	Lymph node metastasis	Gynecomastia particularly under the age of 5
	Distant metastasis	
Histological pattern	1. Yolk sac tumor 2. Paratesticular Rhabdomyosarcoma 3. Immature teratoma 4. Malign type granulosa CT 5. Malign type sertoli CT 6. Gonadoblastoma	1. Mature teratoma 2. Epidermoid cyst 3. Leydig CT 4. Leiomyoma 5. Lipoma
CT: Computed tomography, USG: Ultrasonography, AFP: Alpha feto protein		

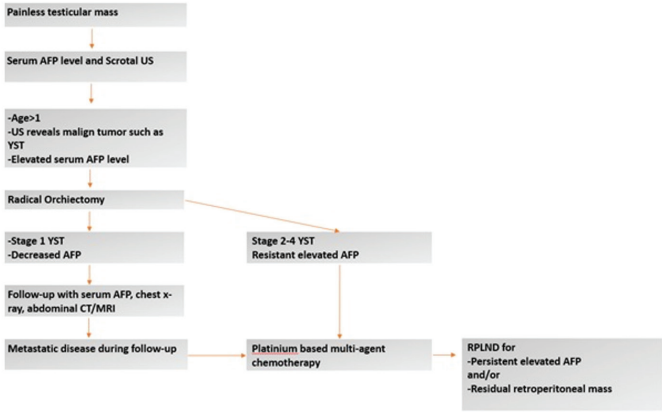

Figure 1. The algorithm for the management of YST

YST: Yolk sac tumor, CT: Computed tomography, AFP: Alpha feto protein, US: Ultrasound, MRI: Magnetic resonance imaging, RPLND: Retroperitoneal lymph node dissection

months in the second year and once a year after the second year (32). In pediatric YST, metastasis occurs in a hematogenous way, unlike in adults (31). Therefore, retroperitoneal lymph node dissection (RPLND) is rarely employed in the management of pediatric TT and should be considered only in patients with chemotherapy and RIO-resistant AFP elevation and residual mass. The use of Platinum-based chemotherapy for TT began in the 1970s and was rearranged for testicular tumor treatment. Chemotherapy provides close to 100% survival in stage 1 and 95% in stage 2-4 YST with recurrence after RIO (33-37).

2. Teratoma

Teratoma is the second most common type of TT in childhood and consists of all three embryological germ cell layers (4,9,38). It is characterized by a heterogeneous appearance consisting of solid and cystic ultrasonic structures and does not cause an increase in AFP. Mature teratoma is more common than immature teratoma in children. Mature teratomas in the prepubertal period are benign (in contrast to adults) and do not require oncological follow-up (39,40). TSS is the first choice in the treatment of prepubertal mature teratomas (4,5,38). In adolescence, RIO is employed, just as in adults (41).

The immature teratoma contains embryonal or incomplete differential tissue fragments, among which the most primitive neuroectodermal structures are observed (42). In the case of complete resection, pediatric immature teratomas gave a benign course and a low risk of recurrence after surgery (39). RIO is sufficient for immature teratomas not accompanied by YST (41).

3. Epidermoid Cyst

The epidermoid cyst is a monodermal variant of a teratoma and accounts for about 15% of all pediatric TT (5,9). It is benign in both adults and children and usually expresses normal levels of AFP. In the scrotal US, keratin epithelium such as an onion skin and cyst are observed. It can also be treated with TSS using a frozen examination and no oncological follow-up is required (5,9,26).

Gonadal Stromal Tumors

1. Leydig Cell Tumor

Leydig cell tumor is the most common tumor among gonadal stromal tumors and is often seen between the ages of five and ten. Patients may present with painless testicular mass and early puberty signs due to the secretion of testosterone from Leydig cells. Leydig cell tumor is detected in 10% of patients with early puberty (43). Feminization signs such as gynecomastia may accompany in approximately 10-15% of patients (44). Leydig cell tumors are not malignant and can be treated with TSS or RIO, but early puberty findings cannot be reversed (1,5,41).

2. Juvenile Granulosa Cell Tumor

Juvenile granulosa cell tumor is a benign tumor that usually appears in the first year of life with a painless testicular mass. It is associated with Y-chromosome structural anomalies, mosaicism, and ambiguous genitalia (45). Solid and cystic structures surrounded by granulosa-like cells are seen in histological preparations. From immunohistochemical evaluation, it can be

separated by staining with inhibin-alpha from YST (45). It can also be treated with RIO or TSS (46). Recurrence or metastasis is not expected (45).

3. Sertoli Cell Tumor

Sertoli cell tumor is the second most common gonadal stromal tumor (47). It is seen in approximately 3% and common before 10 years of age (48). It is hormonally active in 10% of patients and can cause gynecomastia or early puberty (49). It is usually benign in children under the age of five but can also be malignant in older children (45). In the presence of metastasis, RPLND, chemotherapy, and radiotherapy are among the treatment options (50). Also, genetic or endocrinological diseases such as Peutz-Jeghers and Carney syndrome are accompanied in one out of three patients, and should be considered during diagnosis (51).

Other Tumors

Gonadoblastoma

Gonadoblastomas are generally benign and asymptomatic tumors. It is the most common testicular tumor associated with disorders of sexual development and often found in dysgenetic gonads (45). It is noticed by virilization in individuals with 46 XY karyotypes who have a phenotypically female appearance. Malignant tumors occur in about 10% of patients and bilateral in 33% of patients (52). Although it is benign in the neonatal period, it can undergo malignant transformation especially after puberty, and turn into dysgerminoma (45). RIO is recommended in this patient group.

Leukemia-lymphoma

Leukemia and lymphoma are the most common malignant tumors that metastasize to the testicle in children. In acute lymphoblastic leukemia (ALL), the second most common site of extramedullary metastasis after the central nervous system is the testicle (45). Testicular metastasis in patients with ALL is a poor prognostic factor. Follicular lymphoma may appear as a primary testicular tumor (53). Radiotherapy and systemic chemotherapy are standard treatment options used (23).

Testicular Microlithiasis

Controversy on this subject continues: some publications have called into question if an association between microlithiasis and GCT exists at all in children, whereas others continue to cite a strong association between microlithiasis and primary TT (54,55).

Paratesticular Tumors

The paratesticular region consists of the spermatic cord, epididymis, tunica vaginalis, and embryonal residues. Benign and malignant tumors such as leiomyomas, fibromas, lipomas, hemangiomas, rhabdomyomas, and melanotic neuroectodermal tumor scan develop from these tissues.

1. Lipoma

The most common tumor of the paratesticular region at all ages is lipomas (12). It occurs as an asymptomatic scrotal mass. It is characterized as a homogeneous hyperechoic lesion in the scrotal US. CT and MR are employed in case of suspicion of malignancy. Symptomatic masses can be locally excised.

2. Leiomyoma

It is the second most common epididymis tumor at all ages and usually seen in adults (12,56). These tumors tend to grow slowly. It is displayed as a solid-cystic lesion containing calcification when viewed using scrotal US (57). Due to the lack of metastasis and recurrence, TSS can be performed, but in cases where it is adherent to the testicular tissue, it can be taken out of the body by orchiectomy (11).

3. Hemangioma

Scrotal hemangioma is a rare paratesticular lesion mostly seen in infancy. Although it is generally asymptomatic, pain, swelling, and bleeding may occur. It can be mixed with varicocele and magnetic resonance imaging is useful when the scrotal US cannot distinguish specific features. Local excision can be made due to the risk of bleeding and ulceration.

4. Paratesticular Rhabdomyosarcoma

Originates from mesenchymal tissue of the paratesticular region. It represents 40% of all paratesticular malignancies and 5% of all testicular and paratesticular malignancies (6). The incidence is distributed bimodally and increases at the age of 3-4 months and at 16 years (11). Patients usually present with a painless hard mass. Serum AFP and ß-HCG values are observed at normal levels. A heterogeneous mass can be seen in the US, but it cannot provide precise information on whether it is benign or malignant. Although local invasion is common, lymphatic metastasis is observed in 30-40% of patients (6).

It has four histological subtypes: embryonal, pleomorphic, alveolar, and undifferentiated. Embryonal type is the most common in all RMS and is seen in 60%. In paratesticular RMS, approximately 97% of patients appear with this type (58). The algorithm for the management of RMS is displayed in Figure 2.

The Intergroup RMS studies made some recommendations for the treatment of these tumors. According to tem, RIO should be performed in children older than 10 years, and then RPLND and multiagent chemotherapy regardless of the stage. If there

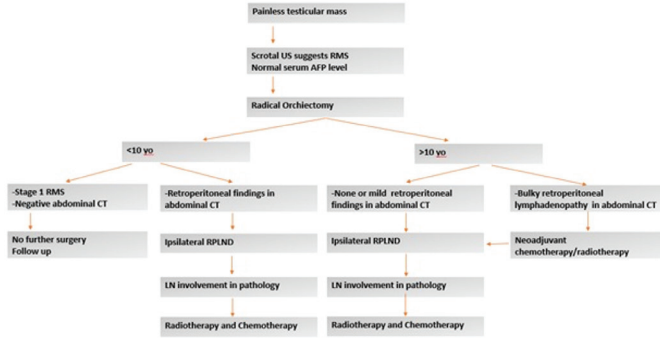

Figure 2. The algorithm for the management of RMS

RMS: Rhabdomyosarcoma, US: Ultrasound, CT: Computed tomography, RPLND: Retroperitoneal lymph node dissection, AFP: Alpha feto protein

is suspicion of retroperitoneal spreading in patients under 10 years of age, RIO and then RPLND should be performed (59). Although some European Collaborative Groups avoid RPLND, COG recommends RPLND for all children older than 10 years hoping to avoid failure in the retroperitoneum and the burden of second-line therapy. Despite the data supporting these recommendations, an analysis of the SEER database recently published showed that one-third of adolescents still do not undergo RPLND, even at the distinct survival advantage (OS at 5 years 92% vs. 64%) (60). Paratesticular rhabdomyosarcoma has a better prognosis than RMS developing in other parts of the body. The 3-year survival rate is reported at 95% in paratesticular RMS and 60-70% in others (61).

Conclusion

Although childhood testicle and paratesticular tumors are rare, testicular mass requires further evaluation. Detailed history, physical examination, serum AFP level, and the scrotal US are essential for differential diagnosis. RIO is the gold standard treatment method. However, due to the high frequency of benign tumors, TSS is often preferred in appropriate cases.

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Mini Review

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Intravesical Bacillus Calmette-Guérin Treatment During The Coronavirus Disease-2019 Pandemic: A Review of Current Recommendations

Fesih Ok

Siirt Training and Research Hospital, Clinic of Urology, Siirt, Turkey

Abstract

Objective: Many outpatient procedures were restricted to reduce the likelihood of transmission during the coronavirus disease-2019 (COVID-19) pandemic. The most effective treatment of high-risk non-muscle-invasive bladder cancer (NMIBC) is the intravesical Bacillus Calmette-Guérin (BCG) therapy, consisting of induction and maintenance, which requires repeated hospital visits. Therefore, treatment protocol adaptation to the pandemic is important.

Materials and Methods: A comprehensive literature review was performed between January 2020 and December 2020 within the PubMed and Google Scholar databases.

Results: Recommendations and updates of two international associations, two national associations, and five intravesical BCG application studies were discussed. During the pandemic, intravesical BCG treatment was delayed for patients with NMIBC in the intermediate-risk group. The general view for patients in the high-risk group is to complete induction therapy, if possible. Recommendations for maintenance treatment vary. With this treatment, planning should be done in less than one year. The existence of suspected or approved COVID-19 disease delayed the BCG treatment for 3 weeks.

Conclusion: Consensus was not found on how intravesical BCG treatment should be applied during the pandemic. However, it is recommended to at least complete induction therapy in high-risk NMIBC as the risk of progression and recurrence is high. BCG instillations can be delayed for at least 3 weeks in patients with confirmed COVID-19 disease.

Keywords: Bladder cancer, intravesical BCG, COVID-19, coronavirus, pandemic

Introduction

In the second half of 2019, new cases of pneumonia emerged in Wuhan, China, and the World Health Organization named this coronavirus disease-2019 (COVID-19) and shortly thereafter declared it a pandemic (1). Clinicians adjusted all their clinical practices, especially life-threatening malignant disorders, to address the COVID-19 pandemic. One such practice involved intravesical Bacillus Calmette-Guérin (BCG) treatment, which is the gold standard method in high-risk non-muscle-invasive bladder cancer (NMIBC). This treatment reduces recurrence rates for NMIBC by 60%-70% and progression by 26% (2). However, it requires repeated hospital admissions, which increase the risk of contamination during the pandemic, thus rearranging the treatment algorithm in this patient group is necessary (3). National and international urological associations (4,5,6,7) have outlined internationally recognized standards of care and published guidelines and recommendations in triaging patients throughout the COVID-19 outbreak. This report aimed to present the guidelines and recommendations updates in the literature regarding intravesical BCG administration during the COVID-19 outbreak.

Materials and Methods

The recommendations and updates published by the national and international urology associations in intravesical BCG treatment application during the pandemic were screened in this literature review.

A comprehensive search of PubMed and Google Scholar was undertaken from January through December 2020 to find available published works in triaging patients with bladder cancer who are candidates for intravesical BCG therapy during the pandemic. The search items used were "coronavirus," "COVID-19," "pandemic," "SARS-CoV-2," "bladder cancer," "urothelial carcinoma," "Bacillus Calmette-Guérin," "intravesical

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Address for Correspondence: Fesih Ok, Siirt Training and Research Hospital, Clinic of Urology, Siirt, Turkey
Phone: +90 507 639 19 87 **E-mail:** drfesihok@gmail.com **ORCID-ID:** orcid.org/0000-0002-8785-9867
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BCG," "treatment," "guidelines," and "recommendations." Original articles, review articles, commentaries, editorials, letters to editors, and research letters were included. Non-English publications and studies on COVID-19 that were outside the scope of our research were excluded.

Therefore, nine publications formed the basis of our review article, wherein two were from the international urology associations, two from the national urology associations, and five from urology experts.

Results

Recommendations of International Urological Associations

The team at the European Association of Urology guidelines department was quick to respond and made recommendations according to the priority levels for various situations that were affected by the pandemic. Intravesical BCG therapy for intermediate-risk NMIBC was given a low priority due to unexpected clinical damage (progression/metastasis) unless the treatment is delayed for >6 months. However, high-grade NMIBC is a high priority, and intravesical BCG instillations should be started within 6 weeks (4).

Some theories suggest that BCG vaccination protects against COVID-19 disease. BCG vaccines showed protection against some DNA and RNA viruses by working on the innate immune system and producing memory-like responses (8,9). Indeed, by the first half of 2020, the lack of a specific COVID-19 vaccine leads to a possible BCG shortage. The American Urological Association also made its recommendations for intravesical BCG application based on the possibility of global BCG shortage. Patients who are at high risk should be given priority for full induction BCG therapy, and with favorable conditions, the dose could be reduced by 1/2 to 1/3 in these patients. Patients with planned maintenance treatment should be given 1/3 BCG doses, limited to one year (5).

National Urological Association Recommendations

The guideline of the British Association of Urological Surgeons (BAUS) (6) regarding intravesical treatment administrations throughout the COVID-19 pandemic was first announced on March 19, 2020. The first version of the BAUS guideline was recommended against intravesical instillations (BCG or chemotherapy) for NMIBC due to possible immunosuppressive effects. A completed induction course is recommended if intravesical BCG therapy is initiated, with delayed maintenance therapy. BAUS published a second version of the guidelines on March 31, 2020, with an update for NMIBC recommending that the risk/benefit ratio of giving or maintaining intravesical instillation (BCG or chemotherapy) be considered.

The Turkish Uro-oncology Association (TUOA) does not recommend delaying intravesical BCG treatment with suitable current conditions of the institution, as the risk of disease progression is high. However, the TUOA suggests that intravesical therapy in patients with low-to-moderate risk NMIBC can be delayed during the COVID-19 pandemic (7).

Expert Opinions and Literature Recommendations

Cases of high-grade NMIBC benefit the most from induction and initial maintenance BCG doses (so-called 6+3) (10). Therefore, Wallis et al. (11) recommend this as the first line of treatment. The decision about BCG therapy initiation immediately following resection depends on the risk of infection with severe acute respiratory syndrome coronavirus 2 and the adverse course of COVID-19, risk of bladder tumors, and available health care capacity. BCG maintenance is not performed after the first 3-month booster series until the risks of COVID-19 are reduced.

A representative collection of urologists from various institutions in the United States with expertise in different sub-specialties of urology also made separate comments and recommendations regarding the induction and maintenance of intravesical BCG during the pandemic. Induction intravesical BCG treatment provides a significant benefit by reducing the disease recurrence and progression in patients with high-risk or intermediate NMIBC, thus prioritized treatment application is recommended. Maintenance therapy is essential; however, maintenance therapy should be stopped during the pandemic since the most significant intravesical therapy benefits are seen during the induction. Its usage and necessity should be reevaluated within 3 months of the induction course (12).

Panels of Italian and U.S. experts (13,14) recommended intravesical BCG therapy continuation throughout the COVID-19 outbreak, as it is the gold standard adjuvant therapy for recurrence and progression prevention in patients with high-risk NMIBC (2). U.S. experts suggested that after the completion of the first four doses of induction therapy, the remaining doses are administered after a few weeks. Treatment application in a healthcare facility poses a higher risk of getting the virus than the risk involved in postponing 5-6 doses for several weeks. However, if the patient is on the third dose of induction therapy, the fourth dose should be given even if the fifth and sixth doses are delayed. The first and second doses can be taken and the third dose can be skipped entirely in maintenance BCG treatment (14).

Current Recommendations for Patients Diagnosed with COVID-19 During Intravesical BCG Treatment

Recommendations were generally related to intravesical BCG treatment application during the pandemic. However, the specific direction was not reported for patients diagnosed with COVID-19 while receiving intravesical BCG therapy. Lenfant et al. (3) suggested that for induction BCG, BCG instillations can be delayed for at least 3 weeks after initial symptoms to allow complete recovery if the patient has COVID-19 disease. For maintenance BCG, patients with intravesical BCG therapy for >1 year can safely terminate this therapy. However, two of the three doses of the maintenance BCG course may be accepted in maintenance treatment <1 year, and treatment should be delayed for 3 weeks if confirmed with COVID-19 disease.

As summarized in Table 1, a consensus was not made on how intravesical BCG treatment should be applied during the

Table 1. Recommendations on intravesical BCG application during the COVID-19 pandemic	
	Recommendations
EAU (4)	High-risk NMIBC is a high priority, should start in 6 weeks Intermediate-risk NMIBC is a low priority, can delay 6 months
AUA (5)	Induction: High-risk patients full dose, if favorable 1/2 or 1/3 dose BCG shortage possibility Maintenance: 1/3 dose BCG limited in 1 year
BAUS (6)	Induction: Should be completed if possible Maintenance: Based on risk/benefit
TUOA (7)	High-risk NMIBC: postponement is not recommended Intermediate-risk NMIBC: can be postponed
Wallis et al. (11)	High-grade NMIBC: Induction and first maintenance BCG (6 + 3) should be given, other maintenance doses may not be given
Katz et al. (12)	Induction: These patients should be prioritized for treatment, though they may also require a delay in therapy depending on local needs/resources Maintenance: Stop maintenance therapy and re-evaluate its usage/necessity in 3 months
Ficarra et al. (13)	Intermediate-risk NMIBC: postpone High-risk NMIBC: do not postpone
BCAN (14)	Induction: The first four doses may be sufficient Maintenance: Take the first and second doses and skip the third dose
Lenfant et al. (3)	Induction: If COVID-19 positive, 3 weeks delay If COVID-19 negative, 1 weekly instillation for 6 weeks Maintenance: Ongoing maintenance <1 year, 2 out of 3 doses (3 weeks delay if COVID-19 positive) Ongoing maintenance >1 year, safely terminated
EAU: European Association of Urology, AUA: American Urological Association, BAUS: British Association of Urological Surgeons, TUOA: Turkish Uro-oncology Association, BCAN: Bladder Cancer Advocacy Network	

pandemic process. However, some critical points stand out. Intravesical BCG treatment was not proven to poses an infection risk during the COVID-19 pandemic; however, this treatment can be delayed in the intermediate-risk group. The general recommendation is complete induction therapy for patients with high-risk NMIBC, if possible.

Conclusion

Intravesical BCG applications during the pandemic may increase the risk of viral contamination for both the patient and the healthcare staff. However, disruption or delay of this treatment may cause bladder cancer recurrence and progression, especially in high-risk patients. Therefore, intravesical BCG treatment adaptation to the pandemic is essential. Induction therapy should be given, especially in patients with high-risk NMIBC. Maintenance treatment administration should not exceed one year. Treatment should be delayed for 3 weeks in patients diagnosed with COVID-19.

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Original Article

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The Comparison of Magnetic Resonance Imaging/ Transrectal Ultrasound Fusion Biopsies with Conventional Transrectal Biopsies in Prostate Cancer Detection

Dursun Baba, Ahmet Yıldırım Balık, Alpaslan Yüksel, Yusuf Şenoğlu

Düzce University Faculty of Medicine, Department of Urology, Düzce, Turkey

Abstract

Objective: The conventional technique for histological prostate cancer diagnosis is transrectal ultrasound (TRUS)-guided random sampling of the peripheral prostate zone. However, due to method insufficiency and recent developments in prostate imaging, new biopsy methods were introduced. This study aimed to evaluate prostate cancer detection rates by the standard and magnetic resonance (MR) fusion biopsy methods. The main purpose of our study is to mutually evaluate prostate cancer detection rates and results of standard and cognitive MR fusion biopsy methods and share our experiences in this process.

Materials and Methods: Patients, who underwent prostate biopsy due to elevated serum prostate-specific antigen levels (>4ng/mL) and/or suspicious rectal examination, were retrospectively evaluated. A total of 160 patients were included in the study between January 2018 and January 2021. Patients were divided into two groups according to the applied method, as standard biopsy (SB) and MR fusion biopsy.

Results: Prostate cancer was reported in 25 (31.3%) of 80 patients who underwent SB, wherein 20 (25%) were determined with clinically significant cancer. Prostate cancer was reported in 30 (37.5%) of 80 patients who underwent MR fusion biopsy, wherein 25 (31%) were reported as clinically significant cancer. A statistically significant difference was found in detecting prostate cancer and clinically significant prostate cancer when the prostate imaging-Reporting and Data System (3,4,5) scores were compared with each other ($p<0.05$, $p=0.00$). The additional SB to MR-targeted fusion biopsy was statistically significant in prostate cancer diagnosis ($p=0.01$, $p<0.05$).

Conclusion: The additional SB to targeted biopsy increased the detection rate of clinically significant prostate cancer. Larger randomized studies are needed to reach a consensus on the ideal biopsy technique.

Keywords: Prostate cancer, MRI-ultrasound fusion, prostate biopsy, targeted biopsy

Introduction

Prostate cancer is the second most common cancer in men (1). For histological diagnosis, 10-12 focal biopsy accompanied using transrectal ultrasound (TRUS) is still the standard (conventional) biopsy method (2). The shortcomings of this method include the increased number of biopsies, the missed diagnosis of clinically significant cancer, and the detection of clinically insignificant cancer. Prostate biopsy diagnosis with standard biopsy (SB) is 25%-40% and 20%-25% of clinical cancers are missed. In addition, a certain rate of clinically insignificant cancers are detected (3,4,5). Clinically insignificant cancer detection causes unnecessary treatments, and, on contrary, missed clinically important cancer causes diagnosis delay. Therefore, a conventional biopsy is questioned in prostate cancer diagnosis and new methods were investigated to increase the diagnostic quality of biopsy. Especially the use of magnetic resonance (MR) in prostate imaging has introduced targeted biopsy (TB) studies. The purpose of integrating multiparametric MRI (mpMRI) into biopsy is to eliminate the deficiency in detecting clinically important cancer, detect lesions in the anterior prostate, which are difficult to sample especially in the conventional biopsy and obtain a TB from the detected lesion. Three different targeted prostate biopsy methods are defined: MR-US fusion biopsy, real-time MRI fusion-guided biopsy, and direct-MRI-guided biopsy (3,6). The rates of prostate cancer detection vary between 38%-80% using the TB methods (7). The MR-USG fusion biopsy protocol lesions were detected by images obtained with mpMRI matched with TRUS image and TB sampling is performed under the guidance of TRUS. As one of the TB techniques, the MR-USG fusion biopsy is advantageous because it is cheap and fast, whereas the lack of standardization and experience is a disadvantage (3,4).

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Address for Correspondence: Dursun Baba, Düzce University Faculty of Medicine, Department of Urology, Düzce, Turkey
Phone: +90 380 542 13 87 **E-mail:** ayildirimbalik@gmail.com **ORCID-ID:** orcid.org/0000-0002-4779-6777
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This study aimed to mutually evaluate prostate cancer detection rates and results of standard and cognitive MFB methods and share our experiences in this process. The comparison of these two methods in the prostate biopsy procedure will guide and be beneficial for all clinicians, especially for urologists who perform prostate biopsy and radiologists who interpret mpMRI.

Materials and Methods

Approval for the study was obtained from Düzce University Ethics Committee (approval no: 2021/51, date: 01.03.2021). Between January 2018 and January 2021, patients who underwent prostate biopsy because of elevated serum prostate-specific antigen (PSA) levels (>4 ng/mL) and/or suspicious rectal examination findings were retrospectively evaluated in our clinic. A total of 160 patients were included in the study. Patients were divided into two groups as patients who underwent SB (n=80) and patients who underwent MFB (n=80). Patients of the MFB group underwent TB from suspicious lesions obtained from mpMRI images and fusion SB (FSB) with standard 12 core. Patients who had previously undergone prostate biopsy for any reason and patients with PSA values above 20 ng/mL were excluded from the study. Prostate imaging was performed with mpMRI before the patient underwent fusion biopsy.

Pre-biopsy urine culture was performed in all patients. Those with positive urine culture were treated and urine culture sterility was achieved. Patients using anticoagulants were consulted to the relevant department and, without contraindications, short-acting anticoagulant treatment was initiated before the procedure. An appropriate dosage of antibiotic prophylaxis (Gentamicin, Genta® ampoule IM) was administered to patients 30 min before the procedure, and then sterile lubricating gel (Cathajell® 12.5 g), which is also a rectal analgesia lubricant, was rectally applied. In a fetal position (lateral decubitus position), 10 cc (5 cc each side) of local anesthesia (Citanest® 2%) was applied between the prostate and seminal vesicles with a 20G 25 cm aspiration needle under the guidance of a TRUS probe. Twelve focal biopsies were systematically taken from 80 patients who underwent conventional biopsy. The biopsy samples were fixed with formol and sent in Eppendorf tubes for histopathological examination. After procedure completion, patients were followed up in the service for 3 hours and were discharged by prescribing ciprofloxacin 500 mg oral tablet twice a day after a spontaneous micturition.

The same preparations were made in patients in the MFB group. For MpMRI, 3 Tesla Siemens AG MagnetomR Skyra (Germany) magnet MRI device was used. T2-weighted imaging was performed in the coronal, axial, and sagittal planes. In addition, diffusion-weighted imaging and dynamic contrast MRI sequences were used. US and MR images were matched regarding information such as zonal anatomy, prostate cyst, and prominent nodule using navigation (V-Nav®) system compatible with the ultrasound device (Logiq s8 GE Healthcare®). Biopsy was taken from the suspicious prostate imaging-reporting and data system (PI-RADS 3 or above) lesions interpreted by the radiology. Conventional biopsy was also performed for all of these patients after the lesion biopsy. Biopsy results reported as malignant were classified as clinically significant or insignificant cancer according to Epstein Criteria defined by Epstein et al. (5). Patients with a PSA density of <0.15 ng/mL, a Gleason score reported as 3+3, clinical staging of T1c, a positive core count of <3, and a cancer rate of <50% per core were defined as clinically insignificant prostate cancer.

Statistical Analysis

In the comparisons between groups, continuous variables were examined with the Independent t or Mann-Whitney U test depending on data distribution, and categorical variables were examined with appropriate cross-table statistics. The Wilcoxon paired two-sample tests were used for dependent group comparisons. A comparison of qualitative variables was made using the chi-square and McNemar tests. Results were evaluated at a 95% confidence interval and significance level of $p<0.05$. The Pearson or Spearman correlation analysis was used for continuous correlation analysis between variables.

Results

The mean PSA of patients who underwent SB was 7.21 ng/mL, and the mean PSA of the MFB patients was 6.54 ng/mL, and the difference between these two groups was not statistically significant. Malignant digital rectal examination (DRE) revealed findings of 53.5% of patients with conventional biopsy and 46.5% of patients with MFB and the difference was not significant ($p>0.05$). The demographic characteristics of the MFB and SB patients are detailed in Table 1.

In the SB group, 38 patients had an abnormal DRE, wherein 15 (39%) had prostate cancer and 14 (36%) of these 15 patients

Table 1. SB and MFB demographic features

	SB		MFB	
	Average-range	Standard deviation	Average-range	Standard deviation
Age (years)	64.96 (50-81)	7.46	63.79 (48-76)	6.64
Serum PSA (ng/mL)	7.21 (0.95-19.3)	4.225	6.54 (1.1-17)	3.089
Serum free PSA (ng/mL)	1.49 (0.166-0.49)	1.097	1.34 (0.24-4.90)	0.843
Prostate volume (mL)	59.6 (20-210)	35.359	57.54 (18-240)	35.813
PSA density (ng/mL²)	0.149 (0.02-0.75)	0.115	0.144 (0.25-0.6)	0.099
Total number of cores	12 (12)	0	14.63 (13-17)	0.986

SB: Standart biopsy, MFB: MRG-US fusion biopsy, PSA: Prostate-specific antigen

had clinically significant prostate cancer. Clinically significant prostate cancer was detected in 6 (14%) of the patients with normal DRE. Thirty (37.5%) of 80 patients in the FSB group were reported as prostate cancer, and 25 (31%) of these patients were reported as clinically significant cancer. In the FSB group, 33 of 80 patients had malignant DRE findings, wherein 22 (66.6%) had prostate cancer. A statistically significant correlation was found between the DRE and fusion biopsy pathology results. ($p<0.05$, $p=0.01$ correlation coefficient: 0.5)

Prostate cancer was detected in the TB of 6 (12.5%) of 48 patients who had PI-RADS 3 lesions on mpMRI. Prostate cancer was detected in 11 (50%) of 22 patients with PI-RADS 4 lesions. Prostate cancer was detected in 6 of 10 (60%) patients with PI-RADS 5 lesions. Clinically significant cancer was detected in 21 of 23 (95%) of patients who had PI-RADS 3,4, and 5 lesions with TB (Table 2). A statistically significant difference was found when the PI-RADS 3, 4, and 5 scores were compared with each other in detecting prostate cancer and clinically significant prostate cancer ($p<0.05$, $p=0.00$). Clinically significant prostate cancer was reported in 90% of patients with PI-RADS 4 lesions and 100% PI-RADS 5 lesions.

While 20 of 80 (25%) patients in the SB group had clinically significant prostate cancer, 25 (31.8%) of 80 patients in the MFB group have prostate cancer. When the MFB group is evaluated as FSB and TB separately; 21 (28.7%) of 80 patients who underwent FSB biopsy have clinically significant prostate cancer, whereas 23 patients have clinically significant prostate cancer in the TB group. In the TB group, 21 (86.9%) of 23 patients had clinically significant cancer (Table 3). When patients in MFB were separately evaluated as FSB and TB group, additional SB to the TB obtained from the lesion provided an approximately 8.9% advantage in prostate cancer diagnosis. This superiority was statistically significant ($p=0.01$, $p<0.05$). The method with the highest number of prostate cancer and clinically significant prostate cancer was MFB. However, no significant difference was found between SB and MFB in prostate cancer or clinically significant prostate cancer detection ($p=0.253$, $p>0.05$).

The comparison of SB and FSB revealed 25 (31.2%) of 80 patients who underwent SB and 28 (35%) of 80 patients who underwent FSB were diagnosed with prostate cancer. This difference was not statistically significant. ($p=0.737$). In 2 (2.5%) patients, cancer was not detected by SB but was detected by TB. However, only one was clinically important cancer. When DRE findings were compared in SB and MFB groups, the cancer detection rate in the MFB group was statistically significant in patients with abnormal DRE ($p<0.05$, correlation coefficient: 0.5).

Table 2. Fusion biopsy PI-RADS classification of prostate cancer

PI-RADS score	3	4	5	Total
Number of patients	48 (100%)	22 (100%)	10 (100%)	80
Have prostate Ca	6 (12.5%)	11 (50%)	6 (60%)	23
Prostate Ca no	42 (87.5%)	11 (50%)	4 (40%)	57
Clinically significant cancer	5 (83.3%)	10 (90.9%)	6 (100%)	21
Clinically unsignificant cancer	1 (16.7%)	1 (9.1%)	0 (0%)	2

PI-RADS: Prostate imaging-reporting and data system

Table 3. SB, MFB comparison

	SB n (%)	MFB	
		FSB n (%)	TB n (%)
Benign	55 (68.8%)	50 (62.5%)	57 (71.2%)
Prostat cancer	25 (31.3%)	30 (37.6%)	23 (28.7%)
Clinically significant prostate cancer	20 (25%)	25 (31.8%)	21 (26.2%)
Clinically unsignificant prostate cancer	5 (6.3%)	5 (6.3%)	2 (2.5%)
Total	80 (100%)	80 (100%)	80 (100%)

SB: Standard biopsy, MFB: MRI-US fusion biopsy, FSB: Fusion standard biopsy, TB: Targeted biopsy

Discussion

Biopsy methods used for prostate cancer diagnosis changed with technological developments. Due to TRUS-guided biopsy deficiencies, which was the SB method for a long time, new techniques were investigated. More sensitive methods are investigated due to the low sensitivity of ultrasound in detecting prostate gland lesions, skipping the diagnosis of clinically important cancer, and detecting clinically insignificant cancer. A cancer diagnosis is missed at a rate of approximately 33% in standard prostate biopsies performed under US guidance (8,9). The use of mpMRI increased in recent years due to the advantages of showing the prostate anatomy more clearly, detecting the intraprostatic lesion more easily, showing the spread of lesion to the extracapsular region more clearly, and detecting small lesions, and has become a guide for targeted procedures in prostate biopsy. Therefore, targeted biopsies increased their popularity in detecting clinically important cancer.

In studies, cancer detection rates vary between 25%-40% in SB and between 38%-80% in targeted biopsies (3,4,5,7). Similar results in cancer detection rates in the literature were found in our study (SB: 31.2%, MFB: 35%). No significant difference was found between the two methods, especially in patients who underwent the first biopsy.

Especially in patients with abnormal rectal examination findings, the rate of cancer detection by fusion biopsy was higher than SB. Therefore, prostatic imaging and subsequent fusion biopsy were superior to SB in diagnosing patients with rectal examination findings.

MRI-US fusion biopsy was not superior in detecting prostate cancer compared to SB in the meta-analysis that examined 16 studies; however, it was reported to have a higher rate of clinically significant prostate cancer detection and a lower rate of clinically insignificant prostate cancer detection (4). Other similar studies revealed that high-risk cancer at a higher rate of up to 30% and a lower rate of low-risk cancer are detected with fusion biopsy compared to SB (3,10). In our study, fusion biopsy was numerically superior to SB in both detecting prostate cancer

and detecting clinically significant prostate cancer; however, this difference was not statistically significant, due to insufficient sample size. Therefore, the insufficient sample reveals the limitations of the study.

When the subgroups of patients who underwent fusion biopsy were examined, a statistically significant prostate cancer detection rate was found when the SB was added to the TB compared to those who had only TB. Therefore, our study supports the idea that an SB should always be added to TB in patients undergoing fusion biopsy. TB taken from the lesion detected in mpMRI is advantageous in studies; however, adding a standard systematic biopsy to patients with TB is controversial (11). However, the study conducted by Siddiqui et al. (10). Revealed that MRI fusion biopsy was more successful in detecting clinically significant cancer than SB, while it was reported that the addition of SB to fusion biopsy also increased the diagnosis of clinically insignificant prostate cancer. Therefore, comprehensive studies investigating the clinical significance of prostate cancers detected by SB in addition to fusion are necessary. Our study compared the MRI-US fusion biopsy and SB, which found no statistically significant difference in detecting prostate cancer and clinically significant prostate cancer.

As the PI-RADS score determined by MpMRI increased, the rate of prostate cancer and clinically significant prostate cancer detection increased in a statistically significant way. However, this increase was significant, especially in patients with PI-RADS scores of 4-5, whereas not statistically significant in patients with PI-RADS scores of 3. Therefore, MR-US fusion biopsy should be recommended primarily for diagnostic success, especially in patients with PI-RADS 4-5 lesion scores. In this context, comprehensive studies are needed on whether MR fusion or SB will be performed in patients with PI-RADS 3 lesion scores. The EAU 2019 guidelines recommend mpMRI with a weak recommendation before biopsy in patients who have not previously undergone a biopsy, whereas the EAU 2020 guideline strongly recommends imaging at the level of 1A evidence. The EAU 2020 guideline strongly recommends a standard 12-core biopsy in addition to the TB if PI-RADS 3 or more lesions are detected on MRI at the level of evidence 2a. (12,13). Therefore, the PI-RADS score, which is evaluated by radiologists before biopsy, is very important.

Study Limitations

The number of patients in the study was small, thus a large sample size was not achieved, which created numerical differences; however, no statistically significant difference was found in some comparisons. The number of cores taken from patients who underwent TB was much lower than the number of cores taken in standard and fusion biopsy, making the calculation and comparison of rates of cancer capture per core difficult.

Conclusion

Improvement in mpMRI imaging, increase in experience of lesion evaluation, and MRI-USG fusion biopsy technique will contribute to the diagnosis, treatment, and follow-up of prostate cancer. No statistically significant difference was found between fusion biopsy and SB in detecting prostate cancer in our study; however, numerically more prostate cancer and clinically significant cancers were detected in fusion biopsy. Therefore, TB alone is insufficient, thus an SB must be added. Larger and randomized studies are needed to rule out clinically insignificant cancers among prostate cancers and create a consensus on the biopsy technique application.

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Critical Review: A.Y., Y.Ş., Supervision: D.B., A.Y., Y.Ş., Concept: D.B., Design: D.B., Data Collection or Processing: A.Y.B., Analysis or Interpretation: A.Y.B., Literature Search: A.Y.B., Writing: D.B., A.Y.B.

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The Predictive Ability of Prostate-Specific Antigen (PSA) Density and Free/Total PSA Ratio in Diagnosing Clinically Significant Prostate Cancer (PCa) in Patients with Histologically Confirmed PCa with a PSA Level of 2.5-10 Ng/ML

Fatih Bıçaklıoğlu[1], Hasan Rıza Aydın[1], Ahmet Özgür Güçtaş[2], Hamit Zafer Aksoy[1]

[1]*University of Health Sciences Turkey, Trabzon Kanuni Training and Research Hospital, Clinic of Urology, Trabzon, Turkey*
[2]*Marmara University, İstanbul Pendik Training and Research Hospital, Clinic of Urology, İstanbul, Turkey*

Abstract

Objective: Many men with non-clinically significant prostate cancer (N-CSPCa) will not progress to symptomatic forms within their lifetime. So, predicting clinically significant PCa (CSPCa) will prevent unnecessary biopsies, overdiagnoses, and overtreatment of patients. Thus, we aimed at demonstrating the predictive ability of prostate-specific antigen (PSA) density (PSAD) and f/t PSA in revealing CSPCa (Gleason score ≥7) in patients diagnosed with prostate cancer on biopsy with a PSA level of 2.5-10 ng/mL.

Materials and Methods: We evaluated 78 patients with PSA 2.5-10.0 ng/mL who underwent transrectal ultrasound guided (TRUSG)-guided prostate biopsy in our clinic between March 2017 and August 2020 and whose histology reported as prostate adenocarcinoma. In addition to the demographic content of the patients, PSA, free PSA, prostate size (with TRUSG), rectal examination findings, and prostate biopsy results were recorded. Clinically significant prostate cancer was defined as a minimum Gleason score of 7.

Results: The mean age of the patients was 66.9±8.4 years, PSA value was 6.9±1.8 ng/mL, free/total PSA ratio was 18±8.1%, and PSAD was 0.150±0.078. The p-values of PSA, free PSA, PSAD, f/t PSA, and prostate volume between CSPCa and N- CSPCa groups were 0.010, 0.780, 0.001, 0.084, and 0.030, respectively. The area under the curve of the PSAD for predicting CSPCa was 0.719 with a 95% CI (0.604-0.835), and the standard errors were 0.062 and 0.059, respectively. When PSAD cut-off was 0.130 for predicting CSPCa, sensitivity and specificity rates were 75% and 63%, respectively.

Conclusion: PSAD can be used in predicting CSPCa, but not f/t PSA. PSAD is not a strong stand-alone tool owing to its sensitivity and specificity, but can be a part of future nomograms for predicting CSPCa and future protocols for active surveillance.

Keywords: Prostate-specific antigen, clinically significant prostate cancer, PSA density

Introduction

Prostate cancer (PCa) is the second most common cancer in men. An estimated 1.1 million cases were diagnosed with PCa worldwide in 2012, accounting for 15% of cancers diagnosed in men (1). For several years, the combination of prostate-specific antigen (PSA) and digital rectal examination (DRE) has been used to diagnose PCa early. Catalona et al. (2) proposed that a total PSA cut-off value of 4 ng/mL should prompt the need for a prostate biopsy to diagnose PCa. However, more than 20% of men diagnosed with PCa have PSA levels lower than 4 ng/mL and early detection would result in a higher probability of curative treatment (3). PSA is not specific for PCa; benign prostate hyperplasia, prostatitis, and other benign events can elevate PSA levels. Therefore, PSA has a low specificity for the diagnosis of PCa at 2.5-10 ng/mL (4). Free/total PSA ratio (f/t PSA), PSA density (PSAD), PSA velocity, and age-specific PSA can be used for early PCa detection in PSA levels of 2.5-10 ng/mL (3,5).

Many men with non-clinically significant PCa (N-CSPCa) will not progress to symptomatic forms within their lifetime (6,7). Currently, there is no universally accepted definition of clinically significant PCa (CSPCa) (8). However, in most studies referenced in recent The European Association of Urology guidelines, CSPCa is defined as an International Society of Urological Pathology

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Address for Correspondence: Hasan Rıza Aydın, University of Health Sciences Turkey, Trabzon Kanuni Training and Research Hospital, Clinic of Urology, Trabzon, Turkey
Phone: +90 505 215 66 61 **E-mail:** hrizaaydin@gmail.com **ORCID-ID:** orcid.org/0000-0002-6272-6929
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(ISUP) grade group ≥2 (Gleason ≥7) (9). Thus, predicting clinically significant PCa (CSPCa) prevents unnecessary biopsies, over diagnoses, and overtreatment in patients. Some studies have shown that PSA, PSAD, f/t PSA can predict a Gleason score and CSPCa at a PSA level of 4-10 ng/dL (10,11). Therefore, we aimed at demonstrating the predictive ability of PSAD and f/t PSA in revealing CSPCa (Gleason ≥7) in patients diagnosed with PCa on biopsy with a PSA level of 2.5-10 ng/mL.

Materials and Methods

The data of the patients who received transrectal ultrasound guided (TRUS) biopsies due to high PSA levels or suspicious findings during DRE were evaluated retrospectively between March 2017 and August 2020. We included all the patients (78 patients) who had PSA levels between 2.5-10 ng/mL, with a histologically confirmed adenocarcinoma of the prostate on TRUS biopsies. We excluded patients who had PSA levels <2.5 or >10 and patients with PSA levels between 2.5-10 ng/mL with benign conditions, ASAP (atypical small acinar proliferation), HGPIN (high-grade prostatic intraepitelial neoplasia), and prostatic malignancy other than adenocarcinoma. In addition to the demographic data of the patients, PSA, free PSA, prostate volume (based on TRUS), DRE findings, and prostate biopsy reports were recorded. Our primary endpoint was to assess the associations of PSAD and f/t PSA with CSPCa. PSAD is the level of serum PSA divided by the prostate volume (9). CSPCa was defined as Gleason score ≥7. Our secondary endpoints were to assess the associations of PSA, free PSA, prostate volume with CSPCa and the associations of PSA, free PSA, PSAD, f/t PSA, and prostate volume with Gleason subgroups. We used the ISUP grading for Gleason subgroups (12) (Table 1). All patients underwent TRUS biopsies in the lateral decubitus position with periprostatic prilocaine block. An 18-gauge automatic disposable needle was used in each case.

Statistical Analysis

Statistical analysis was carried out using the IBM Statistical Package for Social Sciences version 20 software. The suitability of the variables to normal distribution was examined using the Shapiro-Wilk Test. The Mann-Whitney U test was used to compare continuous outcome variables in two groups; One-Way analysis of variance and Kruskal-Wallis H tests were used in three or more groups. Post-hoc Tukey-HSD, LSD, and Tamhane's T2 were used in groups showing normal distribution, and post-hoc Mann-Whitney U test in groups that did not show normal distribution for multiple comparisons. The significance level was set at $p<0.05$. Two receiver operating characteristic (ROC) curves were drawn to obtain the best PSA and PSAD cut-off values for CSPCa.

The study was approved by the Local Ethical Board of our hospital prior to recruitment of files (University of Health Sciences Turkey, Trabzon Kanuni Training and Research Hospital, approval number: 2021/03-01, date: 13.01.2021).

Results

The mean age of the patients was 66.9±8.4 years (44-88), PSA was 6.92±1.85 ng/mL (2.69-9.91), free PSA was 1.20±0.52 ng/mL (0.15-2.56), f/t PSA was 18.04±8.1% (4-46), prostate volume was 53.6±19.4 (18-108), and PSAD was 0.150±0.078 (0.045-0.357). ISUP grade groups of the patients were as follows: 46 patients (59%) in grade group 1, 21 patients (26.9%) in grade group 2, 7 patients (9%) in grade group 3, 4 patients (5.1%) in grade group 4, and none in group 5. We recorded 32 patients (41%) with CSPCa (Gleason ≥7, ISUP group ≥2).

The p-values of PSA, free PSA, PSAD, f/t PSA, and prostate volume between CSPCa and N-CSPCa groups were 0.010, 0.780, 0.001, 0.084, and 0.030, respectively (Table 2).

The p-values of PSA, free PSA, PSAD, f/t PSA, and prostate volume between ISUP grade groups were 0.013, 0.850, 0.001, 0.379, and 0.022, respectively (Table 3).

The area under the ROC curve (AUC) of the PSA and PSAD for predicting CSPCa was 0.671 with a 95% CI (0.549-0.793), 0.719 with a 95% CI (0.604-0.835), and the standard errors were 0.062 and 0.059, respectively. When PSA cut-off was 6.29 ng/mL for predicting CSPCa, sensitivity and specificity were 78.1% and 50%, respectively. When PSAD cut-off was 0.130, sensitivity and specificity were 75% and 63%, respectively (Figure 1).

Discussion

PCa is one of the malignancies with a serum-based biomarker. Since PSA's discovery in 1979 until clinical application in the late 1980s, PSA has evolved into an invaluable tool for detecting, staging, and monitoring PCa in men. For several years, an abnormal DRE, elevated PSA, or both were used to diagnose

Table 1. The International Society of Urological Pathology (ISUP) grading system

ISUP grade groups	Gleason score
Grade group 1	Gleason score ≤6
Grade group 2	Gleason score 3+4=7
Grade group 3	Gleason score 4+3=7
Grade group 4	Gleason score 4+4=8; 3+5=8; 5+3=8
Grade group 5	Gleason score 4+5=9; Gleason score 5+4=9; Gleason score 5+5=10

ISUP: International Society of Urological Pathology

Table 2. Clinically significant (Gleason ≥7) and non-clinically significant (Gleason <7) prostate cancer distributions accordindg to patient's PSA, free PSA, PSA density, free / total PSA ratio and prostate volume

	Gleason ≥7 (ISUP grade group ≥2) (n=32)	Gleason <7 (ISUP grade group 1) (n=46)	p-value
PSA	7.6±1.7[A] (7.66)	6.5±1.8 (6.52)	0.010[Aa]
Free PSA	1.2±0.5 (1.13)	1.2±0.5 (1.10)	0.780[a]
PSA density	0.2±0.07[A] (0.16)	0.1±0.07 (0.106)	0.001[Aa]
Free/total PSA ratio	16.1±7 (15.5)	19.1±8.6 (19)	0.084[a]
Prostate volume	47.9±16.4 (48.5)	57.6±20.6A (61)	0.030[Ab]

ISUP: International Society of Urological Pathology, PSA: Prostate-specific antigen
[A]Represents a statistically significant difference (P<0.05).
[a]Mann-Whitney U Test
[b]2 sample independent t test

Table 3. ISUP grade group distributions accordindg to patient's PSA, free PSA, PSA density, free/total PSA ratio and prostate volume						
	All patients (n=78)	**ISUP grade group 1 (n=46)**	**ISUP grade group 2 (n=21)**	**ISUP grade group 3 (n=7)**	**ISUP grade group 4 (n=4)**	**p-value**
PSA	6.9±1.9 (7.08)	6.5±1.8 (6.52)	7.4±1.8 (7.37)	7.3±1.4 (7.36)	9.2±0.4A (9.22)	0.013[Aa]
Free PSA	1.2±0.5 (1.11)	1.2±0.5 (1.10)	1.2±0.6 (1.09)	1.2±0.4 (1.11)	1.5±0.7 (1.29)	0.850[b]
PSA density	0.150±0.08 (0.131)	0.1±0.08 (0.106)	0.2±0.07 (1.89)	0.1±0.03 (0.11)	0.3±0.08A (0.25)	0.001[Ab]
Free/total PSA ratio	18±8.1 (17)	19.4±8.6 (19)	16.1±7.6 (16)	16.4±6.2 (15)	15.6±7.1 (13,5)	0.379[b]
Prostate volume	53.6±19.5 (54)	57.6±20.6 (61)	45.0±16.3 (47)	61.6±11.5[A] (60)	39.3±12.8 (38)	0.022[Aa]

ISUP: International Society of Urological Pathology, PSA: Prostate-specific antigen
[A]Represents a statistically significant difference (p<0.05).
[a]One-Way ANOVA
[b]Kruskal-Wallis H test

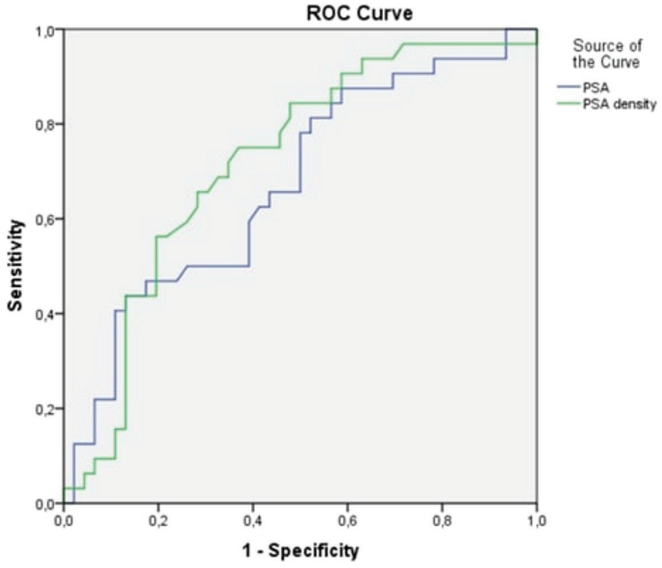

Figure 1. The AUC of PSA, PSA density for predicting clinically significant PCa

PSA: Prostate-specific antigen, ROC: Receiver operating characteristics, PCa: Prostate cancer, AUC: Area undar the curve

PCa. Today, most PCa are diagnosed as clinically non-palpable (stage T1c) with PSA levels between 2.5 and 10 ng/mL (13). PSA screening for PCa leads to a small reduction in disease-specific mortality over 10 years but does not affect overall mortality (14). Nowadays, attention has turned from the detection of any PCa to a focus on detecting CSPCa, often interpreted as a Gleason score ≥7 (13). PSAD and f/t PSA are well-known for PCa detection, especially in PSA levels <10 ng/mL, and this prompted us to carry out this study (3,5).

Recent studies have shown that PSAD is associated with CSPCa. Omri et al. (15) found that PSAD is correlated with CSPCa (based on radical prostatectomy histology reports) in small (<50 cc) and medium (50-75 cc) size prostates and level of PSAD is directly associated with the ISUP grade groups. Liu et al. (11) demonstrated that PSAD predicted CSPCa (based on prostate biopsy pathology reports) in the PSA level ranging 4-10 ng/mL. Compatible with these studies, we found clinical significance between PSAD and CSPCa (Gleason ≥7, ISUP grade group ≥2) (p<0.001). This was not surprising because we found clinical significance between PSA and CSPCa (p<0.010) and prostate volume and CSPCa (p<0.030) (Table 2). Moreover, we also found clinical significance between PSAD and ISUP grade groups, especially for ISUP grade group 4 (Table 3). However, there was no correlation between ISUP grade groups and PSAD as well as between prostate volume and ISUP grade groups. ISUP grade group 3 had the biggest mean prostate volume in our study, and when we excluded that group, we could see a correlation between PSAD and ISUP grade groups (groups 1, 2, and 4). We had no correlation between PSAD and CSPCa for large prostates as in Omri et al. (15) but not fully certain because all ISUP grade groups mean prostate volume were <75 cc in our study.

Ceylan et al. (10) revealed a relationship between a higher Gleason score and decreased f/t PSA and f/t PSA can be an indicator for predicting the Gleason score. Unlike that, there was no clinical significance between f/t PSA and CSPCa in our study. Apart from PSA values, there was no clinical significance between free PSA and CSPCa. The mean free PSA was similar between the CSPCa and N-CSPCa groups in our study (Table 2). Additionally, there was no correlation between free PSA and ISUP grade groups (Table 3).

There was clinical significance between prostate volume and CSPCa in our study. We did not have any inclusion or exclusion criteria related to prostate volume. We postulated that prostate volume differences were also a reason for PSAD significance between CSPCa and N-CSPCa groups. PSAD is the level of serum PSA divided by the prostate volume. Loeb et al. (16) identified 658 men age ≥50 years with PSA levels from 4-10 ng/mL and normal DRE that underwent prostate biopsy. Prostate volume had clinically significant difference between Gleason score <7 and ≥7 groups, as in our study.

PSAD is beneficial, available, cost-effective, and can be used as a tool for predicting CSPCa. Nowadays, PSAD can be combined with MRI for superior predictive ability to detect CSPCa (17,18). PSAD can also be used for predicting N-CSPCa. Therefore, PSAD can be used for better identification of candidates for active surveillance in the future, as Ha et al. (19) stated. They found that adopting a lower PSAD threshold of 0.085 decreased the risk of advanced disease to 17.5-21.7%. In our study, the PSAD cut-off was 0.130 for predicting CSPCa (sensitivity 75% and specificity 63%).

Study Limitations

The first limitation of our study is its sample size. The second limitation is that we used prostate biopsy reports for deciding clinically significant PCa as reported in Liu et al. (11) and Ceylan

et al. (10) However, the latest pathology can upgrade in radical prostatectomy specimens. It may be that some of our N-CSPCa patients had CSPCa in reality. Corcoran et al. (20) revealed that 418 of 1312 patients had an upgrade in Gleason score. Among the1312 patients, 363 had upgraded Gleason 6 to >6. This study found that PSAD was also a predictor of upgrade of biopsy Gleason 6. We could not use radical prostatectomy pathology reports for deciding CSPCa because some of our patients had chosen active surveillance or radiation therapy in our center, while others lost to follow-up or had chosen focal therapy alternatives in other centers.

Conclusion

According to the results of this study, PSAD can be used for predicting CSPCa, but not f/t PSA. PSAD is not a strong stand-alone tool owing to its sensitivity and specificity, but we suggest that PSAD can be a part of future nomograms for predicting CSPCa and future protocols for active surveillance. Therefore, we can prevent patients from overdiagnoses and overtreatment through this predictive ability.

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Ethics

Ethics Committee Approval: The study was approved by the Local Ethical Board of our hospital prior to recruitment of files (University of Health Sciences Turkey, Trabzon Kanuni Training and Research Hospital, approval number: 2021/03-01, date: 13.01.2021).

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Effect of Neoadjuvant Hormonal Treatment on the Necessity of Secondary Radiotherapy in Patients Undergoing Radical Prostatectomy for High-Risk Prostate Cancer

Csaba Berczi[1], Janos Docs[1], Ben Thomas[2], Zsolt Bacso[3], Tibor Flasko[1]

[1]*Department of Urology, University of Debrecen, Debrecen, Hungary*
[2]*Department of Internal Medicine, University of Debrecen, Debrecen, Hungary*
[3]*Department of Biophysics and Cell Biology, University of Debrecen, Debrecen, Hungary*

Abstract

Objective: The goal of this study was to see how neoadjuvant hormonal therapy affected the frequency of secondary radiotherapy after radical prostatectomy for high-risk prostate tumors.
Materials and Methods: Further, 527 patients with high-risk prostate cancer were divided into two groups. In group 1 (n=139), neoadjuvant androgen deprivation treatment was administered prior to surgery, whereas it was not applied preoperatively in group 2 (n=388).
Results: Biochemical progression was observed in 27 patients (19.4%) in group 1 and 54 patients (13.9%) in group 2 (p=0.148). Adjuvant and salvage irradiation were administered to patients with pT2 cancer who received neoadjuvant hvsormonal therapy in 17.3% and 7.1% of the cases, respectively, whereas in cases without prior neoadjuvant treatment, adjuvant and salvage irradiation were administered in 21.6% and 5.4% (p=0.370 and p=0.523). Clinically advanced cancer patients who received neoadjuvant hormonal treatment had adjuvant and salvage irradiation in 34.1% and 2.4% of the cases, whereas patients who did not receive neoadjuvant treatment had adjuvant and salvage radiotherapy in 35.9% and 7.6% of the cases (p=0.856 and p=0.278).
Conclusion: Although neoadjuvant hormonal treatment improved local tumor control, it did not reduce the frequency of secondary radiotherapy significantly. Overall, and in the cT2 subgroup, there was a relative decrease in the number of adjuvant treatments compared to salvage treatments in neoadjuvant-treated patients.
Keywords: High-risk carcinoma, irradiation, neoadjuvant hormonal treatment, prostate cancer, radical prostatectomy

Introduction

The most common type of cancer in men is prostate cancer. Treatment for low- and intermediate-risk prostate tumors has been resolved; however, therapy for high-risk cancers has not been fully resolved yet. According to D'Amico's classification of prostate cancer, a high-risk tumor has a prostatespecific antigen (PSA) of ≥20 ng/mL, a Gleason score of ≥8, or a cT3 grade tumor. Following radical prostatectomy for high-risk prostate tumors, biochemical progression (BCP) occurs in 55-70% of cases (1,2). In in 13% of these cases, distant metastasis occurs, and tumor-related mortality occurs in 6%.

Currently, radiation therapy, in conjunction with hormonal treatment and multimodal treatment, can be used to successfully treat high-risk prostate tumors (1,2,3). After radical prostatectomy, adjuvant or salvage radiation can be administered as part of a multimodal treatment depending on the histology and postoperative PSA levels. In terms of definitive radiation therapy, randomized clinical trials have shown that hormonal treatment combined with irradiation - especially long-term hormonal treatment - improved oncological outcomes (4,5). The role of neoadjuvant hormonal therapy (ADT) prior to radical prostatectomy remains unknown. According to the European Association of Urology guidelines, the routine use of neoadjuvant hormonal therapy is not recommended before radical surgery of high-risk prostate tumors. However, several studies have shown that neoadjuvant hormonal treatment improves local tumor control (5,6,7,8,9). In multimodal

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Address for Correspondence: Csaba Berczi, Department of Urology, University of Debrecen, Hungary
E-mail: berczi@med.unideb.hu **ORCID-ID:** orcid.org/0000-0002-7506-6077
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treatments, the efficacy of neoadjuvant ADT in slowing tumor progression and thus improving tumor-specific survival rates has not been demonstrated (6,10). The effect of neoadjuvant therapy on the frequency of adjuvant and salvage radiotherapy is still unknown.

In this study, we investigated the efficacy of neoadjuvant androgen deprivation hormonal treatment before radical prostatectomy in patients with high-risk prostate cancer, as well as the need, if any, for subsequent adjuvant and salvage radiation treatment. Several studies have looked into the potential benefits of neoadjuvant treatment on tumor progression, but it has not really been investigated for secondary treatments. Our retrospective study included a relatively large number of patients with a long-term follow-up period.

Materials and Methods

From January 1996 to January 2019, our institute treated 527 patients with radical prostatectomy for high-risk prostate cancer.

On all patients with high-risk cancer, imaging was performed to determine the local extension of the tumor. Previously, (computed tomography) CT was usually performed before moving on to magnetic resonance imaging (MRI). There were 243 CT scans, 247 pelvic MRI scans, and 46 endorectal MRI scans. In 394 cases, imaging showed clinically localized cancer, while in 133 cases, imaging revealed locally advanced prostate cancer. In these patients, imaging procedures such as bone scintigraphy revealed no metastases.

Patients with high-risk prostate tumors were divided into two groups. Before radical prostatectomy, patients in group 1 (n=139) received neoadjuvant androgen deprivation treatment. On the other hand, patients in group 2 (n=388) did not receive any hormonal therapy prior to surgery. In group 1, the patients had a mean age of 64.5±6.2 years and a mean PSA level of 32.5±24.5 ng/mL. In group 2, the mean age was 63.8±6.3 years and the mean PSA level was 24.0±21.0 ng/mL. The neoadjuvant hormonal treatment lasted between 3 and 6 months.

In our institute, we primarily used neoadjuvant hormonal treatment when the patient's PSA value was significantly higher or there was a significant extraprostatic tumor extension based on imaging. However, in some cases, the patient already begun hormonal treatment before being referred to our unit for radical prostatectomy.

The histological stage was determined retrospectively using the 2016 UICC TNM system. Following surgery, postoperative treatment was administered according to the current European Association of Urology protocol. During the follow-up period, PSA was measured every 3 months for the first 3 years, then every 6 months for another 5 years, and then annually after that. Imaging was performed on PSA elevation or following patient complaints. BCP was defined as an increase in PSA above 0.2 ng/mL on at least two occasions.

Statistical Analysis

Statistical analyses were performed using the Student's t-test. A p-value of less than 0.05 was considered significant. We used Microsoft (MS) Excel and open-source R-programming packages. First, we visualized data distribution with histograms and boxplots using the "gplots" and "ggplot2" R-packages (R package version 3.0.3; available from https://CRAN.R-project.org/package=gplots) (11). Then, we illustrated the dichotomic clinical data using correlation plots by the "corrplot" package (R package "corrplot": Visualization of a Correlation Matrix-Version 0.84; available from https://github.com/taiyun/corrplot). To assess the statistical difference in frequencies, we calculated the relative risks in the two groups. We then checked to see if their quotient (RR) differed significantly from one another (p-value). The relative risk and its significance were evaluated using MS Excel Pivotal tables or the "epitools" and "epiDisplay" R-packages (R package version 0.5-10.1; available from https://CRAN.R-project.org/package=epitools). We used the Kendall correlation to estimate associations in clinical datasets.

The study was approved by the Ethical Committee of University of Debrecen (approval number: DE RKEB/IKEB: 5504-2020).

Results

Preoperative PSA levels were significantly higher in patients receiving neoadjuvant hormonal therapy (p=0.0007). Based on the imaging, clinically locally advanced prostate cancer was detected in 41 cases (29.5%) in group 1 and 92 cases (23.7%) in group 2 (p=0.194).

In group 1, histology showed locally advanced (pT3) tumors in 52 patients (37.4%) and margin positivity in 26 patients (18.7%) (Table 1).

The occurrence of pT3 stage and margin positivity was significantly lower in the subgroup receiving neoadjuvant treatment. We found no substantial changes in the pN1, BCP, or local recurrence subgroups.

In group 2, pT3 stage tumors were detected in 214 patients (55.2%), with125 patients (32.2%) having a positive surgical margin. Locally advanced prostate cancer and margin positivity were more common in the non-neoadjuvant hormonal treatment group (p=0.00057 and p=0.0017). Lymph node positivity was similar in both groups (p=0.72). The mean follow-up period was 50 months.

During the follow-up period, BCP was diagnosed in 27 patients (19.4%) in group 1 and 54 patients (13.9%) in group 2 (p=0.130).

Clinically organ-confined (cT2) tumors (n=394):

In this subgroup, 98 patients received neoadjuvant hormonal treatment, while 296 patients did not. Among those patients, in the neoadjuvant hormone treatment group, histology showed 36 patients (36.7%) having locally advanced (pT3) tumors, while 18 patients (18.3%) had margin positivity. In the neoadjuvant hormonal treatment group, pT3 grade tumors were found in 154 cases (52%), with 91 patients (30.7%) having a positive surgical margin. Locally advanced prostate cancer and margin positivity were significantly more common in the non-neoadjuvant hormonal treatment group (p=0.012 and p=0.02).

During the follow-up period, BCP was diagnosed in 19 patients (19.3%) in the neoadjuvant hormone treatment group and in 41 patients (13.8%) in the non-neoadjuvant group. There was no statistically significant difference between the two groups.

Table 1. Changes in the frequencies of this clinical trial are shown as a result of radical prostatectomy after neoadjuvant pretreatment. To assess the statistical difference in frequencies, we calculated the relative risks in the two groups and then checked to see if their quotient (RR) was significantly different from one (p-value). We also gave a 95% confidence interval for the risk ratio

Signs	Neoadjuvant	Control	p-value	Risk ratio	95% confidence interval of the RR	
					lower	upper
pT3 (n)	52	214	0.0003	0.68	0.54	0.86
pT3 (%)	37.4	55.2				
pN1 (n)	14	35	0.7048	1.12	0.62	2.01
pN1 (%)	10.1	9				
Margin pos. (n)	26	125	0.0021	0.58	0.40	0.85
Margin pos. (%)	18.7	32.2				
BCR (n)	27	54	0.1301	1.40	0.92	2.12
BCR (%)	19.4	13.9				
Local recurrence (n)	4	11	0.9482	1.02	0.33	3.14
Local recurrence (%)	2.9	2.8				
Distant metastasis (n)	10	8	0.0088	3.49	1.41	8.66
Distant metastasis (%)	7.2	2.1				

Clinically locally advanced (cT3) tumors (n=133):

In this subgroup, 41 patients received neoadjuvant androgen deprivation therapy, while 92 patients did not. In the neoadjuvant hormonal treatment group, histological examination revealed locally advanced (pT3) cancers in 16 cases (39.0%) and margin positivity in 8 patients (19.5%). In the non-neoadjuvant treatment group, pT3 grade tumors were found in 60 patients (65.2%), while 34 patients (36.9%) had positive surgical margin. Locally advanced prostate cancer and margin positivity were significantly more common in the non-neoadjuvant hormonal treatment group (p=0.008 and p=0.05).

During the follow-up period, BCP was observed in 8 patients (19.5%) in group 1 and in 13 patients (14.1%) in group 2. There was no statistically significant difference between the two groups.

Adjuvant and Salvage Treatment

Adjuvant and salvage irradiation were performed in 22.3% and 5.8% of patients in group 1, respectively, and in 25.0% and 5.9% of patients in group 2, respectively (p=0.518 and p=0.940) (Table 2).

Using the risk ratio, we could evaluate relative changes in the numbers of treated patients. Overall, and in the cT2 subgroup, we observed a relative decrease in the number of adjuvant treatments compared to salvage treatments in the cases of neoadjuvant-treated patients. In the cT3 subgroup, however, the opposite trend was observed. None of the changes were statistically significant in terms of the patient numbers we examined.

Figure 1 depicts the distribution of secondary treatments.

Figure 2 depicts the pairwise correlations between neoadjuvant hormone-treated and non-hormone-treated parameters of patients. These analyses show the types of associations that were observed between the various clinical signs of disease monitored, patient outcome, and the therapeutical path taken in neoadjuvant-treated and non-treated cases of the study. Moreover, the linear relationship between the linked parameters is represented by black dots. The white dots represent the inverse relationship, and a lack of dots indicates a nonsignificant association. The size of the dots reflects the extent of the association. In neoadjuvant-pretreated cases, the adjuvant-ADT and adjuvant-irradiation treatment raws were better correlating with the higher preoperative PSA level, the more positive clinical imaging (cT3) sign, the larger preoperative Gleason score, the pT3 and N1, and the margin positivity columns. These correlations indicate the presence of signs, which resulted in the neoadjuvant pretreatment. It is an inherent bias in our study that can be explained by an unintentional exclusion of less severe cases from the non-hormonal-treated group prior to surgery.

In the preoperative non-hormonal-treated cases, margin positivity had a stronger linear correlation with adjuvant-ADT and adjuvant-irradiation therapy than in hormone-treated cases.

Salvage-ADT and salvage-irradiation therapies were found to be more strongly correlated with BCP, local recurrence, metastasis, and increased mortality. The lack of hormonal pretreatment increases the likelihood of reaching more clinically severe outcomes.

Discussion

The most common malignant disease in men is prostate cancer, with 30% of cases being high risk. At present, there are conflicting views on the best way to treat high-risk prostate carcinomas (12,13,14).

Neoadjuvant treatments used prior to surgery serve two purposes: one is to provide local tumor control and the other is to provide systemic management of microscopic metastases. The initially locally advanced tumor may become operable, with a higher chance of eliminating removable tumors due to improved local tumor control.

In high-risk prostate tumors, neoadjuvant treatment prior to radical prostatectomy may also help provide better tumor control, decrease local or locally advanced tumors, and eradicate microscopic metastases.

Table 2. Indicates the changes in the frequency of adjuvant and salvage irradiation treatments after radical prostatectomy when neoadjuvant pretreatment was applied. To assess the statistical difference in the frequencies, we calculated the relative risks in the two groups and then checked to see if their quotient (RR) was significantly different from one (p-value). We also gave a 95% confidence interval for the risk ratio

Signs	Neoadjuvant	Control	p-value	Risk ratio	95% confidence interval of the RR		
					lower	upper	
Adjuvant irradiation (n)	31	97	0.5310	0.89	0.63	1.27	
Adjuvant irradiation (%)	22.3	25.0					
Salvage irradiation (n)	8	23	0.9644	0.97	0.44		2.12
Salvage irradiation (%)	5.8	5.9					
cT2							
Signs	**Neoadjuvant**	**Control**	**p-value**	**Risk ratio**	**95% confidence interval of the RR**		
					lower		**upper**
Adjuvant irradiation (n)	17	64	0.3705	0.80	0.49		1.30
Adjuvant irradiation (%)	17.3	21.6					
Salvage irradiation (n)	7	16	0.5239	1.32	0.56		3.12
Salvage irradiation (%)	7.1	5.4					
cT3							
Signs	**Neoadjuvant**	**Control**	**p-value**	**Risk ratio**	**95% confidence interval of the RR**		
					lower		**upper**
Adjuvant irradiation (n)	14	33	0.8562	0.95	0.57		1.58
Adjuvant irradiation (%)	34.1	35.9					
Salvage irradiation (n)	1	7	0.2783	0.32	0.04		2.52
Salvage irradiation (%)	2.4	7.6					

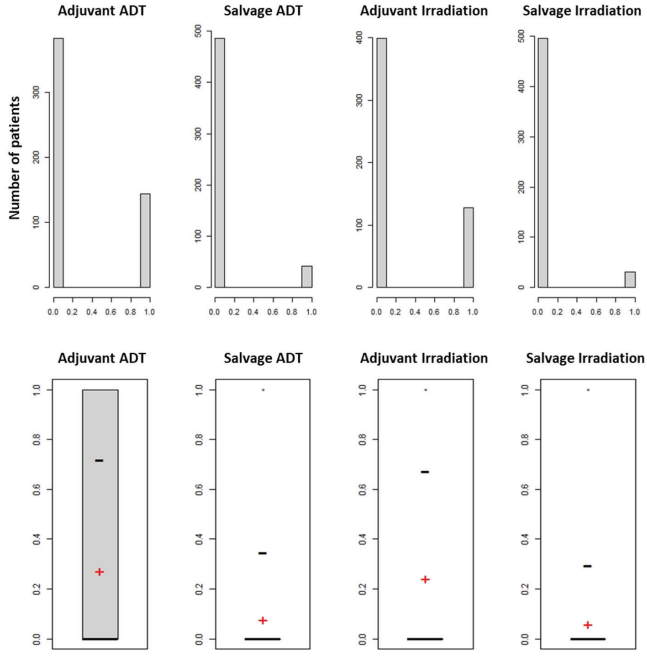

Figure 1. The histograms depict the distribution of the posttreatment data

The upper histograms depict the distribution, while the bottom boxplots show the median (horizontal thick black line), minimum (lowest horizontal line), maximum (top dot), and first and third quartiles (regions shaded to gray) of the posttreatment dataset. Red "+" is the mean, and black "-" is the standard deviation from the mean into the boxplot's positive direction

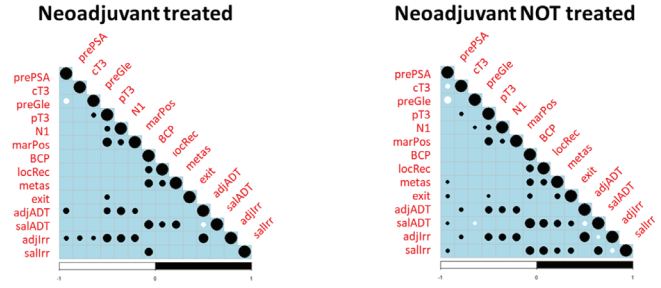

Figure 2. This figure illustrates the pairwise correlations between clinical parameters in the neoadjuvant hormone-treated and non-treated groups

The relationship between the data was calculated using the Kendall correlation coefficients. The size of the black and white dots is proportional to the value of the coefficients. According to the scale below the triangles, the black dot indicates a linear relationship, while the white dot indicates the reverse relationship between the parameters. No dot was included in the table if the deviation of the correlation coefficient's value from 0 was not significant (p>0.05)

McKay et al. (7), in their meta-analysis of ten clinical trials, reported a significant reduction in pathological T-stage prostate tumors after neoadjuvant hormonal treatment, an increase in the proportion of tumors localized to the prostate, a decrease in margin-positive cases, and a decrease in lymph node metastases. In several of their studies, Hsu et al. (15) reported that the significant prognostic factors after radical prostatectomy in cT3 patients are tumor differentiation, marginal positivity, and lymph node positivity. These are the most critical factors determining the 10-year BCP-free survival, clinical progression-free survival, tumor-specific survival, and overall survival (16).

Hu et al. (17), in their meta-analysis of neo-adjuvant hormonal treatments for non-metastatic prostate tumors, found that the time to BCP and overall survival was significantly increased. In their multicenter study of high-risk prostate cancer patients, Tosco et al. (18) also found that neoadjuvant hormonal therapy significantly reduced tumor-induced mortality.

However, most clinical trials of neoadjuvant hormonal therapy before radical prostatectomy found that BCP and overall survival did not improve (7,19).

Although local tumor control was better in our study, there was no significant difference in BCP and survival rates between the two groups.

In our study, we examined the benefits of neoadjuvant hormonal therapy before radical prostatectomy in patients with high-risk prostate cancer, both in terms of oncological outcomes and possible secondary treatment regimens. Several studies have been conducted to investigate the efficacy of neoadjuvant treatment on tumor progression. However, it has not been thoroughly investigated how the frequency of adjuvant and salvage treatments could be adjusted following neoadjuvant treatment. When considering neoadjuvant hormonal treatment before surgery, it is critical to remember that neoadjuvant treatment can have an impact on the overall therapy administered. Adjuvant and salvage therapies administered following radical prostatectomy are essential for improving BCP-free survival, tumor-free survival, and quality of life.

If the frequency of the required adjuvant and salvage treatments was reduced as a result of neoadjuvant therapy, with the same oncological outcome, patients' quality of life would be significantly improved. It is well known that complications are common following adjuvant and salvage radiotherapy.

After adjuvant irradiation, the incidence of early and late complications ranges from 15 to 35% and from 2 to 8%, respectively (20).

However, in our study, there was no significant difference in the frequency of adjuvant and salvage treatments between the two groups. Our data showed that adjuvant radiotherapy was less frequently required in the neoadjuvant hormonal treatment group, although preoperative PSA was significantly higher.

Study Limitations

Our study had some limitations. For starters, it was a retrospective rather than a prospective study. Second, we found no significant benefit of neoadjuvant hormonal therapy in reducing the need for a secondary treatment, and we discovered that only the hormonal pretreatment had a tendency to reduce the number of adjuvant treatments (especially in cT2 subgroup).

Conclusion

Our results showed that neoadjuvant hormonal treatment provided significantly better local tumor control in the cases of radical prostatectomies for locally advanced high-risk prostate tumors. Neoadjuvant hormonal therapy had no effect on tumor progression and did not reduce the number of adjuvant and salvage treatments required. However, the correlation analysis showed that, overall and in the cT2 subgroup, a relative decrease in the number of adjuvant treatments was observed in patients who received neoadjuvant treatment compared to those who received salvage treatments. Although the benefits of the neoadjuvant hormonal treatment for adjuvant irradiation did not reach statistical significance in patients with high-risk prostate cancer, there was strong evidence of a benefit from neoadjuvant treatment.

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Ethics

Ethics Committee Approval: The study was approved by the Ethical Committee of University of Debrecen (approval number: DE RKEB/IKEB: 5504-2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Critical Review: T.F., Concept: C.B., Design: C.B., Data Collection or Processing: C.B., J.D., Analysis or Interpretation: Z.B., Literature Search: Z.B., Writing: C.B., J.D., B.T.

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Original Article

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Comparison of the Efficacy of Definitive Radiotherapy and Radical Prostatectomy in High-Risk Prostate Cancer: A Single-Center Experience

Berrin İnanç[1], Özlem Mermut[1], Uğur Yücetaş[2]

[1]*University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Turkey*
[2]*University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Urology, İstanbul, Turkey*

Abstract

Objective: This retrospective study aimed to examine treatment outcomes and patient selection criteria in individuals with high-risk prostate cancer (PCa) treated with definitive radiotherapy (RT) and androgen deprivation therapy (ADT) or radical prostatectomy (RP).
Materials and Methods: In total, 72 patients treated with definitive RT or RP for high-risk PCa between 2011 and 2018 were included in the study. Patient characteristics, treatment data, and follow-up data were obtained from the patient's file.
Results: Of 72 patients with high-risk PCa, 34 (46.6%) received definitive RT and ADT and 38 (52.1%) had undergone RP. The median follow-up time in the RP group was 44.5 (range, 14-100) months and that in the RP group was 48 (range, 9-108) months. No significant between-group difference was found in the biochemical recurrence-free survival, metastasis-free survival, and overall survival (OS) rates after 3 and 5 years of follow-ups (p≥0.005). In a subgroup analysis, RT was the treatment of choice for patients aged ≥65 years and for those with prostate-specific antigen values of ≥20 ng/dL, a Gleason score (GS) of 9-10, and T stage T3-4 and N+ status (p=0.015, 0.001, 0.035, and 0.022, respectively). In the univariate and multivariate analyses, age ≥65 years and GS of 8-10 were significant risk factors for reduced OS in all high-risk PCa cases.
Conclusion: No significant difference was found in the survival outcome of patients in the RT + ADT and RP groups. RT should be preferred in patients aged ≥65 years and in those with a high T stage and GS of 8-10.
Keywords: Prostate cancer, radical prostatectomy, radiotherapy

Introduction

Prostate cancer (PCa) is the second most common cancer in men and the fifth most common cause of death among men worldwide (1). It has one of the highest mortality rates among all cancers, despite surgery and radiotherapy (RT), with a high rate of relapse and progression, especially in those with high-risk PCa (2). Historically, RT, androgen deprivation therapy (ADT), or a combination of both was the standard treatment for patients with high-risk PCa. Several studies have now suggested that a radical prostatectomy (RP) can control disease progression and improve survival (3,4,5,6). However, there is no consensus on the optimal treatment for patients with high-risk localized PCa [≤T2c or a Gleason score (GS) of 8-10 or prostate-specific antigen (PSA) level of >20 ng/dL]. Current guidelines recommend both RT and RP for high-risk PCa (7).

The advantages and disadvantages of both regimens should be considered in treatment decision making. While RP guides the selection of patients who can benefit from adjuvant therapies by correct staging, it cannot eradicate micrometastatic diseases (8). By contrast, a combination of RP and ADT eliminates pelvic micrometastases in high-risk cases. However, the long treatment period (i.e., 6-8 weeks) is a major disadvantage of RT + ADT.

Regarding patient selection for RT and RP, the side effect profiles of each treatment regimen must be considered. The side effects in patients with high-risk PCa who underwent RP frequently included impotence, urinary incontinence, and bleeding, whereas those in patients who received RT commonly included bladder and bowel complaints (9,10). These RT-related side effects were more common after irradiation using conventional RT techniques, such as conformal techniques, rather than new methods (e.g., image-guided RT and volumetric arc therapy).

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Address for Correspondence: Berrin İnanç, University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Turkey
Phone: +90 212 459 66 92 **E-mail:** byalcin77@hotmail.com **ORCID-ID:** orcid.org/0000-0002-6354-4609
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In patients with high-risk PCa, all treatment decisions regarding the use of RT + ADT or RP should be based on long-term survival data, tumor control rates, and treatment side effects, as well as patient preference.

In this study, we examined treatment outcomes and patient selection criteria in individuals with high-risk PCa treated by definitive RT or radical RP.

Materials and Methods

Patient Characteristics

In this retrospective study, we evaluated 72 patients diagnosed with high-risk PCa who were treated with RT + ADT or RP in İstanbul Training and Research Hospital, Department of Radiation Oncology, between January 2011 and December 2018. All patients underwent pelvic computed tomography (CT) or pelvic magnetic resonance imaging in addition to a bone scan. Some patients underwent prostate-specific membrane antigen positron emission tomography (PSMA PET/CT) to exclude distant metastasis.

The inclusion criteria were as follows: a histologically proven adenocarcinoma of the prostate gland, high-risk PCa according to D'Amico's risk classification criteria (≥T2c or a GS of 8-10 or PSA level of >20 ng/dL), treatment with RP or RT + ADT, and data were available including survival outcomes. Patients who had distant metastases and evidence of clinical pelvic lymph node involvement were excluded. All relevant laboratory and pathology results were obtained from the hospital's database. Data related to the treatment follow-up were obtained from clinical files.

The study was approved by the local ethics committee of our hospital. All patients were given a thorough explanation of the study, and informed consent was obtained from all of them (approval no: 2021-2664).

RT- and Surgery-Related Data

In the definitive RT group, intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT) was applied. The treatment schedule was as follows: external beam RT in 1.8-2.0 Gy daily fractions with 6 MV photon beams at 5 days a week. A total dose of 46 Gy was delivered to the pelvic region, 54 Gy to the seminal vesicle, and 76-78 Gy to the prostate. According to the risk stratification based on Partin's tables (11), the entire pelvic region was included in the RT field in patients whose pelvic lymph node involvement risk exceeded 15%. The gross tumor volume included the prostate volume. The clinical target volume was defined as follows: CTV1 comprised the prostate only, CTV2 comprised CTV1 plus the seminal vesicles, and CTV3 comprised CTV1 plus CTV2 plus pelvic lymph nodes. The planning treatment volume was defined as pelvic lymph nodes with 0.7 mm margin. CTV2 and CTV1 were defined as 8 mm in all directions and 5 mm in the posterior direction.

Postoperative RT was given as adjuvant or salvage treatment in the RP group. Adjuvant RT was administered 4-6 months after surgery. Most of the patients in the RP group had positive surgical margins. Salvage RT was applied in the event of biochemical failure. In the RP group, biochemical failure was defined as an increase in the PSA level of >0.1 ng/mL postoperatively. In the RT group, it was defined according to the Phoenix criteria as a PSA level of 2 ng/mL above the lowest level (12). Postoperative RT was applied to the operating bed with daily fractions of 1.8-2.0 Gy with 6 MV photon beams. Surgical treatment comprised RP and pelvic lymph node dissection.

Outcomes and Follow-up

The biochemical recurrence-free survival (BRFS), metastasis-free survival (MFS), and overall survival (OS) rates of the patients in each treatment group were recorded. BRFS, MFS, and OS were defined as the time from RP/RT until biochemical failure, metastasis, and death from any cause, respectively.

Treatment toxicity was evaluated using the Common Terminology Criteria for Adverse Events version 4.0 (13). During RT, all patients were assessed at least once a week. At this time, they underwent a clinical examination, and their blood count was measured. After RT, their PSA levels were checked every 3 months in the first 2 years, and abdominal/pelvic tomography and bone scanning were performed every 6 months. Follow-up was performed every 6 months for 2-5 years and once a year after 5 years. During the follow-up period, all patients with suspected local or regional recurrence and distant metastasis were referred for PSMA PET/CT and multiparametric magnetic resonance imaging.

Statistical Analyses

The compliance of the variables to normal distribution was examined using histogram graphics and the Kolmogorov-Smirnov test. The mean, standard deviation, and median values were used while presenting descriptive analyzes. Categorical variables were compared using the Pearson chi-square test. The Mann-Whitney U test was used in evaluating nonparametric variables between two groups. BRFS, MFS, and OS rates were evaluated using Kaplan-Meier analysis. The multivariate Cox proportional hazard model was used to evaluate interactions between two groups and prognostic variables for OS outcomes. All analyses were performed at a 95% confidence level with a 0.05 significance level using SPSS for Windows version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

This study included 72 patients with high-risk PCa: 34 (46.6%) patients in the definitive RT group and 38 (52.1%) patients in the RP group. Table 1 provides information on the baseline parameters of the patients and their treatment. The mean age of those in the RP and RT groups was 63.8 (57-76) and 66.7 (51-78) years, respectively, with a significant between-group difference (p=0.045). The proportion of patients with a mean age ≥65 years with a pretreatment PSA level, PSA >20 ng/dL, and last PSA level was higher in the RT group (p=0.015, p=0.001, p=0.001, and p=0.006, respectively). Moreover, the GS in the RT group was significantly higher than that in the RP group (<8 vs 8 and 9-10, p=0.035). Regarding the National Comprehensive Cancer Network (NCCN) risk classification, RP was the treatment of choice in 15 (44.5%) patients in the high-risk group, whereas RT was preferred in 31 (86.5%) patients in

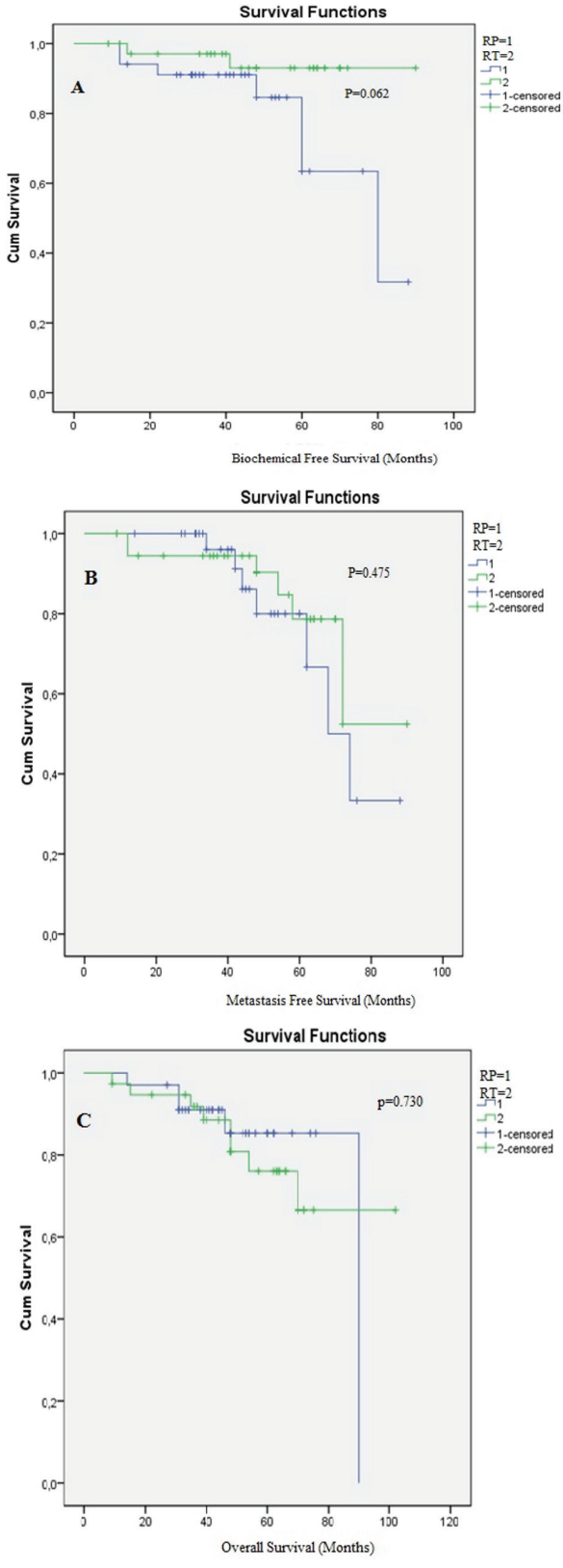

Figure 1. Kaplan-Meier curve for BFS, MFS and OS (A, B, C)

OS: Overall survival, BFS: Biochemical recurrence-free survival, MFS: Metastasis-free survival

the very high-risk group (Gleason pattern 5 and/or >4 score with GS 8-10, p=0.018). According to the 7th American Joint Committee on Cancer Tumor-Node-Metastasis staging system, 33 (82.3%) patients were stage T2 (T2c) and 20 (99.5%) were stage T3 and T4 in the RP group, and 11 (100%) were N (+) in the RT group. RT was the treatment of choice for patients with advanced disease stages, showing a significant difference (p=0.001). The follow-up time was 44.5 (range, 14-100) months in the RP group and 48 (range, 9-108) months in the RT group (p=0.230).

Moreover, 16 (47%) patients received adjuvant RT and 6 (15.7%) patients received salvage RT due to biochemical recurrence in the RP group. In the RT group, ADT (50 mg of bicalutamide and 22.5 mg of leuprolide acetate) was given to all patients who received RT for 3 years. Neoadjuvant ADT was given to six patients before RT because of the tumor size. Only two patients did not receive ADT because of severe heart failure.

The Kaplan-Meier curves for BRFS, MFS, and OS times are shown in Figure 1. No significant difference was found in the BRFS, MFS,

Table 1. Comparison of patients characteristics in treatment groups

	Radical prostatectomy	Definitive radiotherapy	p-value
Age			
Mean, (range)	63.82±4.2 (57-76)	66.79±7.6 (51-78)	0.045
<65 years	24 (60%)	16 (40%)	0.015
≥65 years	10 (31.3%)	22 (68.8%)	
Pretreatment PSA value mean (range)	9.7±14.5 (3.4-66)	25.50±34.10 (4.6-146)	0.001
First PSA			
<10 ng/dL	18 (72%)	7 (28%)	0.001
10-20 ng/dL	10 (52.6%)	9 (27.4%)	
≥20 ng/dL	6 (21.4%)	22 (78.6%)	
Gleason score			
<8	15 (44.1%)	7 (18.4%)	0.035
8	8 (25.8%)	18 (47.5%)	
9-10	11 (32.4%)	13 (34.2%)	
NCCN risk classification			
High	15 (44.5%)	7 (18.5%)	0.018
Very high	19 (55.5%)	31 (85.5%)	
Clinical stage (n)			
T2	33 (82.5%)	7 (17.5%)	0.001
T3-4	1 (0.5%)	20 (99.5%)	
N+	0	11 (100%)	
Last PSA, mean (range)	0.37 (0.08-10.4)	7.3 (0.08-149)	0.006
Follow-up (months)	44.5±16.7 (14-100)	48±20.1 (9-108)	0.230
Alive	29 (85.3%)	30 (78.9%)	0.433
Exitus	5 (14.7%)	8 (21.1%)	

PSA: Prostate-specific antigen, NCCN: National Comprehensive Cancer Network

and OS values between the two groups at 3- and 5-year follow-ups (Table 2). The BRFS time in the RP group was longer than that in the RT group (85.7±3.7 vs 72.4±5.0 months, p=0.062), with the difference close to statistical significance.

Table 3 shows the results of the Cox regression analysis of the OS in the two groups. In the univariate analysis, age (p=0.035) and a higher GS (i.e., ≥8) were significant predictors of OS (p=0.025). In the multivariate analysis, age and a higher GS (i.e., ≥8) were independent predictive factors for OS in both groups (p=0.043 and p=0.027, respectively).

Discussion

In this study, we examined patient outcomes and selection criteria in individuals with high-risk PCa treated with definitive RT or RP. The aim was to shed light on the suitability of different patients for various treatments. We found no difference in the BFS, MFS, and OS of the patients between the two groups, although the BRFS in the RP group was marginally better than that in the RT group.

Table 2. Survival outcomes of the treatment groups

Survival outcomes	Radical prostatectomy	Definitive radiotherapy	p-value
BFS			
Median ± SD (month)	85.7±3.7	72.4±5.0	
3-year BFS (%), (95%, CI)	93 (83.2-102.8)	84.6 (81.5-91.3)	0.062
5-year BFS (%), (95%, CI)	78.1 (67.3-88.9)	63.4 (60.6-66.2)	
MFS (n)			
Median ± SD (month)	75.4±6.8	74±8.9	
3-year MFS (%), (95%, CI)	90.8 (82.7-98.9)	90.3 (83.1-97.5)	0.674
5-year MFS (%), (95%, CI)	70 (65.6-74.4)	78.6 (73-84.2)	
OS			
Median ± SD (month)	92±4.3	91±5.5	0.730
3-year OS (%), (95%, CI)	88 (76.4-99.6)	89.5 (79.9-99.1)	
5-year OS (%), (95%, CI)	85.2 (71.1-99.3)	76.4 (69-83.8)	

BFS: Biochemical recurrence-free survival, MFS: Metastasis-free survival, OS: Overall survival, CI: Confidence interval, SD: Standard deviation

Currently, both RT and RP are recommended as first-line treatments for clinically high-risk PCa cases. However, the optimal treatment has not been established. Many studies have attempted to shed light on this issue in recent years (14,15,16,17). Two recent meta-analyses included studies on treatment outcomes of patients with high-risk PCa (18,19). However, the majority of the studies enrolled in these meta-analyses did not include subgroup analyses according to the T-stage, GS, or RT type. Therefore, no comprehensive data can aid clinicians in treatment selection for patients with high-risk PCa.

RP is generally the treatment of choice in young patients (<65 years) with high-performance status and no comorbidities. Before RP, all patients, particularly younger ones, should be informed about potential surgery-related side effects, which include urine leakage and sexual dysfunction. These side effects can cause psychological problems posttreatment in young patients. In the present study, RP was the treatment of choice for those aged <65 years (p=0.015). Age was a prognostic factor for OS in the univariate and multivariate analyses (p=0.035 and p=0.043, respectively).

A meta-analysis published in 2020 (8) included 25 studies that compared the efficacy of RP and RT in high-risk PCa cases. In the two groups, OS, cancer-specific survival (CSS), BRFS, MFS, and clinical recurrence-free survival were investigated, with detailed subgroup analyses. This meta-analysis revealed that the survival times of the patients who underwent RP were high and that RT delayed disease progression. Based on these findings, the authors concluded that RT should be the primary treatment for patients with a high T-stage or high GS. Similarly, in the present study, RT was the treatment of choice for patients with a high GS (≥8) and high T-stage (p=0.002 and p=0.001, respectively).

Andic et al. (20) evaluated 120 patients with high-risk PCa who received RT + ADT (n=72) or RP (n=40). Distant MFS, CSS, and OS were comparable in both groups, but BRFS was significantly lower in the RP group (p<0.001). In the present study, we did find a significant between-group difference in BRFS, MFS, and OS. However, BRFS was longer in the RP group, with the difference close to significance (p=0.062). We attributed this finding to the fact that 16 (47%) of the patients who underwent surgery

Table 3. Predictive factors in the univariate and multivariate analyses for overall survival

	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Age (mean)	1.103	1.00-1.208	0.035	1.092	1.003-1.189	0.043
Age group (<65 vs ≥65)	0.635	0.213-1.893	0.415	-	-	-
Pretreatment PSA (ng/dL)	1.009	0.994-1.022	0.251	-	-	-
PSA group (<20 vs ≥20)	0.917	0.291-2.892	0.883	-	-	-
Gleason score (<8 vs ≥8)	1.048	0.988-1.222	0.025	2.44	1.001-4.322	0.027
Clinical T-stage (T2 vs T3, T4)	0.637	0.079-5.164	0.673	-	-	-
	0.478	0.052-4.410	0.515			
Last PSA (ng/dL)	0.992	1.044-1.178	0.175	-	-	-
Treatment group (RP vs RT)	1.238	1.401-3.820	0.710	-	-	-

PSA: Prostate-specific antigen, RP: Radical prostatectomy, RT: Radiotherapy, CI: Confidence interval, OR: Odds ratio

also received adjuvant RT. Most of the patients in the RP group required adjuvant RT postoperatively because of positive surgical margins and seminal vesicle involvement. Various studies have reported that RT administered in the early postoperative period after RP reduced PSA levels and improved treatment outcomes (21,22).

In our study, patients with GS of 8-10 were classified in the high-risk group according to the risk classification criteria of the NCCN. Previously, Kishan et al. (23) compared the outcomes of RT + brachytherapy, RT alone, and RP in patients with GS 9-10 and reported comparable survival times. In the present study, a GS of >8 was an independent prognostic factor in both the univariate and multivariate analyses (p=0.027). Moreover, RT was the treatment of choice in very high-risk cases (i.e., a GS of 5).

Several studies have reported that increasing the RT dose in patients with PCa increased BRFS but not OS (24,25). However, these studies have examined outcomes only in patients who received an RT dose of >70 Gy. In the present study, all patients who received RT received a dose of 76 or 78 Gy because of their high-risk status. Therefore, the RT dose was not investigated in this study.

As a result of the rapid developments in RT techniques, high-dose RT can currently be applied to high-risk PCa cases. Many studies (26,27) have compared RP with RT applied with conventional RT techniques. In recent years, many new RT applications, such as image-guided RT and volumetric-modulated arc therapy, have become available. These techniques can deliver high-dose RT to tumor tissues while protecting healthy tissues. Long-term treatment outcomes, including survival analyses, of patients treated with the latest RT techniques and RP are needed to improve patient selection.

In this study, RT + ADT was the treatment of choice for very high-risk cases. A marginal improvement in BRFS was found in the RP group. The possible reason for this was that approximately half of the patients in this group received postoperative adjuvant RT. In making treatment decisions, both RT and surgery should be offered to patients simultaneously.

Study Limitations

This study had some limitations. First, patients' quality of life after RT or RP was not assessed. Second, although brachytherapy is recommended after RT in the treatment of high-risk PCa in the current guidelines (i.e., NCCN), it was not applied in our study because it was not performed in our hospital. Finally, it was necessary to define high-risk PCa cases as high or very high-risk cases. Thus, evaluating treatment outcomes in separate risk categories (i.e., high or very high risk) may be more effective in determining the optimal treatment strategy.

Conclusion

According to the results of this study and literature findings, treatment outcomes, including survival times, are comparable in high-risk PCa treated with RT or RP. Based on the subgroup analyses, RT should be the treatment of choice for patients with a high T stage and a high GS and aged ≥65 years.

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Ethics

Ethics Committee Approval: The study was approved by the local ethics committee of our hospital. All patients were given a thorough explanation of the study (approval no: 2021-2664).

Informed Consent: Informed consent was obtained from all of them.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Supervision: U.Y., Critical Review: U.Y., Concept: B.İ., U.Y., Design: U.Y., Data Collection or Processing: Ö.M., Analysis or Interpretation: B.İ., Literature Search: Ö.M., Writing: B.İ.

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Original Article

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Radical Prostatectomy Outcomes in Patients with Clinical Lymph Node Involvement from The Turkish Urooncology Database

Hasan Hüseyin Tavukçu[1], Oğuzcan Erbatu[2], Bülent Akdoğan[3], Volkan İzol[4], Uğur Yücetaş[5], Sinan Sözen[6], Güven Aslan[7], Bahadır Şahin[8], İlker Tinay[9], Talha Müezzinoğlu[2], Sümer Baltacı[10]

[1]*University of Health Sciences İstanbul Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Urology, İstanbul, Turkey*
[2]*Manisa Celal Bayar University Faculty of Medicine, Department of Urology, Manisa, Turkey*
[3]*Hacettepe University Faculty of Medicine, Department of Urology, Ankara, Turkey*
[4]*Çukurova University Faculty of Medicine, Department of Urology, Adana, Turkey*
[5]*Ministry of Health, İstanbul Training and Research Hospital, Clinic of Urology, İstanbul, Turkey*
[6]*Gazi University Faculty of Medicine, Department of Urology, Ankara, Turkey*
[7]*Dokuz Eylül University Faculty of Medicine, Department of Urology, İzmir, Turkey*
[8]*Marmara University Faculty of Medicine, Department of Urology, İstanbul, Turkey*
[9]*Anadolu Medical Center, Department of Urology, İstanbul, Turkey*
[10]*Ankara University Faculty of Medicine, Department of Urology, Ankara, Turkey*

Abstract

Objective: This study aimed to investigate pathological lymph node involvement in selected patients and the relationship of prostate-specific antigen (PSA) progression-free survival rates between patients with and without lymph node involvement on preoperative conventional radiologic imaging. Limited data is available about local treatment outcomes in patients with prostate cancer (PCa) having clinical lymph node involvement.

Materials and Methods: Using the national PCa database, patients who underwent radical prostatectomy (RP) and pelvic lymph node dissection between 2001 and 2019, with pathologic lymph node involvement, were included in the study. Patients were divided into two groups as those with and without clinical lymph node involvement by preoperative imaging.

Results: A total of 213 patients were included in the final analysis, wherein 164 are with and 49 are without lymph node involvement. After the mean follow-up periods of 33.9 months, a significant difference was not found between the two groups in terms of recurrence, adjuvant treatment necessity, and final status. The multivariate analysis for 5-year PSA recurrence-free survival revealed that surgical margin positivity was the only significant factor (p=0.016, hazard ratio: 2.67, confidence interval: 1.19-5.98).

Conclusion: Our results revealed that preoperative clinical lymph node status did not affect the 5-year PSA recurrence-free survival in pathologic lymph node involvement of patients treated with RP and pelvic lymph node dissection. Therefore, RP stands as an effective treatment option in selected patients with PCa having clinical lymph node involvement.

Keywords: Metastases, prostate cancer, radical prostatectomy, recurrence-free survival, surgical margin positivity

Introduction

The first treatment recommended in the early stage or localized prostate cancer (PCa) is radical prostatectomy (RP) according to European Association of Urology (EAU) guidelines, especially in intermediate and high-risk patients (1). Historically, patients with lymph node involvement were not operated two decades ago; however, this approach has changed in the last decade, as increased long-term survival rates with RP (2) and extended lymph node dissection were reported in such patient groups (3,4,5). In recent years, a more extensive lymphadenectomy during RP should be performed (6,7,8,9,10). Thus, with

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Address for Correspondence: Hasan Hüseyin Tavukçu, University of Health Sciences İstanbul Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Urology, İstanbul, Turkey
Phone: +90 216 542 20 20 **E-mail:** hhtavukcu@yahoo.com **ORCID-ID:** orcid.org/0000-0003-0956-7460
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growing evidence, the latest EAU Guidelines updated to offer RP to selected patients with any clinical N1 as part of multimodal therapy with a strong recommendation, whereas the National Comprehensive Cancer Network (NCCN) guidelines still do not mention surgery in patients with clinical N1 as an option (1,11). A brief correspondence by Moschini et al. (2) reported that clinical lymph node metastases were not a factor in survival determination after RP and pelvic lymph node dissection (PLND) in patients with PCa.

This study investigated the difference in prostate-specific antigen (PSA) progression-free survival rates between patients with and without cN+ disease on preoperative conventional radiologic imaging in patients with pathologically pelvic lymph node metastasis positive (pN+) PCa at RP and PLND.

Materials and Methods

Patient Population

Patients in the database of the Turkish Urooncology Association, who underwent RP and PLND between 2001 and 2019 with pathological lymph node involvement, were included in the study. The study protocol was reviewed and approved by the Institutional Review Board of Marmara University Faculty of Medicine (approval number: 09.2020.639). Patient data from 10 different centers, whose lymph node involvement status was evaluated with preoperative imaging using computed tomography (CT) and/or magnetic resonance imaging (MRI), were recorded. In addition, all bone scan results were negative. The clinical lymph node involvement was defined as malignant if the long axis of the node was >10 mm. Patients were divided into two groups as those with (cN+) and without (cN-) clinical lymph node involvement according to CT and/or MRI results.

Patient Inclusion-Exclusion Parameters

Patients with non-regional lymph node metastasis (M1a), who received preoperative hormonal treatment and/or radiotherapy (RT) and those previously diagnosed with other cancers and non-adenocarcinoma PCa, were excluded. Preoperative age and PSA level, biopsy Gleason grade group, clinical stage, type of operation (open, laparoscopic, and robotic), the total number of lymph nodes removed, the total number of positive lymph nodes, lymph node density, prostatectomy Gleason grade group, pathological stage, surgical margin status, extracapsular extension, seminal vesicle invasion, follow-up time, time to PSA progression, type of adjuvant therapy, postoperative PSA level, and last status (alive or dead), were retrospectively recorded. A total of 10 participating centers are experienced centers in urooncological surgery in our country. Standard lymphadenectomy is defined as extended in the form of fatty tissue removal around the pelvic lymph node borders, including the obturator fossa, internal and external iliac, common iliac vessels, and presacral nodes in some selected cases.

Statistical Analysis

The cN+ and cN- groups were compared in terms of age, preoperative and postoperative PSA levels, biopsy and prostatectomy Gleason grade groups, lymph node density, total and positive lymph node numbers, and time to PSA progression using the Mann-Whitney test. The terms of clinical stage, type of surgery, pathologic stage, surgical margin status, extracapsular extension, seminal vesicle invasion, and last status were analyzed using the χ^2 test. The Kaplan-Meier analysis was used to analyze the time to PSA progression between the two groups. Multivariate analysis including RP T-stage, RP Gleason grade group, the total number of lymph nodes removed, the number of positive lymph nodes removed, lymph node density, surgical margin status, and clinical lymph node positivity parameters were performed for the 5-year PSA relapse-free survival.

Results

Initially, 230 patients with pathologic lymph node involvement were included in the study, and 213 with adequate data and a follow-up period of at least 3 months were included for further assessment. Among these 213 patients, 164 patients with clinical lymph node involvement (cN+) and 49 patients without clinical lymph node involvement (cN-), were divided into two groups according to preoperative imaging. The mean and median preoperative PSA values were 23.34 and 14 ng/mL, respectively. The mean and median follow-up periods of patients were 33.9 and 28 months, respectively, ranging from 3-153 months. Comparison of the two groups revealed that EAU high-risk group was significantly higher in the cN+ group ($p<0.05$), without difference in other parameters (Table 1).

A total of 8 deaths were detected in the patient data, and 1 patient in the cN- group died of PCa. No significant difference was reported between the two groups in terms of recurrence, adjuvant therapy, end status, and time to PSA progression. (Table 2) An overall and cancer-specific survival analysis was not performed as a very limited number of deaths and a short follow-up period were observed. Instead, time to PSA progression was examined using the Kaplan-Meier analysis between the two groups, which revealed no significant differences ($p=0.865$; Figure 1).

The multivariate analysis for 5-year PSA recurrence-free survival revealed surgical margin positivity as the only significant factor ($p=0.016$, hazard ratio: 2.67 confidence interval: 1.19-5.98). The multivariate analysis revealed that factors, such as clinical lymph node involvement, pathological tumor stage, pathological Gleason grade group, adjuvant therapy, positive lymph node number, and lymph node density, do not affect 5-year PSA recurrence-free survival (Figure 2).

Discussion

Our study results found no significant difference in the time to PSA recurrence in patients with pathologically positive lymph nodes in the specimen of extended lymphadenectomy, whether or not these patients had cN+ or cN0 disease. For the first time, Moschini et al. (2) reported that clinical lymph node metastasis was not a determining factor after RP and PLND in such a situation and concluded that it is not an absolute surgical contraindication. To our knowledge, this is the second study in the literature that revealed that in appropriately selected cN+ patients, RP, and extended PLND revealed a similar time to PSA progression rates compared to cN0 patients. A study

Table 1. Descriptive statistics classified according to clinical node status				
	Overall (n=213; 100%)	**Clinical N+ (n=164; 77%)**	**Clinical N- (n=49; 23%)**	**p-value**
Age at surgery				
Mean	63.02	63.08	62.91	0.899
Median	64 (42-78)	61 (42-78)	63 (46-75)	
Follow-up time (month)				
Mean	33.9	34.9	30.5	0.320
Median	28 (3-153)	28 (3-153)	24 (4-120)	
Preoperative PSA				
Mean	23.34	24.84	18.32	0.052
Median	14 (1.01-203)	14.84 (1-203)	13 (4.2-96)	
EAU risk groups				
Low-risk	5 (2.3%)	2 (1.2%)	3 (6.1%)	<0.05
Intermediate-risk	18 (8.5%)	8 (4.9%)	10 (20.4%)	
High-risk	190 (89.2%)	154 (93.9%)	36 (73.5%)	
Positive nodes				
Mean	2.74	2.90	2.22	0.112
Median	2 (1-36)	2 (1-36)	1 (1-10)	
Nodes removed				
Mean	17.48	18.16	15.22	0.124
Median	15	16 (2-77)	13 (1-62)	
Lymph node density				
Mean	0.197	0.182	0.248	0.094
Median	0.133	0.125 (0.02-0.90)	0.187 (0.02-1.0)	
Pathologic stage				
pT2	14 (6.5%)	11 (6.7%)	3(6.1%)	0.628
pT3a	54 (25.3%)	39 (23.7%)	15 (30.6%)	
pT3b	145 (68%)	114 (69.5%)	31 (63.2%)	
Pathologic Gleason grade group				
1	5 (2.3%)	3 (1.8%)	2 (4%)	0.602
2	27 (12.6%)	22 (13.4%)	5 (10%)	
3	55 (25.8%)	39 (23.7%)	16 (32%)	
4	36 (16.9%)	28 (17%)	8 (16.3%)	
5	90 (42.2%)	72 (43.9%)	18 (36.7%)	
Positive surgical margin	153 (71.8%)	120 (73.1)	33 (67.3%)	0.426
Adjuvant hormonal therapy	91 (42.7%)	70 (42.6%)	21 (42.8%)	0.145
Adjuvant radiotherapy	56 (26.2%)	38 (23.1%)	18 (36.7%)	
EAU: European Association of Urology, PSA: Prostate-specific antigen				

by Moschini et al. (2) reported cancer-specific survival rates at their long follow-up period. Our mean follow-up time was 33.9 months and cancer-specific survival data were limited for appropriate evaluation, as our death numbers were low in this relatively limited follow-up period.

In cN+ patients, Seisen et al. (7) reported that almost two-thirds received local therapy (surgery or RT) with or without androgen deprivation therapy (ADT). They also emphasized that patients who received local therapy had significantly lower mortality rates than patients who only received ADT (7). This study

Table 2. Comparison of patients with and without clinical lymph node involvement				
		Clinical N+	**Clinical N-**	**p**
Recurrence	Yes	44 (26.83%)	12 (24.49%)	0.744
	No	120 (73.17%)	37 (75.51%)	
Adjuvant treatment	Yes	120 (73.17%)	39 (79.59%)	0.365
	No	44 (26.83%)	10 (20.41%)	
End status	Dead	6 (3.66%)	2 (4.08%)	0.891
	Alive	158 (96.34%)	47 (95.92%)	

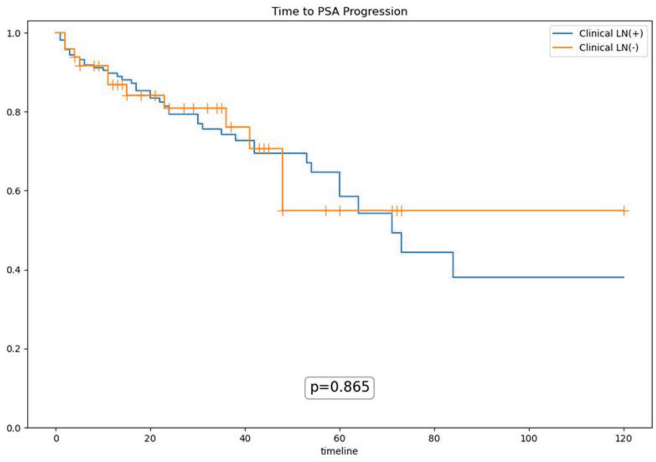

Figure 1. Kaplan Meier analysis between the two groups in terms of time to PSA progression

PSA: Prostate-specific antigen

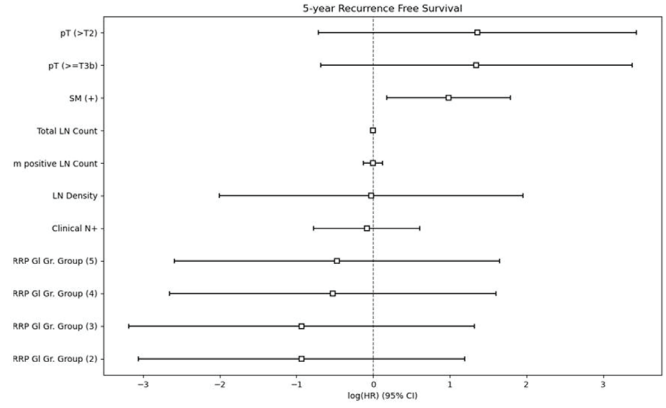

Figure 2. Multivariate analysis of the 5-year PSA recurrence-free survival

PSA: Prostate-specific antigen

revealed an RP ± ADT survival benefit compared to RT ± ADT but was not statistically significant, and 37.8% of their patients were treated with RP + ADT. In our study, the adjuvant ADT ratio was 42.7% and was very similar to the rate of Seisen et al. (7). The additional adjuvant ADT generally depends on the treating Urologist's choice.

The EAU risk classification was used in our study, whereas Moschini et al. (2) used NCCN risk grouping in their study. Of our patients, 89.2% were in the high-risk group, whereas the in Moschini et al.'s (2) study was 64.5%. Our study included predominantly more high-risk patients compared to Moschini et al.'s (2) study, and the time to PSA recurrence was not different in cN+ and cN- patients, which proposes a similar clinical course, following Moschini et al.'s (2) findings.

In our study, cN+ patients had higher positive lymph node counts; however, positive lymph node count and lymph node density were not statistically different between the two groups. While, in Moschini et al.'s (2) study, a statistically significantly higher number of positive lymph nodes were reported in the cN+ group compared to that of the cN- group (2). In our study, the mean and median of the total number of removed lymph nodes was higher than Moschini et al.'s (2) study, which explains the different findings.

Prostatectomy Gleason grade groups and its parameter were similar in our study and Moschini et al.'s (2) study results, wherein significant difference was not found between the groups. Contrarily, Moschini et al. (2) reported that taking pathologic Gleason score 2-6 as a reference, pathologic Gleason score of 8-10 versus 6 was a significant predictor of cancer-specific mortality (p=0.04). Today, pathologic Gleason score of <6 is not an acceptable pathological finding, and in our study, only 2.3% of our pLN+ cases had pathologic Gleason grade group. Contrarily, 17.2 % of patients in Moschini et al.'s (2) study had pathologic Gleason score of 2-6, which explains the difference between the two studies. Moreover, no difference was found between the groups in terms of surgical margin positivity, adjuvant hormonal therapy, and adjuvant RT in both studies. A small number of patients received neoadjuvant hormonal therapy in the study of Moschini et al. (2), and this rate was significantly higher in the group with clinical lymph node involvement. Patients who received neoadjuvant hormonal therapy were excluded from our study to create a more homogeneous patient population.

The multivariable analysis performed in Moschini et al.'s (2) study reported that some positive lymph nodes and Gleason grade group of 8-10 were predictors for cancer-specific mortality compared to 6 or less, and clinical lymph node involvement was not a predictive factor. Similar to that study, we found that clinical lymph node involvement did not affect the 5-year PSA recurrence-free survival. While surgical margin positivity was the only significant factor in multivariable analysis.

Study Limitations

Our study has some limitations. Our results were derived from retrospective data of 10 different centers. The patient follow-up period was short, thus the time to PSA progression was examined, and cancer-specific and overall survival rates were not reported. With a longer follow-up period, we hope to report these results, as well. Centralized pathology was not available in our study but all 10 academic centers had their experienced uropathologists.

Conclusion

Our results revealed that, in pN+ patients who were treated with RP and PLND, preoperative clinical lymph node status (cN+ or cN-) did not affect the 5-year PSA recurrence-free survival. Therefore, in selected patients with PCa with cN+ disease, RP is an effective treatment option.

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Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Institutional Review Board of Marmara University Faculty of Medicine (approval number: 09.2020.639).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.H.T., O.E., T.M., S.B., Design: H.H.T., O.E., T.M., S.B., Data Collection or Processing: H.H.T., O.E., B.A., V.İ., U.Y., S.S., G.A., B.Ş., İ.T., T.M., S.B., Analysis or Interpretation: H.H.T., O.E., B.Ş., Literature Search: H.H.T., S.B., Writing: H.H.T., İ.T., S.B.

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Original Article

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The Relationship Between Histological Changes and Urodynamic Parameters in Patients Undergoing Orthotopic Ileal Neobladder Surgery: A Case-Control Study

Burak Yavuz Kara[1], Ekrem Akdeniz[2], Fatih Yalçınkaya[1], Binnur Önal[3], Mustafa Uğur Altuğ[1]

[1]*University of Health Sciences Turkey Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Urology, Ankara, Turkey*
[2]*Gazi Hospital, Clinic of Urology, Samsun, Turkey*
[3]*University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Pathology, Ankara, Turkey*

Abstract

Objective: The relationship between histological changes and urodynamic findings emerging in neobladders (NBs) in a long term was not previously investigated. This study aimed to investigate the relationship between histological changes and urodynamic findings in the NB.
Materials and Methods: Patients undergoing radical cystectomy and Studer NB were included in the study. Patients with follow-up times <48 months were assigned to group 1 (n = 5) and those with follow-up times >48 months in group 2 (n = 6). Metabolic, endoscopic, histologic, urodynamic, and continence parameters were evaluated after surgery.
Results: No metabolic disorders or pathology was observed in the endoscopy of any patients. Histological evaluation revealed a decreased chronic inflammation and villus length severity over the years, with increased goblet cell numbers and fibrosis rates. Maximum reservoir capacity, compliance, and voiding pressure values for groups 1 and 2 were 418±42.1 and 401.33±67.8 mL, 15.65±2.7 and 18.54±4.98 mL/cm H_2O, and 28.2±2.28 and 30.6±7.4 cm H_2O, respectively. Maximum reservoir capacity was higher in group 1 than in group 2, whereas compliance and voiding pressure were lower, without significant differences (p = 0.84, p = 0.64, and p = 0.97; respectively).
Conclusion: No effects were observed on urodynamıc parameters resulting from the development of long term histological changes in the NB. However, the NB appeared to adapt to its new function by gradually assuming a similar morphology to the urothelium, maintaining a sufficient capacity and compliance. Daytime continence was achieved at a rate of 90.9%, without metabolic pathology.
Keywords: Neobladder, urodynamic, continence, histology, endoscopy

Introduction

Radical cystectomy (RC) is the standard treatment for localized bladder cancer in most developed countries (1,2). RC and urinary diversion constitute two steps of the same surgical procedure. Creating a continent, orthotopic neobladder (NB) diversion by pouch anastomosis prepared from the gastrointestinal tissue to the urethra, is one commonly employed technique for urinary diversion (1). Studer et al. (3) reported that the detubularized ileal pouch is used as an orthotopic bladder in patients with a healthy urethra after cystectomy and that the applicability of orthotopic bladder substitutions significantly increased thereafter. Orthotopic bladder substitutions are currently the method of choice in patients scheduled for RC due to their long term reliability and safety (4,5).

Various changes occur in the mucosa, which consists of a single-layer prismatic epithelium, due to constant urine exposure by the orthotopic NB. The absorptive and secretory functions of the mucosa decrease and microvilli are lost and shorten as a result of these changes. The cellular dynamics of the ileal mucosa undergo alteration, providing NB expansion and contraction. Thus, the NB replaces the bladder and begins adapting to its new environment. Micturition is achieved through abdominal muscle contraction, intestinal peristalsis, and sphincter relaxation. Various urodynamic changes and different urinary characteristics occur in these patients. The urodynamic analysis provides objective data concerning several urine volume measurements, enterocystometric pressure functions, and lower urinary tract functions (6,7,8).

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Address for Correspondence: Burak Yavuz Kara, University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Clinic of Urology, Ankara, Turkey
Phone: +90 312 596 20 00 **E-mail:** dryavuzburakkara@gmail.com **ORCID-ID:** orcid.org/0000-0002-5262-0346
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Several previous studies have investigated metabolic, functional, urodynamic, and histological NB findings (3,6,7,8,9,10,11). However, the relationship between histological changes and urodynamic findings emerging in NBs in the long term was not previously investigated. Therefore, this study aimed to investigate the relationship between histological changes and urodynamic NB findings and to collectively evaluate metabolic, endoscopic, functional, urodynamic, and histological findings emerging in the long term.

Materials and Methods

Study Population

The study protocol was approved by the ethics committee of the Dışkapı Yıldırım Beyazıt Training and Research Hospital (no: 92/22). Patients who had undergone RC due to muscle-invasive urothelial carcinoma (pT2N0M0) in recent years and received Studer orthotopic NBs as urinary diversions were included in the study. Patients were given detailed information about the study, and informed consent was obtained from all participants. Male patients, without surgical complications during the operation that affects the NB, not receiving adjuvant therapy, without urethral or anastomotic stenosis, not undergoing clean intermittent catheterization, without diabetes, and was operated on at least 36 months previously, were enrolled. A total of 20 patients initially provided the consent of participation; however, it was completed with 11 patients (Figure 1). Patients were given no additional medications during the postoperative period. All medical procedures in the study were performed by a physician (B.Y.K.).

Surgical Methods

A standard open surgical approach was adopted during all operations, and standard techniques were applied for orthotopic NB reconstruction, which involved a 45-50 cm ileal segment isolation approximately 20-25 cm proximal to the ileocecal valve. A proximal 15 cm ileum segment was left as an afferent limb. Next, approximately 30-35 cm of the ileal segment was subjected to antimesenteric border detubularization. The adjacent detubularized limbs were next folded into a U shape. The ureters were then anastomosed to the proximal afferent limb using the Wallace technique (Figure 2).

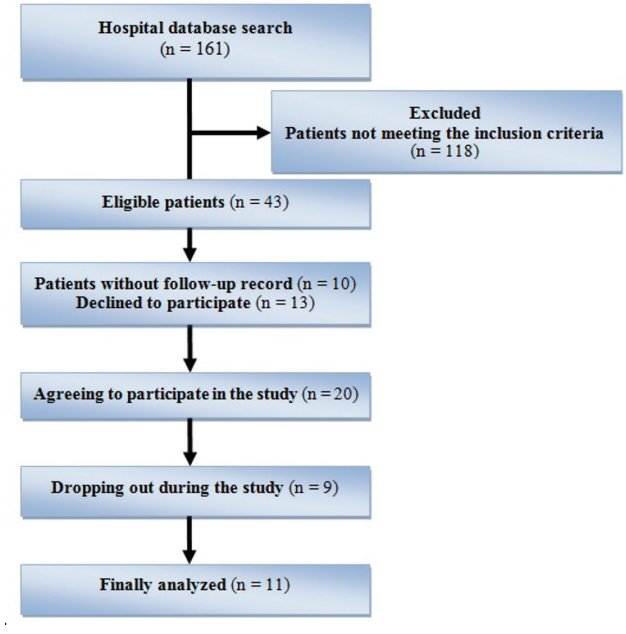

Figure 1. Flow chart showing the constitution of the study population

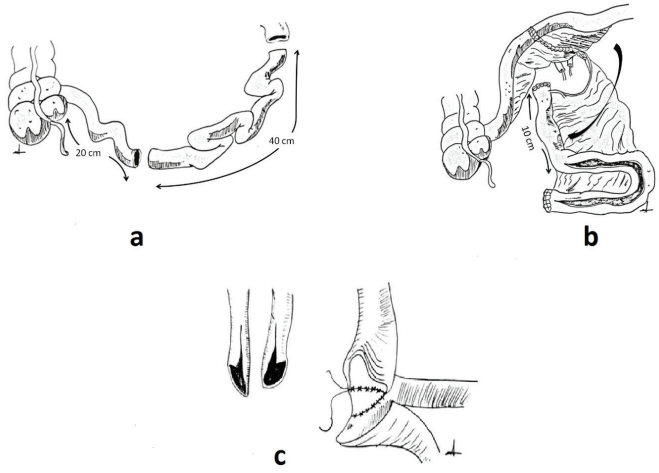

Figure 2. Surgical technique (a: Intestinal resection; b: Studer pouch preparation; c: ureteroilial anostomosis using the Wallace method)

Metabolic and Radiologic Evaluation

Hematological, serum biochemistry, and complete urine examination tests were carried out using commercial kits in line with the manufacturers' instructions. Arterial blood gas (ABG) was immediately studied on an autoanalyzer with specimens collected from the radial artery. The upper urinary tract was evaluated using renal ultrasonography.

Continence Assessment

Patients' daytime, night-time, and total continence were evaluated using standard assessment forms described by the International Continence Society (12).

Urodynamic Study and Evaluation of Voiding Function

Before the urodynamic study, patients were asked to void and postvoid residual volume (PVR) was evacuated by catheterization. Standard three-channel filling cystometry was performed using a 7 Fr transurethral catheter and 10 Fr rectal balloon catheters. Maximal cystometric capacity was determined through involuntary leakage or abdominal discomfort. In addition to maximal capacity, the first sensation of bladder filling, normal filling sensation, strong filling sensation, and compliance values were determined using cystometry (Figure 3). Uroflowmetry was performed after cystometry, after which PVR was measured using a fine catheter.

Endoscopic Evaluation

All endoscopic procedures were performed with the patient under general anesthesia. Mucous and accumulated debris were

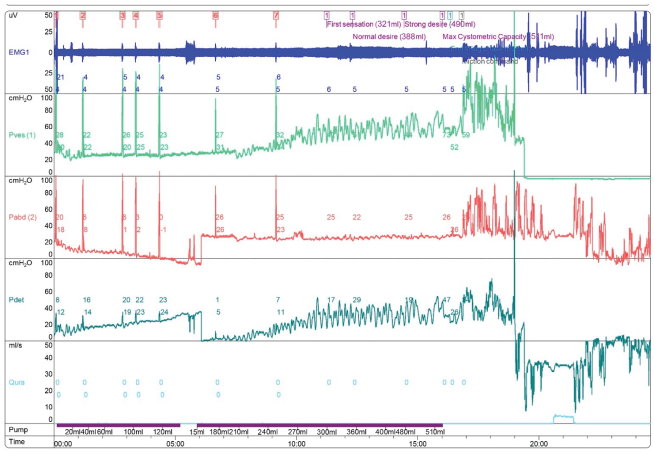

Figure 3. Urodynamic findings from one patient at 60 months postoperative

irrigated from the NB during the initial inspection as required. The pouch was first evaluated using systematic endoscopy, and multiple biopsy specimens were collected from four different regions: inferior, posterior, right, and left, using punch biopsy forceps.

Pathological Evaluation

Paraffin-embedded specimens were stained using hematoxylin & eosin (H&E) and periodic acid-Schiff (PAS). Villus length, crypt depth, inflammatory cell rates, muscularis mucosa thickness (MMT), dysplasia, and malignancy were evaluated on the H&E-stained slides, as previously described by Gatti et al. (8). Goblet cells were assessed with PAS staining. Villus length, crypt depth, and MMT on H&E-stained slides were determined numerically using an oculometer. The goblet cell ratio (GCR) was determined by calculating the proportion of positive cells to the total number of cells in the magnification field, as described by Gatti et al. (8).

The assessment of chronic inflammation defined moderate chronic inflammation as an intact mucosal epithelium, without erosion, preserved mucosal glandular structure and crypts, and inflammatory cells (lymphocytes and plasmocytes) infiltrating the mucosa. Severe chronic inflammation was defined as intensive chronic inflammatory cells causing mucosal surface epithelium erosion, eliminating the glandular structures and filling the mucosa. Samples were analyzed by the same unblinded pathologist.

Statistical Analysis

Data analysis was performed on Statistical Package for the Social Sciences 25 software (SPSS-IBM Corp., Armonk, NY, USA). The independent samples t-test was applied to determine the presence of significant differences in normally distributed continuous measurement variables between the two groups, and the Mann-Whitney U test for non-normally distributed continuous measurement variables.

Our study was conducted in compliance with the relevant directives and regulations (the Declaration of Helsinki and international good clinical practice guidelines). Detailed informed consent was obtained from all participants before procedures.

Results

Patient Characteristics

Eleven patients with a mean age of 62.63±6.63 years (range, 49-72) and mean follow-up duration of 48.54±13.54 months (range, 36-72) were included in the study. Patients were divided into two groups: 1) with follow-up durations of <48 months (group 1, n = 5) and 2) with >48 months (group 2, n = 6). Mean follow-up durations were 38.4±1.69 months (range, 36-45) for group 1 and 59±3.61 months (range, 48-72) for group 2. Patients had no previous urinary tract infections requiring hospitalization.

Metabolic and Radiologic Results

All patient urine cultures were sterile, but mucorrhea persisted in 10 patients (90.9%) at complete urine examination. Laboratory values were normal, without statistically significant difference between the groups. ABG pH values were 7.36±0.1 (range, 7.35-7.45) in group 1 and 7.37±0.1 in group 2 (p = 0.57) and bicarbonate values were 23±1 mEq/L (range, 22-26) in group 1 and 22.8±0.75 mEq/L in group 2 (p = 0.38). Mild hydronephrosis was observed in all patients in the renal ultrasonography but without kidney stones.

Endoscopic Results

The ureteral nipple was located in all patients in the endoscopic examination, with urine jet flow from the ureteral orifice. Pathological findings, such as stone, organized mucus, or anastomotic stricture, were not detected.

Urodynamic Parameters and Continence

The mean maximum reservoir capacity in the entire patient group was 409.09±131.98 mL (range, 138-561), mean compliance was 17.23±9.56 mL/cm H_2O (range, 2.15-32.85), and mean residual volume was 11.36±15.34 mL (range, 0-40).

The maximum reservoir capacity, compliance, voiding pressure, mean peak flow rates, and PVR for groups 1 and 2 were 418±42.1 mL vs 401.33±67.8 mL, 15.65±2.7 mL/cm H_2O vs 18.54±4.98 mL/cm H_2O, 28.2±2.28 cm H_2O vs 30.6±7.4 cm H_2O, 12.4±1.63 mL/s vs 16.3±2.18 mL/s, and 7±4.8 mL vs 15±7.52 mL, respectively. The group urodynamic and continence parameters are shown in Table 1.

No sensation of bladder filling occurred in any patients. Procedures were concluded due to abdominal pain in 9 patients and overflow incontinence in 2. The patients continued voiding by relaxing their pelvic muscles and continued with the Crede maneuver, which starts with abdominal straining.

Ten patients (90.9%) were daytime continent and eight (72.72%) were night-time incontinent. Two patients (18.18%) were fully continent and one (9.09%) was totally incontinent (Table 1).

No complications were observed in any patients during or after invasive procedures.

Histology

Light microscopy revealed significant histological changes. Severe chronic inflammation was observed in four patients in

Table 1. Comparison of urodynamic and continent parameters between the groups			
Urodynamic parameters (mean ± SD, min-max)	**Group 1 (n = 5)**	**Group 2 (n = 6)**	**p-value**
Max capacity (mL)	418±42.1 (283-537)	401.3±67.8 (138-561)	0.84
Compliance (mL/cm H_2O)	15.65±2.7 (8.3-24.4)	18.54±4.98 (2.1-32.8)	0.64
First desire (mL)	208.8±25.31 (131-287)	213±36.57 (50-321)	0.92
Normal desire (mL)	282±24.39 (213-336)	271.83±36.85 (119-388)	0.83
Strong desire (mL)	377.6±36.45 (273-494)	379.83±63.65 (129-526)	0.97
Pres first desire (cm H_2O)	15.8±4.6 (6-32)	11.16±1.57 (6-17)	0.33
Pres normal desire (cm H_2O)	20.2±3.44 (12-30)	21.16±4.85 (9-42)	0.88
Voiding pressure (cm H_2O)	28.2±2.28 (22-34)	30.16±7.4 (14-64)	0.97
Peak flow rate (mL/s)	12.4±1.63 (9-18)	16.3±2.18 (8-22)	0.2
Avarege flow rate (mL/s)	10±1.44 (6-13)	10±1.26 (6-13)	0.85
Voided volume (mL)	389±36.1 (286-505)	391.3±63.33 (143-550)	0.85
Residual volume (mL)	7±4.8 (0-25)	15±7.52 (0-40)	0.48
Day time continence			
Continent	5	5	0.81
Incontinent	-	1	
Night-time continence			
Continent	1	2	0.43
Incontinent	4	4	
Max: Maximum, Min: Minumum, Pres: Reservoir pressure, SD: Standard deviation			

group 1, and three in group 2 (p = 0.54). However, fibrosis was present in two patients in group 2, but in none in group 1. The mean villus length, crypt depth, MMT, and GCR values in groups 1 and 2 were 176±31.09 µm vs 140±41.06 µm, 196±25.41 µm vs 183.33±31.26 µm, 60±10.83 µm vs 34.16±11.43 µm, and 42±8.6 vs 55±10.56, respectively (Figure 4). No significant differences were observed in any histological values between the groups, and no neoplastic degeneration was determined in any patient.

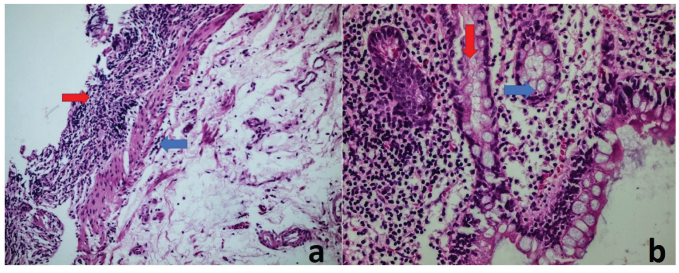

Figure 4. Histological evaluation of the neobladder; a, the muscular layer (blue arrow) and mucosa, but the mucosa is inflammatory (red arrow) and does not contain crypts and villi, H&E, x200 magnification; b, histological close-up view of the ileum mucosa: mucosal appearance with crypts (red arrow) and villi lined with numerous goblet cells (blue arrow), H&E, x400 magnification)

Discussion

This study investigated the histological NB changes and their effect on urodynamic parameters for several years (>36 months), which is the first in the literature to the best of our knowledge. The severity of chronic inflammation, villus length, and MMT in the NB histologically decreased over the years, whereas fibrosis and GCR increased. These histological changes were accompanied by increased urodynamic compliance, voiding pressure, peak flow rates, and residual volume, as well as decreased maximum capacity and first sensation volume. However, histological and urodynamic change differences between the groups were not statistically significant.

The current consensus is not available on the subject of NB urodynamic evaluation, and urodynamic parameters were similarly assessed in the intact bladder (13). The average maximum capacity of the ileal NB is 400-500 mL (13,14). The maximal reservoir capacities in the study groups in the present study were 418 and 401 mL, respectively. The compliance defined as the change in bladder pressure for a specific volume change is 5-10 mL/cm H_2O (14). NB compliance volumes postoperatively at 12-18 months in the literature range between 27.4 and 53.54 mL/cm H_2O (13,15). The mean compliance values in the present study were 15.65±2.7 in group 1 and 18.54±4.98 mL/cm H_2O in group 2. These low compliance values are due to the NB that achieves reservoir adaptation by undergoing histological changes due to the long follow-up period.

Daytime continence rates between 85% and 100% and night-time continence rates between 40% and 96.5% were reported in previous studies (14,16). Daytime continence rates in the present study were 100% in group 1 and 83.33% in group 2. The equivalent figures for night-time continence were 20% and 33.33%, respectively. Daytime continence was determined in 90.9% of the entire patient group and night-time continence in 27.28%. Our daytime continence rate was similar to that in the previous literature, but our night-time continence rate was lower. Due to the absence of afferent feedback and detrusor

sphincter reflex in the NB, urine begins to leak when the NB is filled as a result of nigh-time urine production (17). Age, physical condition, pelvic muscles, regular exercise, and excessive night-time urine production are all important factors in continence (14). The significance of these parameters in increased nocturnal incontinence rates is unavailable due to the limited number of patients with night-time incontinence.

Gatti et al. (8) reported villus length, crypt depth, MMT, and GCR basal values of 390 µm, 118 µm, 40 µm, and 16.1, respectively. Comparing these values in the present study, villus length significantly decreased in both groups, whereas marked increases were observed in crypt depth and GCR. Gatti et al.'s (8) study revealed villus length, crypt depth, and MMT values of 240 µm, 195 µm, and 52 µm, respectively in the fourth year postoperative. The comparable values in the present study for group 1 were 176 µm, 196 µm, and 60 µm, respectively. Except for the villus length, the morphological changes observed in this study were similar to those in Gatti et al. (8). These ileal histological changes lead to a decreased absorption capacity of the ileal epithelium and permit a functional reservoir the development.

Gatti et al. (8) reported that ileal adaptation occurs in two phases associated with chronic urine contact. In the first phase, aggressive injury occurs, such as shortening of the villi and increased crypt depth and MMT. In the second phase, these changes become permanent, with goblet cell predomination among the enterocytes. The rise in goblet cells increases over time. The first phase is concluded at the end of the first postoperative year, and then the second phase commences. Mucosal secretions change to sialomucins in association with increased goblet cells. This new secretion protects the mucosa against urine and allows the NB to adapt to the new environment. Gatti et al. (8) reported a basal GCR value of 16.1, rising to 32 at the end of 12 months and to 38 after 18 months. GCR values in the present study were 42±8.6 in the fourth year (group 1) and 55±10.56 in the fifth (group 2). GCR in the NB continues to increase in a time-dependent manner.

The mean MMT value in group 2, with a mean follow-up period of 59 months, was 34 µm. The equivalent value for group 1 was 60 µm. Gatti et al. (8) reported a basal MMT value of 40 µm, rising to 68 µm at the end of the fifth year, and decreasing over time to 52 µm in the fourth year. In the present study, fibrosis findings were present in group 2, but not in group 1. Although without statistical presentation, decreased MMT is related to fibrosis development in association with chronic inflammation in the muscularis mucosa. The urodynamic examination revealed the first desire, normal desire, and voiding reservoir pressures in groups 1 and 2 as 15.8±4.6 vs 11.16±1.57, 20.2±3.44 vs 21.16±4.85, and 28.2±2.28 vs 30.6±7.4 cm H_2O, respectively. A correlation was not found between MMT and urodynamic reservoir pressures in the present study.

Study Limitations

There are several limitations to this study. The most important is the limited number of patients. In addition, the patient's psychological state, regrets concerning surgery, and quality of life were not evaluated, which represents another major limitation. Despite these handicaps, this study is still valuable as the first of its kind in the literature. Further large, prospective investigation, and long term follow-up are necessary to confirm our findings and establish definite conclusions.

Conclusion

Long term histological NB changes do not affect urodynamic parameters. However, due to chronic urine exposure over the years, the NB adapts to the new environment by adopting a morphology resembling that of the urothelium. In the long term, sufficient capacity and compliance are maintained and daytime continence is established in 90.9% of patients, without metabolic pathology.

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Authorship Contributions

Supervision: M.U.A., Critical Review: M.U.A., E.A., Concept: B.Y.K., F.Y., B.Ö., Design: B.Y.K., F.Y., Data Collection or Processing: B.Y.K., E.A., B.Ö., Analysis or Interpretation: E.A., F.Y., B.Ö., Literature Search: F.Y., Writing: B.Y.K., E.A., M.U.A., B.Ö.

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Original Article

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The Predictive Role of Nephrometry Scores in Evaluating The Effect of Partial Nephrectomy on Postoperative Kidney Functions in T1 Renal Cell Tumors

Müslüm Ergün, Osman Akyüz, Ahmet Hamdi Tefekli

Atlas University Faculty of Medicine, Medicine Hospital, Clinic of Urology, İstanbul, Turkey

Abstract

Objective: We aimed at demonstrating the predictive role of different nephrometry scores in evaluating the effect of partial nephrectomy on postoperative kidney functions in patients with T1 kidney tumors.

Materials and Methods: We included 44 patients with clinical stage T1 renal tumors who underwent laparoscopic partial nephrectomy between June 2018 and January 2020. Then, we performed abdominal cross-sectional imaging with computed tomography and magnetic resonance imaging. We recorded the warm ischemia time, operation time, and amount of intraoperative bleeding. The resulting changes were evaluated by determining preoperative, and third month postoperative creatinine and estimated glomerular filtration rates (eGFR). RENAL nephrometry, Preoperative Aspects and Dimensions Used for an Anatomic (PADUA) classificationand Diameter- Axial- Polar (DAP) scores were calculated for each patient. The relationship between a decline in renal function, duration of ischemia and RENAL/PADUA/DAP scores was equally explored to achieve the aim of the study.

Results: The mean age of the patients at the time of surgery was 55.07±12.92 years, and the preoperative creatinine and eGFR values were 0.87 mg/dL and 93.17 mL/min, respectively. The third month postoperative creatinine and eGFRvalues were determined at 0.96 mg/dL and 86.52 mL/min, respectively. The mean RENAL (6.2±1.4), PADUA (6.8±1.0), and DAP (5.57±1.5) scores were also determined. Changes in creatinine and eGFR levels correlated significantly with RENAL/PADUA/DAP scores and the ischemia time ($p<0.05$), but not with the operation time, the amount of bleeding, length of hospital stay, tumor size, and location ($p>0.05$).

Conclusion: Changes in kidney functions and ischemia time correlates significantly withRENAL/PADUA/DAP nephrometry scores.

Keywords: Glomerular filtration rates, creatinine, nephrometry score, partial nephrectomy, renal tumor

Introduction

RENAL cell carcinoma (RCC) constitutes approximately 2% of all adult cancers, with an increasing annual incidence worldwide (1). Due to the extensive use of radiological imaging methods, the number of patients diagnosed incidentally is also increasing. In addition, technical developments in imaging methods such as dynamic imaging, have facilitated the diagnosis of local end-disease stage tumors in majority of patients (2).

Surgical treatment is an option for patients at the local stage ofRCC and includes partial and radical nephrectomy (3). Partial nephrectomy (PN) has become the standard method in the treatment of T1a RCC (4). With the application of kidney-sparing surgery, the risks of chronic kidney disease and of cardiovascular disease have greatly decreased (5). Multiple factors can affect kidney function in PN. The presence of comorbidities, the volume of renal parenchyma, and intraoperative ischemia time are listed among these factors (6). Studies have shown that other additional factors related to tumor, patient, and PN techniques may also affect renal functions in the postoperative period (7,8). Nephrometry scores, which are used as preoperative predictors ofrenal function after PN, may be useful in deciding the type of surgery in cT1 kidney masses. For this reason, various nephrometry scores have been developed in order to define masses in patients scheduled for PN and to standardize the choice of the appropriate surgical method (9,10).These developed scoring systems correlate with warm ischemia time and are predictors of postoperative renal functions (11,12). In this study, we aimed at demonstrating the predictive role of different nephrometry scores in our own clinical experience in evaluating the effect of PN on postoperative kidney functions in patients with T1 kidney tumors.

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Address for Correspondence: Müslüm Ergün, Atlas University Faculty of Medicine, Medicine Hospital, Clinic of Urology, İstanbul, Turkey
Phone: +90 535 764 65 83 **E-mail:** muslumergun@gmail.com **ORCID-ID:** orcid.org/0000-0002-7297-5785
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Materials and Methods

We analyzed computerized files and written file records of 64 patients who underwent laparoscopic PN (LPN) with an initial diagnosis of renal mass between January 2018 and December 2020 in our institution. Patients with preoperative creatinine values above the reference range (n=4), those with a single kidney (n=1), cases with clinical TNM stage ≥T2 renal tumors (n=7), multiple tumors in the same kidney (n=2), and patients who underwent open PN (n=6) were excluded from the study. The remaining 44 patients were included in the study.

Preoperatively, abdominal cross-sectional imaging (at least one computed tomography and magnetic resonance imaging), which is the gold standard method in the evaluation of renal masses was appliedin 44 patients with clinical stage T1 renal tumors undergoing laparoscopic PN. Complete blood count, blood group determination, and kidney function tests were performed in all patients before surgery. The estimated glomerular filtration rates (eGFRs) before and three months after the operation was estimated using The Simplified Modification of Diet in RENAL Disease Modification of Diet in RENAL Disease equation as follows: (eGFRs = 186 × Serum kreatinin (mg/dL)$^{-1.154}$ × age (years)$^{-0.203}$ × 0.742 (female) × 1.210 (if Africans) (13). At least one of the abdominal imaging methods (ultrasonography, computer tomography or magnetic resonance imaging) was applied three months after the operation and the patients were followed up thereafter.

Preoperative cross-sectional imaging of the patients was examined for laterality, and size of the lesion, while clinical TNM stage and intrarenal location of the lesion (its exophyticity, proximity to the renal sinus and collecting system) were equally determined. Using preoperative cross-sectional imaging methods, RENAL (lesion size, its exophytic-endophytic nature, proximity to renal sinus, location and distance to the pelvis), Preoperative Aspects and Dimensions Used for an Anatomic (PADUA) (size, exophytic-endophytic nature, lateralityof the lesion, its proximity to collecting system and renal sinus, itsdistance to minor calyx) and Diameter- Axial- Polar (DAP) (lesion size, axial distance, polar distance) scores were determined. The patients were divided into three groups according to the RENAL scoring system as having low (4-6 pts), intermediate (7-9 pts) and high (10-12 pts) risks for PN. According to the PADUA scores (which predict the postoperative course after PN), the patients weredivided into low (6-7 pts), intermediate (8-9 pts) and high (10-14 pts) risk categories. According to the predictive DAP scores, the patients were classifiedas low (3-5 pts) and high (6-9 pts) risk groups. During surgery, the duration of artery clamping time (ischemia time), operation time (minute), blood loss (cc), intraoperative complications, requirements for intraoperative transfusion- and hemostatic agent were recorded. Postoperative drainage time, hospital stay, postoperative transfusion need, and postoperative complications were recorded. The relationship between changes in renal functions, duration of ischemia and RENAL/PADUA/DAP scores was examined.

This study was conducted in accordance with the Declaration of Helsinki, and the ethical approval was obtained from our institutional review board (register no: 2018/15-07).

Statistical Analysis

We analyzed data using the Statistical Package for Social Sciences Statistical Analysis Software version 22.0. Chi-square test was employed for nominal data, t-test for parametric variables, and Mann-Whitney U test for non-parametric variables. Mean ± standard deviation was used for parametric data, and median ± distribution width for non-parametric data. A value below $p<0.05$ was considered statistically significant.

Results

The mean age of the patients at the time of surgery was 55.07±12.92 years, and the female/male ratio was 17/27. Right-side surgery was performed in 47.7% (21/44) and left-side surgery in 52.3% (27/44) of participants. The mean tumor size was 3.4±1.35 (0.8-6.5) cm, and 28 (70%) patients were in clinical stage T1a while 12 (30%) patients in clinical stage T1b (Table 1). Mean RENAL (6.2±1.4: range 4-9 pts), PADUA (6.8±1.0: range: 6-9 pts), and DAP (5.57±1.5: range:4-9 pts) scores were calculated. When the patients were grouped according to the RENAL scoring system, 33 patients (75%) were in the low-, and 11 patients (25%) in the intermediate- risk groups. No patients were in the high-risk group. According to the PADUA scoring system, 33 patients (75%) were in the low-, and 11 (25%) patientsin the high-risk groups. No patient was in the high-risk group as well. According to the DAP scoring system, 25 patients (56.8%) were in the low-, and19 patients (43.2%) in the high-risk groups (Table 2).

Preoperative median (range) values for hemoglobin (13.5 g/dL: 8.3-17.1 g/dL), creatinine (0.87 mg/dL: 0.58-1.39 mg/dL), hematocrit (41.5%: 25.8-51.2 %) and eGFR (93.17 mL/min: 58.33-136.81 mL/min) were obtained accordingly. Postoperative third month median (range) creatinine (0.96 mg/dL: 0.6-1.66 mg/dL) and eGFR (86.52 mL/min: 46.5-119.26 mL/min) values were also calculated. A significant difference was found between preoperative andpostoperative creatinine and eGFR values of the patients ($p<0.05$) (Table 3). Changes in eGFR showed a significant correlation with RENAL/PADUA/DAP scores and duration ofischemia ($p=0.045$, $p=0.037$, $p=0.041$, and $p=0.003$, respectively); Operation time, amount ofbleeding, hospital stay, tumor diameter, and location did not show any significant correlation ($p=0.212$, $p=0.880$, $p=0.620$, $p=0.078$, $p=0.091$, and $p=0.081$, respectively) (Table 4).

The mean operation time was 130.23±13.97 (100-160) minutes and the mean amount of blood loss was 290.34±107.58 (110-600) cc. Warm ischemia was applied to the kidney during tumor resection in all patients who underwent PN. Arterial clamping, andselective arterial clamping were applied in 81.8%, and 18.2% of the patients who underwent PN with warm ischemia, respectively. Hemostatic agents were used in the tumor bed in 88.6% (39/44) of the patients who underwent PN. Considering the intraoperative and postoperative complications, there were no complications except the requirement for blood transfusion in three patients. Blood transfusion was required intraoperatively in 4.5% (2/44) of the patients, and in 2.3% (1/144) of cases during the postoperative follow-up.No case of postoperative mortality was recorded.

Table 1. Demographic, and operative data of the patients		
Variables	Mean ± SD or number, ratio	
Age (years)	55.07±12.92 (28-85)	
Gender (M/F)	27/17 (44)	
Indication of RPN	44	
Elective	44	
Mandatory	0	
Laterality (right/left)	21/23 (44)	
Tumor size, cm	3.4±1.35 (0.8-6.5)	
Tumor classification		
Endophytic	12 (27.%7)	
Exophytic	32 (72.3%)	
Central	0	
Tumor location		
Upper pole	9 (20.5%)	
Midpole	9 (20.5%)	
Lower pole	22 (50%)	
Anterior	1 (2.3%)	
Posterior	3 (6.8%)	
OpeOperative time, min	130.23±13.97 (100-160)	
Warm ischemia time, min	20.07±4.38 (10-34)	
Average blood loss, mL	290.34±107.58 (110-600)	
Conversion to open surgery	0/44	
Transfusion	3/44	
Ürinoma	0/44	
Perinephritic hematoma	0/44	
Drain dwell time	2.02±0.89 (0-5)	
Hospital stay, days	3.8±0.79 (3-6)	
Pathology		
Malignant	40 (90.9%)	
Benign	4 (9.1%)	
Positive surgical margin	1/44 (2.27%)	
RCC type		
Clear cell	26 (59.1%)	
Papillary	8	(18.2%)
Chromophobe	2	(4.5%)
Chromophobe + eosinophilic	1	(2.3%)
Mucinous tubular	2	(4.5%)
İnvasive squamous	1	(2.3%)
RCC grades		
1	12	(30%)
2	26	(65%)
3	2	(5%)
4	0	(0%)
RCC stage		
PT1a	28	(7%0)
PT1b	12	(30%)
Benign	4	(9.1%)
Oncocytoma	3	(6.8%)
Atypical lipomatous tumor	1	(2.3%)
RCC: RENAL cell carcinoma, SD: Standard deviation, M: Male, F: Female		

Table 2. Nephrometry scores of the participants			
Scores		**n - mean scores**	
RENAL	Low	33/44 (75%)	6.2±1.4 (4-9)
	Intermediate	11/44 (25%)	
	High	0/44 (0%)	
PADUA	Low	33/44 (75%)	6.8±1.0 (6-9)
	Intermediate	11/44 (25%)	
	High	0/44 (0%)	
DAP	Low	25/44 (56%.8)	5.57±1.5 (4-9)
	High	19/44 (43%.2)	
Data in parentheses represent percentages. n: Number of patients			

Table 3. Changes in creatinine, and eGFR values of the patients during follow-up period relative to preoperative values	
	PreoperativePostoperative (mean ± SD, max-min) (mean ± SD, max-min) p-value
Creatinine (mg/dL)	0.87±0.17 (0.58-1.39) 0.96±0.20 (0.6-1.66) 0.032
eGFR (mL/min)	93.17±15.66 (58.33-136.81) 86.52±16.81 (46.5-119.26) 0.04
eGFR: Estimated glomerular filtration rates, SD: Standard deviation, min: Minimum, max: Maximum	

Table 4. Statistical comparison between intraoperative, and postoperative findings of the participants according to changes in eGFR, and creatinine values		
	Changes in egfr p-values	**Changes in creatinine p-values**
Amount of bleeding	0.880	0.856
Drain dwell time (days)	0.212	0.308
Hospital stay (days)	0.620	0.452
RENAL score	0.045*	0.046*
PADUA score	0.037*	0.040*
DAP score	0.041*	0.039*
Tumor diameter	0.078	0.069
Exophytic renal tumor	0.091	0.071
Endophytic renal tumor	0.080	0.066
Ischemia time	0.003*	0.013*
Intraoperative transfusion	0.174	0.584
Perioperative transfusion	0.198	0.108
*: Statistically significant, eGFR: Estimated glomerular filtration rates, PADUA: Preoperative Aspects and Dimensions Used for an Anatomic, DAP: Diameter- Axial- Polar		

Histopathological evaluation of the patients, revealedthat 40 patients (90.9%) had malignant tumors and 4 (9.1%) had benign lesions. Malignant pathologies were reported as clear cell RCC in 26 patients (59.1%), papillary RCC in 8 patients (18.2%) and other RCCs in 6 (13.6%) patients. Three of four patients with benign pathology had oncocytomas. Surgical margin positivity was seen in one patient. Table 1 displays

data regarding histological subtypes and RCC grades in the pathology specimens of the patients. Mean drain dwell time was 2.02±0.89 (0-5) days, and the mean hospital stay was 3.8±0.79 (3-6) days.

Discussion

In experienced centers, LPN has proven to be an alternative method to open surgery owing to its peroperative and oncological results in both stage 1a and stage 1b tumors (14,15). The fact that LPN is technically more complicated, needing advanced laparoscopic skills and the long learning curve makes it difficult to perform LPN outside centers with a heavy patient load. In a multicenter study performed in patients with solitary kidney, it was stated that the warm ischemia time should be limited to 20-35 minutes in order to prevent irreversible kidney damage (16). In our series, the median warm ischemia time was 20.07 (10-34) minutes, and the median operative time was 130 (100-160) minutes, consistent with the literature. Severalstudies have indicated that the use of intravenous mannitol during PN, the total operative time, amount of blood loss and additional comorbidities may affect postoperative eGFR, while others have stated that these parameters will not necessarily affect postoperative eGFR (17,18).

One of the main goals of PN surgery is to preserve as much functional kidney tissue as possible as well as preserving kidney functions in the shortest possible warm is chemia period. In our study, arterial clamping, and selective arterial clamping were applied in 81.8%, and 18.2% of the patients who underwent LPN under warm ischemia, respectively, and a significant relationship was found between the ischemia time, a decrease in the eGFR and an increase in creatinine levels of the patients in the postoperative third month. Shah et al. (19) examined changes ineGFR values in the follow-up period of 315 patients who underwent elective ischemic and zero-ischemic PN. They showed that although there was a significant decrease in eGFR in the early postoperative period in patients with ischemic PN, this difference disappeared at the 6th postoperative month. Mir et al. (20) reported demonstrate no relationship between ischemia time and preserved renal function. Porpiglia et al. (21) employed renal scintigraphy at the third postoperative month to evaluate the patients they applied PN, and reported lack of any significant difference in terms of loss of renal function between ischemicand zero-ischemic groups. In another study, it was reported that postoperative function was worst in patients with poor basal kidney function (22).

In our study, postoperative changes in eGFR and creatinine values showed a significant correlation with all nephrometry score groups. Recently, Selvi and Başar (23) showed that RENAL and PADUA scores were more important predictors of decline in eGFR than tumor size and stage. Considering the lack of high-risk patients in our study according to assessments performed with RENAL and PADUA scoring systems, we anticipate that this correlation may be more pronounced in patients with high-risk scores. In a series of 188 patients, Borgmann et al. (11) demonstrateda correlation between RENAL, PADUA, and DAP scores with ischemia time. Similarly, in a series of 101 patients, Okhunov et al. (12) revealed thatRENAL and PADUA scores correlated positively with warm ischemia time. As a matter of fact,in our study, durationofischemia demonstrated a significant correlation with the RENAL, PADUA, and DAP scores.

No significant correlation was found with the operation time, tumor diameter, length of stay, amount of bleeding, endophytic, and exophytic nature of the tumor and changes in GFR. Although some studies demonstrate changes in eGFR depending on the exophytic or endophytic nature of the tumor, we believe that this is related to the experience of the surgical team. In our series, we think that the surgical team consisting of the same experienced urologists was an effective factor on our successful outcomes. As a matter of fact, Kim et al. (24) reported that size, location, type of the tumor and duration of ischemia had no effect on postoperative renal functions.

Study Limitations

Our study has some limitations that should be considered. First, the use of eGFR instead of direct GFR measurments will create an error in analysis. Second, low number of patients and failure to follow-up our patients for sufficiently longer period can be counted among other limitations.

Conclusion

From our results, preoperative nephrometry scores are as important as surgical factors in determining the possibility of decreased kidney function in cT1 kidney tumors. Considering the positive correlation between duration ofischemia and renal functions, the importance of surgical experience comes to play. In our study, a significant correlation existed between renal functions, duration ofischemia and RENAL/PADUA/DAP scores. This result indicates the importance of nephrometry scores in predicting the postoperative decline in renal function. Still, more advanced and validated predictive nomograms are needed to predict short- and long-term kidney function.

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Ethics

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Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.E., O.A., A.H.T., Design: O.A., M.E., A.H.T., Data Collection or Processing: M.E., O.A., A.H.T., Analysis or

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Original Article

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Non-Tumoral Factors Affecting The Preference of Nephron-Sparing Surgery in The Treatment of Stage 1 Renal Cell Carcinoma Patients in Turkey

Barış Kuzgunbay[1], Özgür Yaycıoğlu[1], Tayyar Alp Özkan[2], Bülent Akdoğan[3], Sinan Sözen[4], Yıldırım Bayazıt[5], Volkan İzol[5], Ender Özden[6], Ozan Bozkurt[7], Sümer Baltacı[8], İlker Tınay[9], Süleyman Ataus[10]

[1]*Başkent University Faculty of Medicine, Department of Urology, Adana, Turkey*
[2]*Acıbadem Hospital, Clinic of Urology, Kocaeli, Turkey*
[3]*Hacettepe University Faculty of Medicine, Department of Urology, Ankara, Turkey*
[4]*Gazi University Faculty of Medicine, Department of Urology, Ankara, Turkey*
[5]*Çukurova University Faculty of Medicine, Department of Urology, Adana, Turkey*
[6]*Ondokuz Mayıs University Faculty of Medicine, Department of Urology, Samsun, Turkey*
[7]*Dokuz Eylül University Faculty of Medicine, Department of Urology, İzmir, Turkey*
[8]*Ankara University Faculty of Medicine, Department of Urology, Ankara, Turkey*
[9]*Anadolu Medical Center, Clinic of Urology, İstanbul, Turkey*
[10]*İstanbul Forte Urology Center, Clinic of Urology, İstanbul, Turkey*
[11]*Dr. Members of Kidney Cancer Study Group*

Abstract

Objective: Nephron-sparing surgery (NSS) is the first-line treatment for T1N0M0 renal tumors (RT). The aim of this multicentric retrospective study is to investigate the national trends and the effect of non-tumoral factors in the preference of NSS as treatment of T1 RT in Turkey.
Materials and Methods: Relevant data for patients operated between 1997 and 2017 was collected from the Urologic Cancer Database-Kidney Urooncology Association, Turkey (UroCaD-K).
Results: We included 3195 T1N0M0 RT patients in this study. There was a significant increase in the number of NSS performed with time, 9.26% between 1997-2002 to 54.78% between 2013-2017 (p<0.001). NSS proportion decreased with increasing age (p<0.001); but increased with better hospital facility (p<0.001). From multivariate analysis; younger age, later operation date, larger hospital size with higher nephrectomy centers like university hospitals were independently associated non-tumoral factors favoring NSS over radical nephrectomy (RN).
Conclusion: We observed significant disparity in the use of NSS for T1 RT among the elderly (>61 years), small hospital size (≤500 beds), lower nephrectomy volume (<100 nephrectomies/year), and Non-University Hospitals. This disparity can be resolved by persistent education of the residents and urologists with periodic courses and practical training, increasing the funds and strengthening the technical equipment of centers, thereby favoring the performance of NSS even in smaller centers. This will ensure that suitable patients are treated with NSS rather than RN, regardless of the hospital type.
Keywords: Surgical treatment, renal cell carcinoma, nephron-sparing surgery, non-tumor factors, nephrectomy volume

Introduction

Renal cell carcinoma (RCC) represents 2-3% of all cancers. There is a 1.5:1 male predominance, with a peak incidence between 60 and 70 years of age. Smoking, obesity, hypertension, and having a first-degree relative with RCC are known etiological risk factors for RCC. Data from Europe and the United States show that the incidence of RCC increased by about 2% over the last two decades, probably due to an increased use of and advancement in radiologic imaging such as ultrasonography, computed tomography, and magnetic resonance imaging. This has also caused an increase in the proportion of incidentally diagnosed small low-stage tumors (1).

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Address for Correspondence: Tayyar Alp Özkan, Acıbadem Hospital, Clinic of Urology, Kocaeli, Turkey
E-mail: alpozkan@gmail.com **ORCID-ID:** orcid.org/0000-0003-3115-3141
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The tumor node metastasis (TNM) classification is recommended for the staging of RCC (1). According to the 2017 TNM classification; T1 is defined as a tumor <7 cm or less in the greatest dimension, limited to the kidney. Moreover, T1 is divided into two: T1a if tumor <4 cm or less; T1b if tumor >4 cm but <7 cm (1). The European Association of Urology Guidelines strongly recommend nephron-sparing surgery (NSS) as the first-line treatment of T1 renal tumors (RT) since radical nephrectomy (RN) and NSS have similar oncological outcomes as well as safety and complication rates independent of the surgical technique; be it open, laparoscopic or robotic surgery (1,2,3,4). However, many systematic reviews and meta-analyses showed overall survival, cardiac-specific survival, renal reserve, and quality of life benefits in favor of NSS (4,5,6,7,8,9). A recently published study concluded that the prognostic risk of chronic kidney disease in patients with kidney cancer increases when the preoperative glomerular filtration rate is less than 60 mL/min/1.73 m^2 or the postoperative rate is less than 45 mL/min/1.73 m^2 (10). It was also emphasized that additional factors, including non-surgical causes of chronic kidney disease and the degree of albuminuria, can also alter the consequences of chronic kidney disease after surgery. However, NSS is not suitable for some patients with localized RT due to insufficient parenchyma left, renal vein thrombosis, unfavorable tumor location, and use of anticoagulants (1). Several studies analyzed the national trends for NSS practice over time and the effect of non-tumor-related factors such as the hospital facility or patient characteristics for the choice of NSS in RT (11,12). The trend of increased NSS practice was not universal.

NSS has also been increasingly practiced in Turkey as the treatment of T1 RT in line with recent guidelines. Thus, the aim of this multicentric retrospective study is to investigate the national trends and the effect of non-tumoral factors on the preference of NSS in the treatment of T1 RT in Turkey.

Materials and Methods

Data was obtained from the Urologic Cancer Database-Kidney Urooncology Association, Turkey (UroCaD-K) which is the largest renal cancer database in Turkey. Study data were collected and managed using REDCap electronic data capture tools hosted at Urooncology Association (13,14) REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to enable data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

We evaluated the data of 3195 patients who underwent surgical treatment for T1N0M0 RCC at 32 different hospitals in Turkey between 1997-2017. The patients were divided into two groups according to the operation type; RN and NSS groups. The effects of patient-dependent non-tumoral factors such as age, sex, performance score, and hospital-dependent factors such as hospital type, bed size, tumor nephrectomy volume, laparoscopy experience, year of NSS were evaluated. Performance score was defined as ECOG 0 and ≥1. Hospital type was grouped as University Hospital or Non-University Hospital. Hospital volume for RN or PN was calculated each year and categorized into four groups across all years (<50, 50-100, 100-150, ≥150 nephrectomies per year, respectively). In addition, hospital beds were counted and hospitals were categorized into three groups accordingly; small, medium, and large-capacity (≤500, 501-999, ≥1000 beds, respectively). Patients were grouped in ten-year periods, according to age. Operation dates were grouped in 5-year periods.

Statistical Analysis

The Stata MP statistical software package (StataCorp, Texas, USA) version 14.2 was used for the analyze collected data. The Shapiro-Wilk normality test was used to evaluate normal distribution, and a histogram was used to evaluate homogeneity. In the descriptive statistics, mean ± standard deviation and median (interquartile range) were used. For continuous variables, a t-test was used for data with normal distribution, and the Wilcoxon rank-sum test for data without normal distribution. Fisher's exact test was used to compare categorical variables. The logistic regression method was used for univariate and multivariate analyses. A p-value less than 0.05 was considered to be statistically significant.

This study was approved by Baskent University Institutional Review Board with project number: KA18/221 and supported by Baskent University Research Fund.

Results

The study cohort included 3.195 patients who underwent surgical intervention at 32 different centers for a renal tumor smaller than 7 cm diagnosed between 1997 and 2017. Nineteen of the centers were University Hospitals, while thirteen of them were Non-University Hospitals. One of the University Hospitals was small, six of them were medium and twelve of them were large hospitals, while one of the Non-University Hospitals was small, eleven of them were medium and one of them was a large hospital according to their bed counts. Three of the University Hospitals performed <50, 9 of them 50-100, 6 of them 100-150, one of them ≥150, while 2 of the Non-University Hospitals performed <50, 7 of them 50-100, 4 of them 100-150 and none of them ≥150 nephrectomies per year.

Among these, 1962 (61.4%) patients underwent RN, and 1233 (38.6%) patients underwent NSS, consecutively. The non-tumoral demographic and hospital factors according to procedure types are shown in Table 1. There was a significant increase in the proportion of NSS performed with time, increasing from 9.26% in the first quarter to 54.78% in the fourth quarter ($p<0.001$) (Figure 1). However, there was a significant decrease in NSS practice as the patient age increased ($p<0.001$). In addition, there was a significant increase in the NSS practice as the hospital size and nephrectomy volume of the hospital increased ($p<0.001$). However, the practice of NSS was similar according to sex. Univariate and multivariate analyses of non-tumoral factors affecting NSS practice between 1997-2017 are presented in Table 2. In general, younger age, recent operation date, larger hospital size with higher nephrectomy volume were parameters that were independently associated to a preference of NSS over RN. Although there was a significant increase in the

number of NSS performed according to the performance status of the patient and laparoscopic experience of the center in the univariate analysis (p<0.001), no difference was observed in the multivariate analysis of these two parameters.

Discussion

Our study showed that the NSS ratio for T1 RT increased six-fold in the last two decades in Turkey, similar to other countries in the world. Previously, Hollenbeck et al. (15) had demonstrated an increase in NSS rate from 3.7% in 1988-1990 to 12.3% in 2000-2002, regardless of the tumor size. Dulabon et al. (11) analyzed the SEER (Surveillance, Epidemiology and End Results) data in the United States and showed an increase in NSS ratio for T1a RT, from 20% in 1999 to 45% in 2006. Finally, Patel et al. (12) revealed an increase in the frequency of partial nephrectomy nationally from 15.3% in 2002 to 24.7% in 2008 (12). Zini et al. (16) on the other hand, revealed an increase from 41% to 86% for masses less than 2 cm and 15% to 70% for masses between 2 to 4 cm, from 1987 to 2008 at tertiary European medical centers (16). These increments are certainly influenced by the increased number of incidentally diagnosed small tumors that urologists have been treating over the years. Thus, the surgeons and their centers have been gaining experience and perfecting their skills in NSS. Moreover, the addition of laparoscopic and robotic surgery to the urologic armamentarium has probably caused an increased comprehension of minimally-invasive techniques in urology, resulting in more NSS performed either through the open, laparoscopic, or robot-assisted approach.

Table 1. Non-tumoral demographic factors of the patients according to procedure type; Radical Nephrectomy vs Nephron-Sparing Surgery (RN vs NSS), between 1997-2018

Procedure type % (n)	Radical Nephrectomy 61.4 (1962)	Nephron-Sparing Surgery 38.6 (1233)	p
Age groups (years)*, % (n)			<0.001
41-50	57.11 (510)	42.89 (383)	
51-60	58.23 (538)	41.77 (386)	
61-70	61.22 (521)	38.78 (330)	
71-80	72.81 (324)	27.19 (121)	
>80	84.21 (64)	15.79 (12)	
Gender†, % (n)			0.225
Women	60.23 (748)	39.77 (494)	
Men	62.37 (1205)	37.63 (727)	
Operation date, % (n)			<0.001
1. quarter (1997-2002)	90.74 (294)	9.26 (30)	
2. quarter (2003-2007)	76.24 (690)	23.76 (215)	
3. quarter (2008-2012)	57.22 (424)	42.78 (317)	
4. quarter (2013-2017)	45.22 (554)	54.78 (671)	
Performance status, % (n)			<0.001
ECOG 0	58.08 (1301)	41.92 (939)	
ECOG >1	69.21 (661)	30.79 (294)	
Hospital type, % (n)			0.051
Non-University Hospital	64.25 (532)	35.75 (296)	
University Hospital	60.41 (1430)	39.59 (937)	
Hospital size, % (n)			<0.001
Small (≤500)	74.64 (103)	25.36 (35)	
Medium (499-999)	62.94 (866)	37.06 (510)	
Large (≥1000)	59.07 (993)	40.9 (688)	
Nephrectomy volume (number/year), % (n)			<0.001
≤50	92.16 (94)	7.84 (8)	
50-100	73.13 (950)	26.87 (349)	
100-150	57.61 (765)	42.39 (563)	
≥150	32.83 (153)	67.17 (313)	
Laparoscopic experience, ‡ %(n)			<0.001
No	88.33 (159)	11.67 (21)	
Yes	59.73 (1796)	40.27 (1211)	

*6 missing, † 21 missing, ‡ 8 missing, RN: Radical nephrectomy, NSS: Nephron-sparing surgery

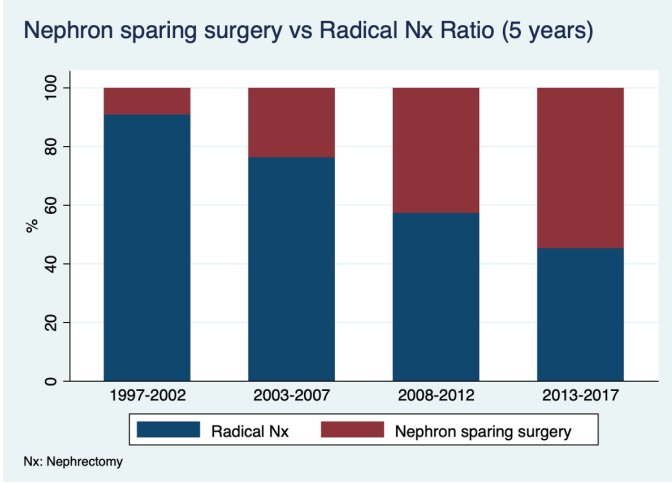

Figure 1. Proportion of NSS practice versus radical nephrectomy over time

We observed a significant decrease in the frequency of NSS as age of patients increased, suggesting that the surgeons preferred RN in older patients. This may be due to an effort to avoid increased time of operation and complications of NSS in older patients with comorbidities. However, such patients are also at an increased risk for baseline renal insufficiency as reported in studies in Europe and United States (11,12,15,16). Although Kim et al. (17) reported a marked increase in the proportion of elderly patients (>70 years) with T1 renal tumor undergoing NSS from 15.2% to 27.4% from 2002-2003 to 2010-2011 in the United States and NSS preference was not different with respect to age.

We also noticed alterations in the preference of NSS according to hospital depended on factors such as hospital type, size, and nephrectomy volume. We observed that larger hospitals with higher nephrectomy volume centers like University Hospitals were independently associated NSS practice. Certainly, this is an indicator of the effect of increased experience on the choice of NSS, a more challenging and time-consuming procedure with higher perioperative complication rates than RN (2). Hospital case volume is also known to be a structural indicator of the

Table 2. The univariate and multivariate analysis of non-tumoral factors affecting the preference of Nephron-Sparing Surgery (NSS) between 1997-2017

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Age groups (years)				
41-50	1 Reference		1 Reference	
51-60	0.95 (0.79-1.15)	0.631	0.92 (0.75-1.13)	0.443
61-70	0.84 (0.69-1.02)	0.081	0.75 (0.61-0.93)	0.009
71-80	0.50 (0.38-0.63)	<0.001	0.57 (0.32-0.56)	<0.001
>80	0.25 (0.13-0.47)	<0.001	0.17 (0.09-0.34)	<0.001
Operation date				
1. quarter (1997-2002)	1 Reference		1 Reference	
2. quarter (2003-2007)	3.05 (2.03-4.58)	<0.001	2.73 (1.79-4.18)	<0.001
3. quarter (2008-2012)	7.32 (4.90-10.96)	<0.001	5.91 (3.77-9.25)	<0.001
4. quarter (2013-2017)	11.86 (8.01-17.57)	<0.001	9.53 (6.15-14.77)	<0.001
Performance status				
ECOG >1	1 Reference		1 Reference	
ECOG 0	1.62 (1.38-1.90)	<0.001	1.15 (0.95-1.39)	0.144
Hospital type				
Non-University Hospital	1 Reference		1 Reference	
University Hospital	1.17 (0.99-1.38)	0.051	1.40 (1.10-1.77)	0.005
Hospital size				
Small (≤500)	1 Reference		1 Reference	
Medium (499-999)	1.73 (1.16-2.58)	0.007	1.57 (1.32-1.73)	<0.001
Large (≥1000)	2.04 (1.37-3.03)	<0.001	1.55 (1.28-1.72)	0.001
Nephrectomy volume (number/year)				
<50	1 Reference		1 Reference	
50-100	4.32 (2.07-8.97)	<0.001	1.93 (0.90-4.11)	0.087
100-150	8.65 (4.16-17.94)	<0.001	3.27 (1.51-7.10)	0.003
≥150	24.04 (11.38-50.75)	<0.001	10.30 (4.61-22.98)	<0.000
Laparoscopic experience				
No	1 Reference		1 Reference	
Yes	5.10 (3.22-8.09)	<0.001	1.32 (0.80-2.20)	0.272

CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group

quality of care for many procedures (18). Surgeons working in larger hospitals with higher nephrectomy volumes are more likely to face more-challenging cases and are therefore more prone to attend postgraduate courses and fellowship programs; thereby improve their experience and more-challenging surgical techniques such as like NSS. On the contrary, surgeons working in smaller hospitals with low nephrectomy volumes are unlikely to perform NSS for patients with T1 tumors. Thus, some patients with T1 RT who live in cities away from large-volume hospitals are unlikely to receive the recommended management following urological guidelines. Studies from the United States and Western European countries also revealed similar findings confirming that not every patient was able to receive the optimal treatment for their small RT (11,12,15). Dulabon et al. (11) demonstrated that patients who lived in a rural setting in the United States had significantly lower odds of undergoing NSS than their urban counterparts as tertiary care centers or "centers of excellence" are typically more in metropolitan areas. Also, they concluded that they recognize these disparities to eliminate these biases and ensure the equal delivery of quality healthcare to all patients in the United States. Similar to Dulabonet al. (11), Patel et al. (12) also reported a two-fold difference in NSS rates between urban/teaching hospitals (23.8%) and rural/non-teaching hospitals (12.3%), and the large regional differences in the United States (25.4% in the Northeast vs 18.1-18.5% elsewhere) demonstrating that high volume nephrectomy centers are more likely to perform NSS for RT than lower volume centers. Moreover, those with private health insurances and higher income were more likely to undergo NSS even after adjusting for age, comorbidity, and a host of hospital factors. According to these results, they concluded that the rising tide has not lifted all boats (12). Hollenbeck et al. (15) revealed that

patients treated at urban (odds ratio 1.1), teaching (odds ratio 1.3), and high nephrectomy volume (odds ratio 2.5) hospitals were significantly more likely to undergo NSS. Zini et al. (16) presented that institutional NSS is one of the independent factors of the individual probability of treatment of small renal tumor with NSS according to results from six tertiary care centers in Europe.

Study Limitations

This study has several strengths and limitations. To begin with, this is the first multicentric study investigating the national trends and the effect of non-tumoral factors for the preference of NSS in the treatment of T1 RT in Turkey from 1997 to 2017. However, this is a retrospective study with a smaller sample compared to the literature. The Body Mass Index and prior renal surgery status of the patients were lacking. Also, individual surgeon experience could not be standardized. Although 32 centers were included in our study, this was still a small proportion of the whole health system in Turkey.

Conclusion

In our multivariate analysis, we observed significant disparity in the use of NSS for T1 RT among the elderly (>61 years), small hospital size (≤500 beds), small nephrectomy volume (<100 nephrectomies/year), Non-University Hospitals. This disparity could be resolved by persistent education of the residents and urologists with periodic courses and practical training, and by increasing the funds and strengthening the technical equipment of centers. This will lead to NSS been performed even in smaller centers. Thus, this will ensure that suitable patients can be treated with NSS rather than RN in centers other than larger centers.

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Contribution: Güven Aslan, Dokuz Eylül University Faculty of Medicine, Department of Urology; Talha Müezzinoğlu, Celal Bayar University Faculty of Medicine, Department of Urology; Çağ Cal, Ege University Faculty of Medicine, Department of Urology; Levent Türkeri, Acıbadem University Faculty of Medicine, Department of Urology.

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Ethics

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Informed Consent: Retrospective study.

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Authorship Contributions

Supervision: S.A., Critical Review: B.A., S.S., Y.B., V.İ., E.Ö., O.B., S.B., İ.T., Concept: B.K., Ö.Y., T.A.Ö., Design: B.K., Ö.Y., T.A.Ö., Data Collection or Processing: B.K., Ö.Y., T.A.Ö., Analysis or Interpretation: B.K., Ö.Y., T.A.Ö., Literature Search: B.K., Ö.Y., T.A.Ö., Writing: B.K., Ö.Y., T.A.Ö.

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Original Article

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Prognostic Value of Systemic Immune-Inflammation Index in Patients with Testicular Cancer: A Retrospective Case-Control Study

Yunus Emre Göger[1], Mehmet Serkan Özkent[2], Mustafa Karaağaç[3], Harun Uçmak[1], Mehmet Artaç[3]

[1]*Necmettin Erbakan University Meram Faculty of Medicine, Department of Urology, Konya, Turkey*
[2]*Konya City Hospital, Clinic of Urology, Konya, Turkey*
[3]*Necmettin Erbakan University Meram Faculty of Medicine, Department of Medical Oncology, Konya, Turkey*

Abstract

Objective: The primary aim of this study was to evaluate the correlation between the systemic immune-inflammation index (SII) and clinicopathological outcomes of patients with testicular cancer (TCa). The secondary aim was to evaluate the relation of SII with overall survival (OS).
Materials and Methods: A total of 244 patients were included in the study. Patients were divided into the testicular tumor (group 1, n=184) and control group (group 2, n=60). Preoperative complete blood count, tumor markers, and imaging tests of the patients in group 1 were recorded. A subgroup analysis was performed according to the clinical stage, pathological stage, tumor type, and tumor size. Then, the effectiveness of TCa on SII was evaluated among the groups.
Results: A significant difference was observed between the SII, neutrophil, and neutrophil-to-lymphocyte ratios between groups 1 and 2. The median SII was 719.92 in group 1 and 510.93 in group 2 ($p<0.001$). In the subgroup analysis, the median SII value was higher in patients with advanced disease stage and metastasis ($p<0.001$). In the receiver operating characteristics curve analysis, the area under the curve was 0.784, and the SII cut-off point was 719, with a sensitivity of 81% and specificity of 65.4%. The median follow-up time was 55 (interquartile range, 8-132) months. Ten patients died of TCa. In the multivariable analysis, SII (7.6-fold increase; $p=0.005$) and presence of metastasis (4.3-fold increase; $p=0.001$) were independent predictors of OS.
Conclusion: SII can be an important marker in the diagnosis and follow-up of TCa. However, SII needs to be evaluated using larger data, especially in the risk assessment in TCa.
Keywords: Systemic immune-inflammation index, testicular cancer, cancer prognosis, overall survival

Introduction

In western countries, 3-10 in 100,000 men are diagnosed with testicular cancer (TCa) annually, representing 1% of all male neoplasms and 5% of all urological tumors (1,2). The recurrence rate of TCa has been steadily increasing in recent decades, especially in developing countries (3). It is the most common solid tumor in men aged 20-34 years with a globally rising tendency (4). TCa is divided into two main subcategories, namely, seminoma and non-seminomatous germ cell tumor (NSGCT) that makes up 95% of all malignant tumors in the testes (5). According to a population-based patient series within developed countries, at the initial stage of diagnosis, stage I TCa is diagnosed in 75%-80% of patients with seminoma and in 55%-64% of patients with NSGCT (2,6). TCa survival outcomes are quite high with 95% of the patients attaining 5-year cancer-specific survival (CSS) mainly due to early clinical staging of the tumor grade at TCa diagnosis. Only 10% of TCa cases present with metastatic disease, lowering the 5-year CSS to 73% (4).

Inflammation has an important function in the biology and etiology of versatile tumors and is thought to be a characteristic of cancer (7). Several systemic inflammation markers (e.g., leukocytes, neutrophils, and thrombocytes) can be evaluated with simple and routine blood tests. Compared with platelet (Plt)-, neutrophil-, or lymphocyte-based tools, systemic immune-inflammation index (SII) emerges as a more powerful tool in cancer diagnosis and follow-up as it combines three independent prognostic factors (8,9).

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Address for Correspondence: Yunus Emre Göger, Necmettin Erbakan University Meram Faculty of Medicine, Department of Urology, Konya, Turkey
Phone: +90 533 415 07 53 **E-mail:** dr_yegoger@yahoo.com **ORCID-ID:** orcid.org/0000-0002-4480-9093
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Systemic inflammation markers and their ratios in particular have been verified for their prognostic values in malignancies such as genitourinary cancers like urothelial cancer, kidney cancer, and prostate cancer (9,10,11,12). Compared with Plt-, neutrophil-, or lymphocyte-based tools, SII emerges as a more powerful tool in cancer diagnosis and follow-up as it combines three independent prognostic factors (8). A high SII activity is considered a poor prognosis criterion, such as cancer progression, metastasis, and low overall survival (OS) (13,14,15,16). However, studies on SII related to TCa are limited.

With the above background, the primary aim of this study was to evaluate the correlation between SII and clinicopathological outcomes, and the secondary aim was to evaluate the relation of SII with OS.

Materials and Methods

In this study, records of patients with TCa followed up at the urology and oncology clinics of Necmettin Erbakan University Meram Medical Faculty and at the Urology Clinic of Konya Training and Research Hospital between January 2008 and December 2020 were evaluated retrospectively. Cases with extragonadal GCT, missing information about systemic inflammatory markers, or incomplete follow-up information were excluded from the study.

Patients were divided into the testicular tumor group (group 1) and the control group (group 2). Group 1 consisted of patients with TCa, while group 2 was composed of patients without testicular tumors who presented to the hospital with different complaints, such as varicocele and hydrocele, during the same period.

Before radical orchiectomy, patients' age, complete blood count [hemoglobin (Hb), neutrophils, Plt, mean platelet volume (MPV), lymphocytes, etc.], alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (HCG), and lactate dehydrogenase values were recorded. Clinical staging was performed based on abdominal and thoracic computed tomography before treatment. Patients were classified according to age, TNM stage, and International Germ Cell Consensus Classification (IGCCCG) risk groups. Pathology results were recorded. According to patients' clinical and pathological stages, treatment and follow-up protocols were arranged according to the The European Association of Urology guideline. In addition, Hb, MPV, Plt, neutrophil-to-lymphocyte ratio (NLR), and SII (NxP/L) were calculated.

The recorded values were compared between the two groups. The relationship between SII value and pathological and clinical stages of TCa was evaluated, and the correlation between prognosis and SII value was also examined.

All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all patients. The study was approved by the Meram Medical Faculty Ethics Committee of Necmettin Erbakan University (protocol no: 2021/2980).

Statistical Analyses

Non-parametric tests were used to analyze parameters that deviated from the normal distribution. Parameters with normal distribution were analyzed by parametric tests. Variables with continuous normality distribution were expressed as mean ± standard deviation. Categorical variables were presented as percentage, and variables without normal distribution were expressed as median and interquartile ranges (IQR). The Mann-Whitney U test or independent t-test was used to evaluate statistical differences between groups. The chi-square test was also used to analyze categorical variables.

Kaplan-Meier analysis was conducted to estimate OS using product-limit method, and log-rank test comparisons were performed subsequently. To define differences in SII-based prognoses, a multivariable analysis was conducted using Cox proportional hazards model. The areas under the receiver operating characteristic curves (ROC) of SII were used to predict TCa.

Statistical Package for Social Sciences version 23.0 (IBM Corp., Armonk, NY, USA) was used to analyze data. A confidence interval (CI) of 95% and a p-value of <0.05 were considered for the threshold level of significance. All reported p-values were two-sided.

Results

A total of 244 participants were enrolled in this study, of which 184 (75.4%) were classified in group 1 (TCa group) and 60 (24.6%) in group 2 (control group). The mean age of all patients was 37.72±9.9 (19-66) years, and those in groups 1 and 2 were 36.82±9.8 (19-66) years and 40.28±9.9 (22-61) years, respectively. The median SII values were 719.92 (IQR: 225.73-2802.5) in group 1 and 510.93 (IQR: 235.24-1436.94) in group 2, in favor of group 1 (Mann-Whitney U=1309; Z=-4.001; $p<0.001$). The mean values of Hb, Plt, lymphocytes, neutrophil, and MPV were 15.27±1.7, 279.68±62.3, 2.17±0.6, 5.96±2.1, and 8.54±1.8, respectively. The mean neutrophil, mean NLR, and median SII values were higher in group 1 than in group 2 ($p<0.001$; $p=0.002$; $p=0.001$, respectively) (Table 1).

In this study, 78 (42.4%) patients had NSGCT and 106 (57.6%) had seminoma GCT. In addition, 123 (66.8%) patients had stage I cancer, and 61 patients (33.2%) had stage II and over. In the pathological evaluation, lymphovascular invasion (LVI) was present in 109 (59.2%) patients (Table 2).

The mean tumor size was 4.55±2.1 cm (1-13 cm). The median SII value was 911.50 (IQR: 225.73-2802.5) in tumors ≤4 cm in size. However, the SII value was 827.57 (IQR: 355.93-2402.28) in tumors >4 cm in size. No difference was found between the groups in terms of tumor size (Mann-Whitney U=1124; Z -1.027; $p=0.235$) (Table 2). The median AFP and beta-HCG values were 2783 (IQR: 401-563495) and 5.38 (IQR: 0-265000), respectively.

The median SII value of 138 patients (75%) with pathological T1-2 stage was 815.97 (IQR: 225.73-2201.4) and that of 46 patients (25%) with pathological >T2 stage was 1631.71 (IQR: 513.6-2802.5).

Regarding clinical tumor stage, the median SII value was 683.33 (IQR 225.73-2512.18) for clinical I stage tumors and 1036.00 (IQR 387.88-2802.50) for clinical stage II and over. The SII value was higher in advanced-stage tumors (Mann-Whitney U=713; Z=-3.652; p<0.001).

In total, 32 (17.4%) patients had metastasis: lung metastasis, 20 patients; liver and lung metastasis, 6 patients; bone metastasis, 5 patients; brain metastasis, 1 patient. The SII value was the highest in patients with metastasis than in those without it. The median SII value was 1204 (IQR 506.64-2802.50), and it was higher in patients with metastasis than in those without metastasis (Mann-Whitney U=1518; Z=-5803; p<0.001).

The SII value did not affect the LVI (Mann-Whitney U=1544; Z=-0.049; p=0.961). The median SII value was 715.81 (IQR 225.73-2310.8) in tumors without LVI and 810.06 (IQR 241.43-2802.50) in tumors with LVI (Table 2).

Table 1. Demographic findings of the patients

	Group 1	Group 2	p-value
Patients (n)	184 (75.4%)	60 (24.6%)	
Mean age (years)	36.82±9.8	40.28±9.9	0.062
Hemoglobin value	15.27±1.7	15.55±1.2	0.172
Mean platelet level	279.68±62.3	272.45±57.3	0.810
Mean neutrophil level	5.96±2.1	4.71±1.7	<0.001
Mean reticulocyte level	13.06±1.8	12.81±0.8	0.399
Mean monocyte value	0.59±0.1	0.56±0.2	0.437
Mean MPV	8.54±1.8	9.93±0.7	<0.001
Mean NLR	2.88±1.4	2.16±0.9	0.002
Median SII	719.92	510.93	0.001
Median AFP value	2783	N/A	N/A
Median beta-HCG value	5.38	N/A	N/A

LVI: Lymphovascular invasion, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, MPV: Mean platelet volume, AFP: Alpha-fetoprotein, HCG: Human chorionic gonadotrophin, N/A: Not available

Table 2. Median systemic immune-inflammation index value of the patients

Variables		Patient number (n) (%)	Median SII value	P value
Pathological stage	T1-2 ≥T2	138 (75) 46 (25)	815.97 1631.71	0.027
Size	≤4 cm >4 cm	101 (54.9) 83 (45.1)	911.50 827.57	0.235
Pathology	Seminoma Non-seminoma	106 (57.6) 78 (42.4)	752.34 801.45	0.084
Stage	Stage I Stage ≥ II	123 (66.8) 61 (33.2)	683.33 1036	0.001
LVI	Yes No	109 (59.2) 75 (40.8)	810.06 715.81	0.961
Metastasis+	Yes No	32 (17.4) 152 (82.6)	1204.04 823.00	0.001

LVI: Lymphovascular invasion, SII: Systemic immune-inflammation index
+Metastasis: Lung metastasis, 20 patients; liver and lung metastasis: 6 patients; bone metastasis: 5 patients; brain metastasis: 1 patient

A cut-off point of 719 was obtained, with an area under the ROC (ROC) curve of 0.784 (Figure 1). The sensitivity at this cut-off point was 81%, and the specificity was 65.4%.

After the initial chemotherapy sessions, retroperitoneal lymph node dissection was performed in 10 patients. The median follow-up time was 55 (IQR 8-132) months. Ten patients died of TCa.

In the univariate Cox regression analysis, factors affecting OS were the presence of metastasis [hazard ratio (HR) 27.865; 95% CI 3.274-3638.245; p=0.03], clinical stages II–III (HR 41.832; CI 4.922-5461.637; p=0.02), pathological TNM classification over T2 (HR 24.054; CI 2.818-3142.170; p=0.04), NLR (HR 1.789; CI 1.170-2.669; p=0.006), and SII (HR 1.004; CI 1.243-1.875; p<0.001). In the multivariable analysis, SII (7.6-fold increase; HR 1.005; CI 1.279-4.251; p=0.005) and presence of metastasis (4.3-fold increase; HR 1.710; CI 0.279-6.730; p=0.001) were independent predictors of OS. Although pathological TNM classification (HR 0.727; CI 0.011-7.973; p=0.80) and NLR ratio (HR 0.398; CI 0.027-1.162; p=0.16) affect the OS, in the multivariable analysis, they did not affect OS. In addition, tumor size (HR 0.717; CI 0.000-50108.01; p=0.17) and tumor type (seminoma or non-seminoma) (HR 0.398; CI 0.069-1.796; p=0.28) did not affect OS (Table 3).

In the Kaplan-Meier estimates of the probabilities of OS according to the SII, the cut-off value of SII was 719 to predict survival [-2Log (LR) 8.3178; p=0.003) (Figure 2).

Discussion

In this study, the SII value was observed to be effective in predicting testicular tumor diagnosis. SII, especially between stage 1 and stages 2-3, is more effective than other inflammatory

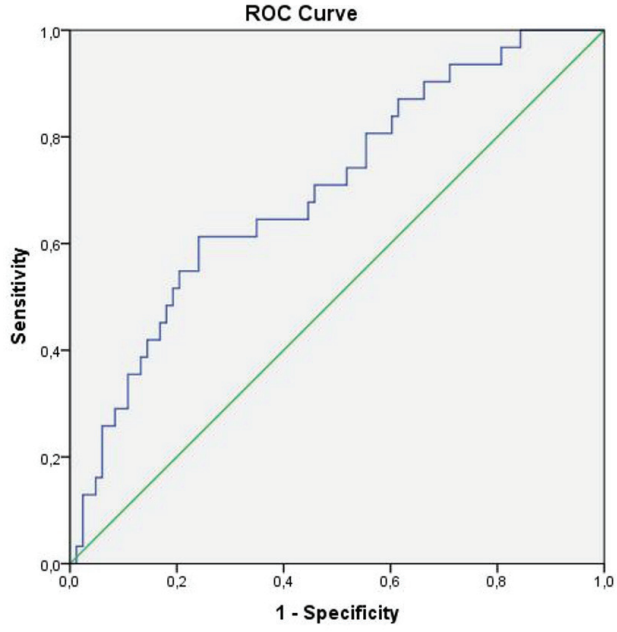

Figure 1. Receiver operating characteristics curve of systemic immune-inflammation index

Table 3. Univariate and multivariate analyses of the factors affecting OS						
	Univariate analysis			Multivariate analysis		
Variables	Hazard ratio	Confidence interval	p-value	Hazard ratio	Confidence interval	p-value
Metastasis	27.865	3.274-3638.245	0.03	1.710	0.155-6.730	0.001
Pathological stage T1-2 vs ≥ T2	24.054	2.818-3142.170	0.04	0.727	0.011-7.973	0.80
Clinical stage I vs stage II-III	13.831	0.021-707.844	0.04	1.105	0.013-5.121	0.01
Tumor size	0.717	0.000-50108.01	0.17	0.548	0.130-3.717	0.87
Tumor type	0.398	0.069-1.796	0.27	0.813	0.002-4.128	0.47
NLR	1.789	1.170-2.669	0.006	0.398	0.027-1.162	0.16
SII	1.004	1.243-1.875	<0.001	1.005	1.279-4.251	0.005
NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, OS: Overall survival						

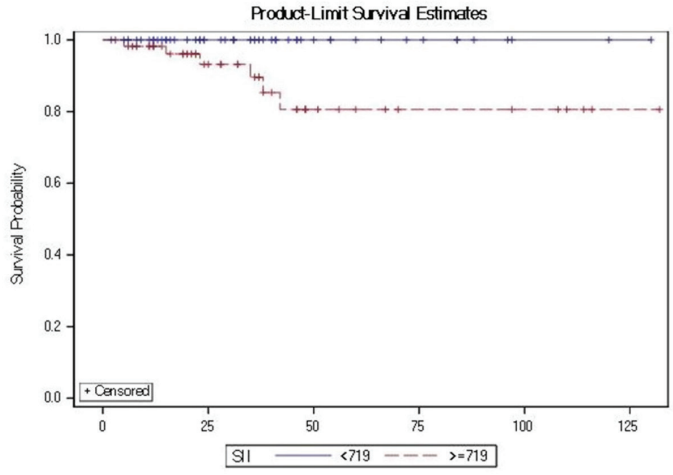

Figure 2. Kaplan-Meier estimates of the probabilities of the overall survival according to the systemic immune-inflammation index

markers and can be used in clinical evaluation and follow-up. The SII value was determined to be one of the important factors affecting testicular tumor prognosis. The inflammatory reaction plays a significant role in the development and prognosis of tumors in several ways, from the genesis of the tumor, progression, to metastasis (17). Inflammation-associated peripheral cells (neutrophils, lymphocytes, and Plt) obtained from the peripheral blood are associated with the progression of various tumors (13,14). In addition, inflammatory indices (II) derived from different combinations of these peripheral cells, such as the NLR and platelet-to-lymphocyte ratio (PLR) have been evaluated in various prognostic factor studies of malignant solid tumors (9,18,19).

SII, a recent inflammatory index, is calculated as follows: SII = P*N/L, where P, N, and L are the peripheral Plts, neutrophil count, and lymphocyte count (17). It has recently been investigated as a prognostic marker in various malignancies. Studies have suggested that SII is superior to alternative systemic inflammation indices such as PLR and NLR and could serve as a more objective marker that reflects the balance between host inflammatory and immune response status (8,20,21).

One of the first studies of TCa using complete blood count indices was conducted using NLR. Şahin et al. (22) reported that NLR was higher in the TCa group than in the varicocele group. Yuksel et al. (23) eported that the NLR is a simple and effective marker in TCa stage I (23). However, Jankovich et al. (24) could not find a difference between metastatic and non-metastatic TCa in their study, but they determined significance in cancer grades above T1 in NLR <4 according to the TNM classification. Tan et al. (25) revealed NLR ≥3.0 and above as significant in patients with lymph node involvement and patients with metastasis, which had worse CSS. In the present study, the NLR was significantly higher in patients with TCa. Moreover, OS was determined in the univariate analysis.

To the best of our knowledge, this study is the first to compare the relationship between SII and TCa with a control group. SII increases significantly in TCa, with an area under the ROC curve of 0.784 (Figure 1). The sensitivity and specificity at this cut-off point were 81% and 65.4%, respectively. The findings of this study suggest that SII can be used effectively in the diagnosis of TCa.

The SII value is closely related to those reported by studies evaluating the prognosis of urological cancers (26). The median progression-free survival was 6.3 months in patients with metastatic renal cell carcinoma with SII ≥730 and 18.7 months in those with SII <730 (27). In another study, Lolli et al. (28) examined patients with metastatic prostate cancer and reported an overall median OS of 17.3 months, with 21.8 months in the SII <535 group and 14.7 months in the SII ≥535 ($p<0.0001$). A retrospective study of muscle-invasive bladder cancer determined that SII >843 is considered a poor prognostic criterion (29). Chovanec et al. (16) conducted one of the rare studies on TCa and SII, and they determined a median SII value of 1003 in patients with metastatic TCa. In the multivariate Cox analysis, the OS in the poor prognostic group according to IGCCCG was affected by SII. However, progression-free survival was not affected.

Fankhauser et al. (15) reported that high SII, neutrophil, and NRL values, together with IGCCCG risk groups, are prognostic predictors of OS in metastatic TCa before first-line chemotherapy. In their ROC analysis of SII, they revealed that 1428 was the ideal cut-off value for clinical decision making. In the subgroup analysis, although neutrophils and leukocytes were high in patients with bone visceral organ and brain metastases, no difference was found in NRL and SII.

Especially, Fankhauser et al. (15) and Chovanec et al. (16) found that SII had potential to provide a more efficient prediction of oncological outcomes in patients with metastatic GCT compared with the well-established IGCCCG classification system. In the present study, in which the mean SII value was 719, the SII value increased to 1036 in cases with advanced stages. The fact that the majority of our participants had stage 1 TCa might be the underlying reason for the lower SII value obtained when compared with other reported values. However, it was the highest in the metastatic group. In addition, unlike other studies, the present study compared the relation of SII level with pathology type, LVI, and tumor size. In line with similar studies, the present study found a cooperative relationship was found between clinical stage and metastasis and SII. It is one of the factors that affect OS. Improved prediction of oncological outcomes could affect the oncologists' decisions concerning systemic treatment and thus might enable a more personalized and eventually a more effective treatment option for eligible patients with metastatic GCT.

In this study, the majority of the patients had TCa stages 1 and 2. Patients with seminoma and non-seminoma GCT had a 6%-18% risk of recurrence even those in the low-risk groups. At the time of diagnosis, 15% and 50% of the patients with seminomas and non-seminomas, respectively, have subclinical stage 2 as determined during patient surveillance. One of the important points is that we can classify patients correctly at these stages, initiate effective treatment, and predict the risk of recurrence after treatment.

Considering other current studies, this study is the first to evaluate SII values with the clinical stage of TCa. Especially, identifying patients with high-risk TCa at the time of initial diagnosis requires a closer follow-up program or an intensified treatment algorithm. In the present study, SII values can be used in the diagnosis and defining the treatment modality of patients with high-risk status.

In patients with TCa stage 1, the treatment plan is made according to pathological prognostic factors. Metastatic TCa treatment preferences are based on IGCCCG classification. Despite surgery and adjuvant chemotherapy, progression, and metastasis can be seen in some patients with stage 1 TCa, while some may experience serious side effects of treatment. However, despite IGCCCG risk estimation and effective chemotherapy regimens, first-line chemotherapy fails in some patients with metastatic TCa and may die eventually. These classifications have been in use for over 20 years. At present, available data are mostly based on findings from the 1990s. Since then, advances in diagnostics (mainly imaging), as well as new treatment protocols and more standardized follow-up regimens, have also been applied to the management of TCa.

The TCa update using a more up-to-date cohort is currently under preparation (30). With updated information, it is possible to better predict oncological outcomes and plan the treatment algorithm in early-stage or metastatic GCT. Better risk stratification is possible by combining conventional clinical and pathological data with new biomarkers, genetic tests, and new imaging techniques.

Study Limitations

This study has some limitations. First, the study has a retrospective design and may be underrepresented in early-stage and metastatic data. Second, some imbalances exist between datasets that could be responsible for the differences in the median SII value. Third, most of the participants had stage 1 and 2 diseases, which might have affected the data obtained. SII could yield more accurate data in patients with advanced disease stages.

Conclusion

SII is a simple examination that can be evaluated through a simple blood test. SII has the potential to contribute to disease-specific diagnosis and treatment algorithms. It can provide additional information to urologists, especially in post-treatment follow-up. However, more cohort, prospective studies are needed.

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Ethics

Ethics Committee Approval: The study was approved by the Meram Medical Faculty Ethics Committee of Necmettin Erbakan University (protocol no: 2021/2980).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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An Overview of Seminomatous and Non-Seminomatous Germ Cell Testicular Tumors: A Single-center Experience

Selin Aktürk Esen[1], Öznur Bal[1], Yakup Ergün[1], Yusuf Açıkgöz[1], Gökhan Uçar[1], Merve Dirikoç[1], Özlem Aydın İsak[3], İrfan Esen[4], Efnan Algın[1], Doğan Uncu[1]

[1]*Ankara City Hospital, Clinic of Medical Oncology, Ankara, Turkey*
[2]*Batman Training and Research Hospital, Clinic of Medical Oncology, Batman, Turkey*
[3]*Ankara Dışkapı Training and Research Hospital, Clinic of Medical Oncology, Ankara, Turkey*
[4]*Ankara Keçiören Medicalpark Hospital, Clinic of Internal Medicine, Ankara, Turkey*

Abstract

Objective: Although germ cell tumors (GCT) are rare malignancies, they are the most common solid tumors in men aged 15-40 years. This study aimed to compare the demographic and clinical characteristics, treatment responses, and survival characteristics of patients with seminomatous GCTs (SGCT) and non-seminomatous GCTs (NSGCTs) followed in our center.

Materials and Methods: Patients with histologically confirmed testicular GCTs and followed up in our hospital between January 2005 and January 2021 were included in this retrospective study. This study was approved by the Institutional Ethics Committee of Ankara City Hospital.

Results: Of the 360 patients, 65.8% (n=123) had NSGCTs and 34.2% (n=237) had SGCTs. The median age at diagnosis of the SGCT group was 36 years and that of the NSGCT group was 28 years (p=0.000). Both the diagnostic and postoperative levels of β-human chorionic gonadotropin were significantly higher in the NSGCT group (p=0.000, p=0.000 respectively). Rates of retroperitoneal lymph node dissection (3.3% vs 9.3%; p=0.036), adjuvant radiotherapy (RT) (17.1% vs 3%; p=0.000), adjuvant chemotherapy (CT) (61.1% vs 40.4%; p=0.003), and metastatic first-line CT (22.8% vs 47.3%; p=0.000) were different between the two groups. The 10-year overall survival expectancy rate was 89% in the SGCT group and 83% in the NSGCT group.

Conclusion: This study drew attention to the characteristics and treatment responses of patients with NSGCTs and SGCTs. In this study, NSGCTs were diagnosed at an earlier age than SGCTs. The proportion of patients with stage 1 disease at diagnosis was higher in the SGCT group, while that of patients with stage 3 and metastasis at diagnosis were higher in the NSGCT group. In addition, the rates of adjuvant CT and adjuvant RT were higher in the SGCT group, while the metastatic first-line CT rate was higher in the NSGCT group.

Keywords: Testicular germ cell tumors, chemotherapy, radiotherapy, autologous stem-cell transplantation

Introduction

Although germ cell tumors (GCTs) are rare malignancies, they are the most common solid tumors in men aged 15-40 years (1). Testicular cancers constitute only 0.5% of all cancers in men. Even if its etiology is not yet fully clarified, risk factors include family history, cryptorchidism, contralateral testicular tumor, infertility, and testicular microlithiasis (2). Moreover, 95% of testicular cancers are GCTs and 5% are non-GCTs and various non-specific stromal tumors. Testicular GCTs is divided into two groups, namely, as seminoma and non-seminoma. Non-seminomatous GCTs (NSGCTs) are divided into five subtypes: embryonal carcinomas, yolk sac tumors, choriocarcinomas, teratomas, and mixed GCTs (MGCTs) (3).

The majority of the patients can be treated by orchiectomy and, if necessary, systemic or local treatments (4). Patients with GCTs have excellent survival rates because of advances in chemotherapy (CT), radiotherapy (RT), and surgery (5). A cure is expected in 95% of all patients with testicular cancer and approximately 80% of patients with metastatic disease (4).

In this study, we aimed to compare the demographic and clinical characteristics, treatment responses, and survival data of patients with seminomatous GCTs (SGCT) and NSGCTs followed in our center.

Materials and Methods

This study was approved by the Institutional Ethics Committee of Ankara City Hospital (decision no: EI-21-1661). Patients with

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Address for Correspondence: Selin Aktürk Esen, Ankara City Hospital, Clinic of Medical Oncology, Ankara, Turkey
Phone: +90 541 356 61 38 **E-mail:** drselin16@hotmail.com **ORCID-ID:** orcid.org/0000-0002-3426-9505
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histologically confirmed testicular GCTs and followed up in our hospital between January 2005 and January 2021 were included in this retrospective study. Clinicopathological characteristics of the patients and treatment modalities were recorded from the patient registration database of the hospital. β-human chorionic gonadotropin (BHCG), lactate dehydrogenase (LDH), and alpha fetoprotein (AFP) levels were measured upon diagnosis and 30 days after orchiectomy. Patients with a second cancer were excluded from the study.

Testicular cancer was staged using the Eighth Tumor, Node, Metastasis staging system developed jointly by the American Joint Committee on Cancer and the Union for International Cancer Control, which applies to both SGCT and NSGCTs (6).

According to the RECIST guidelines, responses were calculated using the following measurements: complete response (CR) (complete resolution of target lesions), partial response (PR) (≥30% decrease in the sum of the diameters of the target lesions compared with the baseline), progressive disease (PD) (≥20% increase in sum of the diameters of the target lesions compared with baseline or new metastatic lesions), and stable disease (SD; neither fitting in PR or PD categories). CR/PR, SD, and PD as per RECIST were independently analyzed (7).

The diagnosis of recurrent testicular GCTs was typically made based on an increase in serum tumor markers or evidence of disease progression on radiographic or physical examinations. Biopsy confirmation was also performed in cases where the recurrence symptom was atypical.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as median with the 25th percentile and 75th percentile. Categorical variables were presented as percentage. The normality of quantitative data has been analyzed by the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Pearson chi-square test was used for the comparison of categorical variables between two groups, and independent sample t-test or Mann-Whitney U test was used for comparison of continuous variables between two groups. Survival analysis was calculated according to the Kaplan-Meier (Log rank, Breslow, and Tarone-Ware analyses) method. P-value <0.05 was considered significant.

Results

Of the total 360 patients, 65.8% (n=237) had NSGCTs and 34.2% (n=123) had SGCTs. The median age at diagnosis of the SGCT group was 36 years and that of NSGCT group was 28 years (p=0.000). The tumor diameter measure by computed tomography was 4.5 cm in the SGCT group and 4 cm in the NSGCT group. No significant difference was found in the mean tumor diameter between the two groups. The median BHCG levels upon diagnosis and after surgery were significantly higher in the NSGCT group (p=0.000 and p=0.000, respectively). No difference was noted between the two groups in terms of LDH levels upon diagnosis and after surgery (Table 1).

Of the NSGCTs, 74% were MGCTs, 12.2% were embryonal carcinomas, 7.2% were teratomas, 5.1% were yolk sac tumors, and 0.8% was choriocarcinomas. Of the MGCTs, 80.1% were embryonal carcinomas, 63.5% were teratomas, 49.7% were yolk sac tumors, 35.4% were seminomas, and 11.6% were choriocarcinomas (Table 2).

The proportion of patients with stage 1 disease at diagnosis was 73.9% in the SGCT group and 46.8% in the NSGCT group (p=0.000), while the proportion of patients with stage 3 disease at diagnosis was 9.2% in the SGCT group and 30.4% in the NSGCT group (p=0.000). The proportion of patients with stage 2 disease at diagnosis was comparable between the two groups. The proportions of patients with SGCTs and NSGCTs in the good-risk group were 93.4% and 59.5%, respectively (p=0.000). The proportion of the patients in the intermediate-risk group were 6.4% and 25.7%, respectively (p=0.000). The rates of patients with positive lymph nodes (LNs) at diagnosis were 27.8% and 52.3% in the SGCT and NSGCT groups, respectively. The proportions of patients with metastasis at diagnosis were 0.8% and 27% in the SGCT and NSGCT groups, respectively. Moreover, the proportions of patients with LN positivity and metastatic disease were significantly higher in the NSGCT group (p=0.006 and p=0.000, respectively) (Table 1).

The recurrence rate was 17.1% in the SGCT group and 18.6% in the NSGCT group. The proportion of patients with recurrence was not different between the two groups (p=0.727). The rate of patients who underwent retroperitoneal LN dissection (RPLND) was significantly higher in the NSGCT group (9.3%, n=22) than in the SGCT group (3.3%, n=4) (p=0.036). While one patient in the SGCT group had post-CT RPLND and three patients had primary RPLND, 16 patients with NSGCT had post-CT RPLND and six patients had primary RPLND. In patients with SGCT who underwent RPLND, seminoma was detected in one patient (stage 1 disease) and necrosis was detected in three patients (two and one patient has stage 2 and 1 disease, respectively). In patients with NSGCT who underwent RPLND, 27.3% of the patients had teratomas (four and one patient had stage 2 and 3 disease, respectively), 18.2% had necrosis (one, two, and one patient had stage 1, 2, and 3 disease, respectively), 31.8% had other non-seminomatous subtypes (two, three, and two patients had stage 1, 2, and 3 disease, respectively), 9.1% had seminomas (two patients had stage 3 disease), 9.1% had reactive LNs (one and one patient had stage 1 and stage 3 disease), and 4.5% were non-diagnostic (one patient had stage 2 disease) (Table 3).

The proportion of patients receiving adjuvant RT was significantly higher in the SGCT group (17.1%, n=21) than in the NSGCT group (3%, n=7) (p=0.000). In the SGCT group, only one patient received testicular RT, while 20 patients received RT for para-aortic ± iliac LNs (n=11) or inguinal LNs (n=9). All patients with NSGCTs received RT to para-aortic ± iliac LNs (n=5) or inguinal LNs (n=2) (Tables 3 and 4).

The proportion of patients receiving adjuvant CT was significantly higher in the SGCT group (61.1%, n=44) than in the NSGCT group (40.4%, n=76) (p=0.003). As adjuvant CT in the SGCT group, 31.8% of the patients received carboplatin and 15.9% received cisplatin, etoposide, bleomycin (BEP, bleomycin 30 U IV weekly on days 1, 8, and 15 + etoposide 100 mg/m^2 IV on days 1-5 + cisplatin 20 mg/m^2 IV on days 1-5/repeat every 21 days) + cisplatin, etoposide (EP, etoposide 100 mg/m^2 IV on days 1-5 + cisplatin 20 mg/m^2 IV on days 1-5/repeat every 21 days) and

Table 1. Demographic and clinicopathological characteristics of the patients						
		SGCT n=123 (34.2%)		NSGCT n=237 (65.8%)		
		Median (minimum; maximum)	%	Median (minimum; maximum)	%	p-value
Follow-up period (years)		7.75 (0.70; 33)		8.79 (0.68; 22.08)		
Age at diagnosis (years)		36 (17; 62)		28 (15; 67)		0.000
Tumor diameter (cm)		4.50 (0.50; 12)		4.00 (1; 10)		0.411
BHCG at diagnosis (IU/mL)		2 (0.1; 2891)		17 (0.1; 275486)		0.000
LDH at diagnosis (U/L)		284 (127; 4720)		261 (120; 5400)		0.651
AFP at diagnosis (ng/mL)				110 (1; 128000)		
Postoperative BHCG (IU/mL)		0.2 (0.1; 1907)		2 (0.1; 596000)		0.000
Postoperative LDH (U/L)		187 (90; 1799)		217 (91; 3577)		0.055
Postoperative AFP (ng/mL)				10 (0.1; 116000)		
Recurrence	Yes		17.1%		18.6%	0.727
	No		82.9%		81.4%	
Stage at diagnosis	Stage 1		73.9%		46.8%	0.000
	Stage 2		16.8%		22.8%	0.146
	Stage 3		9.2%		30.4%	0.000
Risk group	Good		93.4%		59.5%	0.000
	Intermediate		6.4%		25.7%	0.000
	Bad				14.8%	
Tumor	T1		61.1%		50.4%	0.233
	≥T2		38.9%		49.6%	
Node positivity	Negative		72.2%		47.7%	0.006
	Positive		27.8%		52.3%	
Metastasis at diagnosis	No		99.2%		73.0%	0.000
	Yes		0.8%		27.0%	

SGCT: Seminomatous germ cell tumors, NSGCT: Non-seminomatous germ cell tumors, BHCG: β-human chorionic gonadotropin, LDH: Lactate dehydrogenase, AFP: Alpha fetoprotein

Table 2. Subtypes of non-seminomatous germ cell tumors				
		%		%
Pathological subtype	MGCTs	74.7%	Teratoma	63.5%
			Embryonal carcinoma	80.1%
			Yolk sac tumor	49.7%
			Choriocarcinoma	11.6%
			Seminoma	35.4%
	Teratoma	7.2%		
	Yolk sac tumor	5.1%		
	Choriocarcinoma	0.8%		
	Embryonal carcinoma	12.2%		

MGCT: Mixed germ cell tumors

52.2% received BEP. In the NSGCT group, 23.6% of the patients received BEP + EP, 73.6% received BEP, and 2.6% received EP. The proportion of patients receiving metastatic first-line CT was significantly higher in the NSGCT group than in the SGCT group (47.3% and 22.8%, respectively) (p=0.000). No difference was found between the two groups in terms of metastatic first-line treatment responses, rates of metastatic second-line treatment responses, metastatic second-line treatment responses, or autologous stem cell transplantation (ASCT) rates. ASCT was performed in four patients in the SGCT group and in 10 patients in the NSGCT group. In the SGCT group, PD was attained in one patient and SD was attained in three patients. In the NSGCT group, two patients had CR, one had PR, three had PD, and four had SD (Table 3).

The 10-year overall survival (OS) expectancy rate was 89% in the SGCT group and 83% in the NSGCT group. In the survival analysis, OS did not reach the median in either group (Figure 1).

Discussion

NSGCTs are seen in men aged 20-30 years, while SGCTs typically occur between age 30-40 years (8). In this study, the median age of the patients diagnosed with SGCTs was 36 years, while those with NSGCTs was 28 years, and a significant difference was found between the two groups. No difference was found in tumor size between the two groups, and 34.2% of the patients had SGCTs and 65.8% had NSGCTs. In another study conducted in Turkey, the incidence of NSGCT was higher, reporting 77.6%, similar to our study (9). In a retrospective analysis conducted in

Table 3. Treatments and treatment responses of patients with germ cell testicular tumors

n (%)		SGCT	NSGCT	
		n (%)	p-value	
RPLND	Yes	4 (3.3%)	22 (9.3%)	**0.036**
	No	119 (96.7%)	215 (90.7%)	
Adjuvant RT	Yes	21 (17.1%)	7 (3%)	**0.000**
	No	102 (82.9%)	230 (97%)	
Adjuvant CT		44 (61.1%)	76 (40.4%)	**0.003**
Metastatic first-line CT	Yes	28 (22.8%)	112 (47.3%)	**0.000**
	No	95 (77.2%)	125 (52.7%)	
Metastatic first-line CT response	CR	6 (21.4%)	27 (24.1%)	0.191
	PR	13 (46.4%)	53 (47.3%)	0.093
	PD	5 (17.9%)	17 (15.2%)	0.586
	SD	4 (14.3%)	15 (13.4%)	0.503
Metastatic second-line CT	Yes	20 (16.3%)	41 (17.3%)	0.803
	No	103 (83.7%)	196 (82.7%)	
Metastatic second-line CT response	CR	6 (30%)	7 (17.1%)	0.247
	PR	8 (40%)	16 (39%)	0.942
	PD	3 (15%)	9 (22%)	0.525
	SD	3 (15%)	9 (22%)	0.525
ASCT	Yes	4 (3.3%)	10 (4.2%)	0.653
	No	119 (96.7)	227 (95.8%)	
ASCT response	CR	0 (0%)	2 (20%)	
	PR	0 (0%)	1 (10%)	
	PD	1 (25%)	3 (30%)	
	SD	3 (75%)	4 (40%)	

SGCT: Seminomatous germ cell tumors, NSGCT: Non-seminomatous germ cell tumors, RPLND: Retroperitoneal lymph node dissection, CT: Chemotherapy, RT: Radiotherapy, ASCT: Autologous stem cell transplantation, CR: Complete response, PR: Partial response, PD: Progressive disease, SD: Stable disease

Table 4. Adjuvant radiotherapy localization and adjuvant chemotherapy regimens

Adjuvant RT location	Para-aortic +iliac LN	11 (52.3%)	5 (71.3%)
	Testicular	1 (4.76%)	0 (0%)
	Inguinal LN	9 (42.8%)	2 (28.7%)
Adjuvant CT	Carboplatin (AUC 7)	14 (31.8%)	0 (0%)
	BEP+EP	7 (15.9%)	18 (23.6%)
	BEP	23 (52.2%)	56 (73.6%)
	EP	0 (0%)	2 (2.6%)

BEP: Bleomycin 30 U IV weekly on days 1, 8, and 15 + etoposide 100 mg/m^2 IV on days 1-5 + cisplatin 20 mg/m^2 IV on days 1-5/repeat every 21 days, EP: Etoposide 100 mg/m^2 IV on days 1-5 + cisplatin 20 mg/m^2 IV on days 1-5/repeat every 21 days, AUC: Area under the curve, LN: Lymph node

Germany, SGCTs constituted 64.5% of all testicular GCTs, while NSGCTs constituted 35.5% (10). In another study conducted in Japan, seminomas and non-seminomas were found in 46.7% and 53.3% of the patients, respectively (11). In another study conducted in Turkey (12), 46.4% of the patients with testicular tumors had seminomas and 53.6% had non-seminomas.

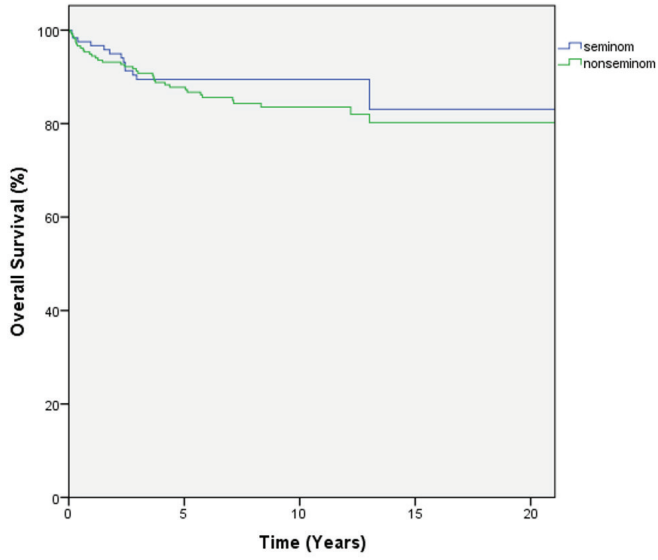

Figure 1. Overall survival curve of seminomatous and non-seminomatous germ cell tumors

In another study (13), these rates were 49.2% and 50.7%, respectively. Ethnic differences and environmental factors are possible reasons for the differences in the rates of testicular GCTs in different countries.

In the SGCT group, the rates of stage 1, 2, and 3 diseases were 73.9%, 16.8%, and 9.2%, respectively. In the NSGCT group, the corresponding rates were 46.8%, 22.8%, and 30.4%, respectively. The widespread use of ultrasonography and increased awareness of the public about testicular cancer and testicular self-examination are possible reasons for the higher rates of early-stage testicular tumors compared with metastatic tumors. In addition, testicular cancer may be more easily noticed as it manifests itself with painless scrotal swelling. The rates of stage 1 disease in the SGCT group and stage 3 diseases in the NSGCT group were significantly higher than in those of other stages. In another study, while the rates of stage 1, 2, and 3 diseases were 80.2%, 13.5%, and 6.3%, respectively, in the SGCT group, those in the NSGCT group were 53.3%, 27.1%, and 19.6%, respectively (1). Moreover, the proportion of patients with SGCT in the good-risk group was higher than that of patients in the NSGCT group. Patients with moderate risk were higher in the NSGCT group than in the SGCT group. In the present study, 74.7% of the NSGCTs were MGCT, 12.2% were embryonal carcinomas, 7.2% were teratomas, 5.1% were yolk sac tumor, and 0.8% was choriocarcinomas. The subcomponents of MGCTs were as follows: 80.1% were embryonal carcinomas, 63.5% were teratomas, 49.7% were yolk sac tumors, 35.4% were seminomas, and 11.6% were choriocarcinomas. In a study conducted in Turkey, 77.6% of the patients had MGCT histology and 82.2% of them contained histological components of embryonal carcinoma, 53.3% of teratomas, 49.6% of yolk sac tumors, 37.8% of seminomas, and 5.9% of choriocarcinoma (9). In another study, approximately 65.3% of NSGCTs were MGCT, 18.7% were embryonal carcinomas, 7.2% were yolk sac tumors, 4.5% were teratomas, and 1.6% was choriocarcinomas (13).

In the present study, BHCG levels measured at diagnosis and in the postoperative period were significantly higher in the NSGCT group than in the SGCT group, but no significant difference was found between the two groups in terms of LDH levels. In similar study, while HCG levels were higher in the non-seminoma group at diagnosis, no difference was found between the seminoma and non-seminoma groups in terms of LDH (1).

The American Urological Association (AUA) guidelines on testicular cancer and European Association of Urology (EAU) guidelines in testicular cancer recommend active surveillance after orchiectomy in stage 1 SGCTs and stage 1 NSGCTs (14,15). Adjuvant CT may be a good option in high-risk cases to reduce the risk of recurrence (16). If adjuvant CT will be given, one course of carboplatin (area under curve 7) CT for SGCT and one course of BEP CT for NSGCT can be considered (14,15). In this young patient group, in addition to recurrence, long-term side effects of the treatments, such as cardiovascular events and secondary malignancy, should not be ignored (17). The ratio of patients receiving adjuvant CT was higher in the SGCT group, while proportion of patients receiving metastatic first-line CT was higher in the NSGCT group. Metastatic second-line CT rates were comparable between the two groups. However, CT response rates in patients receiving first- and second-line CT were not different between the two groups. In this study, the recurrence rates after adjuvant therapy were comparable in both groups. In addition, 81% and 88.6% of the patients diagnosed with recurrent SGCTs and NSGCT, respectively, had relapsed within 3 years. Kollmannsberger et al. (18) reported that the recurrence rate was the highest in the first 3 years after adjuvant CT in these patients.

Post-CT resection of residual masses or RPLND is often associated with normalization of tumor markers and long-term survival (19). The EAU guideline recommends nerve-sparing RPLND to highly selected patients with stage 1B NSGCTs, i.e., those with contraindication to adjuvant CT and unwilling to accept surveillance (strong recommendation), and primary RPLND in men with post-pubertal teratomas with somatic malignant components (weak recommendation) (15).

According to the AUA guideline recommendation for patients with stage 1A NSGCTs, RPLND or one cycle of BEP CT is an effective and appropriate alternative treatment option for patients who does not accept surveillance or had incompatible status (14). The guideline offers surveillance, RPLND or one or two cycles of BEP CT based on shared decision-making for patients with stage 1B NSGCTs (14). The AUA guideline also stated that clinicians may offer RPLND as an alternative to CT in select patients with clinical stage 2B NSGCTs with normal post-orchiectomy serum AFP and beta-hCG. To date, little data are available on outcomes for men receiving RPLND as primary treatment for SGCTs (14). In a study using data from the Surveillance, Epidemiology, and Final Results program, the rates of RPLND were 1.3% in stage 1 disease and 10.6% in stage 2 disease in men diagnosed with testicular SGCTs between 1988 and 2013 in the United States (20). In this study, RPLND was performed in 3.3% of the patients with SGCTs and 9.3 of those with NSGCTs. In all patients who underwent RPLND, the viable tumor, necrosis, and reactive LN and non-diagnostic LN rates were 57.6%, 30.7%, and 11.5%, respectively. In a single-center analysis of 504 patients with NSGCTs who underwent RPLND, 51% had fibrosis/necrosis, 37% had teratomas, and 15% had viable GCTs (21). Similar results were reported in another study (22). Seminomatous GCTs are extremely sensitive to RT, while NSGCTs are more radioresistant. In the present study, 17.1% of the patients with SGCTs and 3% with NSGCTs received adjuvant RT. In the SGCT group, only one patient received testicular RT, while 20 patients received RT for para-aortic ± iliac LNs. All patients with NSGCTs received RT to para-aortic ± iliac LNs.

In this study, a total of 14 patients had undergone ASCT. While 3 of 14 patients received high-dose CT + ASCT as third-line therapy, 11 patients received second-line therapy. Moreover, 2% of the 14 patients had CR, 1 had PR, 7 had SD, and 4 had PD. Randomized studies have reported no improvement in high-dose CT outcomes with ASCT (23,24). However, in non-randomized studies, better results have been reported when high-dose CT/ASCT was used as second-line CT, rather than third-line CT. In other studies, treatment-related mortality was <5%, and long-term disease-free survival was between 40% and 70% (24,25,26).

In the present study, the 10-year OS expectancy rate was 89% in the SGCT group and 83% in the NSGCT group. The median OS could not be reached. Although the incidence of testicular cancer has increased, related mortality decreased over time (27). In the 1970s, the application of cisplatin-based CTs decreased the mortality rate while increasing the life expectancy rate to 95% (28). In one study, the 10-year OS expectancy rate was 90.8% in patients with testicular cancer diagnosed at age <50 years, while the OS expectancy rate was 80.4% in those diagnosed at age >50 years. In another study, the 5-year OS expectancy rates were 93.8% and 87.9% in the SGCT and NSGCT groups, respectively (29).

Study Limitations

The retrospective study design was the most important limitation of this study. Thus, surgical techniques, RT doses, and number of CT cycles could not be found in patient records.

Conclusion

In this study, clinical and laboratory characteristics, treatment responses, and survival characteristics of patients with SGCTs and NSGCTs who were followed up in our center were examined. The aim was to draw attention to the similar and different characteristics and treatment responses between the two groups. Compared with SGCTs, NSGCTs were diagnosed at an earlier age. The proportion of patients with stage 1 disease at diagnosis was higher in the SGCT group, and those with stage 3 disease and metastasis at diagnosis were higher in the NSGCT group. In addition, the rates of adjuvant CT and adjuvant RT were higher in the SGCT group, while RPLND and metastatic first-line CT rates were higher in the NSGCT group. Evaluation of the clinical laboratory and survival data of 360 patients with GCTs was the strength of the study. However, studies involving a large patient population from different ethnic and geographical regions are warranted.

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Ethics

Ethics Committee Approval: This study was approved by the Institutional Ethics Committee of Ankara City Hospital (decision no: EI-21-1661).

Informed Consent: Retrospective study.

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Authorship Contributions

Critical Review: Y.E., Y.A., G.U., E.A., Concept: Ö.B., Design: S.A.E., Ö.B., M.D., D.U., Data Collection or Processing: S.A.E., Ö.B., M.D., Ö.A.İ., Analysis or Interpretation: S.A.E., Y.E., Y.A., İ.E., Literature Search: S.A.E., G.U., Writing: S.A.E., İ.E.

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Original Article

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Urologists' Role and Attitude in the Systemic Treatment of Urologic Cancers

Serdar Madendere[1], Müslim Doğan Değer[2], Engin Denizhan Demirkıran[3], Hüseyin Alperen Yıldız[4]

[1]*Gümüşhane State Hospital, Clinic of Urology, Gümüşhane, Turkey*
[2]*Edirne Sultan 1st Murat State Hospital, Clinic of Urology, Edirne, Turkey*
[3]*Şırnak State Hospital, Clinic of Urology, Şırnak, Turkey*
[4]*Malazgirt State Hospital, Clinic of Urology, Muş, Turkey*

Abstract

Objective: The goal of this study was to investigate Turkish urologists' role and attitude toward the systemic treatment of urologic cancers.
Materials and Methods: An 18-item survey was e-mailed to 2305 certified Turkish urologists. The survey included questions designed to evaluate urologists' knowledge of chemotherapy procedures and their ability to manage complications, as well as how many of them perform systemic therapies and believe urologists should perform these therapies for urologic cancers.
Results: We evaluated 305 responses. Most urologists (89.6%) perform hormonotherapy for prostate cancers. Further, the majority refer patients to medical oncologists for chemotherapy. Moreover, 65.9%, 70.8%, and 72.1% of the urologists believe that only medical oncologists should deliver chemotherapy for prostate, bladder, and testicular cancers, respectively. Only 23.9% of urologists believe they are competent to perform chemotherapy, while 16.7% believe they are capable of dealing with chemotherapy complications.
Conclusion: Turkish urologists have a lack of performance and interest in administering systemic therapies in urologic cancers. We want to emphasize that urology is more than just surgery. Urologists should be involved in all stages of cancer treatment.
Keywords: Adjuvant treatments, bladder cancer, testicular cancer, prostate cancer, neoadjuvant chemotherapy

Introduction

Urologic cancers accounted for 19.5% of all cancers diagnosed in the USA in 2019 (1). Among all cancer types, the estimated mortality rate from urologic cancers was 10.9% (1). The most common urologic cancers were prostate, bladder, kidney, testicular, and penile cancers, respectively (1).

In the diagnosis and management of urologic cancers, urologists are the first point of contact for patients. They perform open, laparoscopic, and robotic surgeries for genitourinary malignancies (2). Systemic therapies may also be necessary at any stage of urologic cancer. In some countries, such as Germany and Japan, urologists administer chemotherapy themselves (3). On the other hand, most urologists in some countries refer patients to medical oncologists due to a lack of expertise in administering chemotherapy and dealing with its complications (4).

The first medical oncology department was established in 1972, and it was recognized as a subspecialty of internal medicine in 1982 in Turkey (5). Urologic oncology is not yet an official subspecialty of urology in Turkey.

Without oncology approval, urologists in Turkey can prescribe bleomycin, etoposide, cisplatin (BEP), neoadjuvant (NA) and adjuvant cisplatin-gemcitabine (CIS-GEM), docetaxel (DCX), goserelin-bicalutamide (GOS-BIC), and zoledronic acid (ZOA). Other systemic therapies, such as abiraterone (ABI), enzalutamide (ENZ), denosumab (DEN), sunitinib (SUN), and pembrolizumab (PEM), require the approval of medical oncologists. All of these systemic therapies are legally permissible to be performed by urologists (6).

In the present study, we conducted a survey among Turkish urologists to obtain a general perspective on the use of systemic therapies for urologic cancers. Of course, diagnosing urologic cancers and performing surgeries are common tasks of

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Address for Correspondence: Serdar Madendere, Gümüşhane State Hospital, Clinic of Urology, Gümüşhane, Turkey
Phone: +90 541 626 28 12 **E-mail:** serdarmadendere@gmail.com **ORCID-ID:** orcid.org/0000-0001-7020-0276
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urologists. However, we believe that urologists should do more in the treatment of urological cancers, such as administering chemotherapy and other systemic therapies themselves. With this study, we aimed to investigate urologists' role and attitude in the systemic treatment of urologic cancers because we believe there is a deficiency. This study also highlights urologists' interest in and ability to deliver chemotherapy and manage its toxicity. We hope that this study will emphasize that urology is more than just a surgical discipline.

Materials and Methods

This study included an online survey that was prepared after reviewing relevant articles in the current literature. The survey was constructed using the checklist for reporting results of online E-Surveys (CHERRIES) (7). The survey consists of 18 questions with yes/no or multiple-choices answers about systemic genitourinary cancer treatment from the perspective of urologists. Systemic therapies include hormonotherapy (GOS, BIC), chemotherapy (BEP, CIS, GEM, DCX, ABI, ENZ, SUN, PEM), and supportive therapies (ZOA, DEN). The first section of the survey asks whether urologists perform systemic therapies in their hospitals. The second section includes the opinions of the urologists on whether urologists should perform systemic therapies. In the third section, we investigated respondents' capability to provide and manage complications of systemic treatments. The final question evaluates their understanding of systemic therapies and whether they require oncology approval. Responses indicating that it was necessary for therapies requiring oncology approval or unnecessary for therapies not requiring oncology approval were accepted as true knowledge.

Following a feasibility test with ten respondents, a total of 2305 certified urologists (2223) and urology residents (82) in their final year of training were invited to participate in this study via e-mail. After 4 weeks, reminder e-mails were also sent. Because the study was not based on patient groups, informed consent was not necessary. Between June and October 2020, the survey was available via the online program Google Forms (Alphabet Co., Mountain View, CA). The study was approved by the Local Ethics Committee (2020/10-5).

Statistical Analysis

Descriptive statistics were used to analyze demographics and practice patterns. The participants were classified according to institute type, academic title, and experience in urology. We demonstrated the proportions of urologists who perform and believe urologists should perform these systemic therapies for genitourinary malignancies. To compare the frequencies, the chi-square test was used. A p-value of <0.05 was considered statistically significant. We used the IBM Statistical Package for Social Sciences, version 21.0, to conduct statistical analyses (IBM SPSS Corp., Armonk, NY, USA).

Results

A total of 317 urologists out of 2305 participated, with a response rate of 13.8%. After excluding 12 incomplete questionnaires from the study, 305 responses were evaluated. The median age of respondents was 36 (27-66). The respondents had experience in urology for a median of 10 (4-39) years. Table 1 depicts the practice patterns and demographics.

Although most urologists perform hormonotherapy to patients with prostate cancer (PCa) by themselves, many refer patients with genitourinary cancers to medical oncologists for chemotherapy. In contrast to hormonotherapy, most respondents believe that oncologists, rather than urologists, should administer chemotherapy (Figure 1).

There was a significant difference that favored academic institutions in performing first-line chemotherapy for testicular cancers (p=0.006). There was no significant difference in performing chemotherapy for other genitourinary cancers between the institutions. Table 2 summarizes the current status of systemic therapies and urologists' attitudes toward them based on institution type and academic title.

A minority of respondents (n=73, 23.9%) stated that they could perform chemotherapy (Table 3). However, 39 (53.4%) of those did not feel competent in dealing with chemotherapy complications. It was observed that the rate of urologists who felt capable of managing chemotherapy complications was significantly higher in the group administering chemotherapy ($p<0.01$).

Table 4 shows the proportions of urologists who can determine whether the given systemic treatments require the approval of a medical oncologist. Urologists with less than 15 years of experience had a higher percentage of true knowledge about DEN, PEM, and SUN (p=0.020, $p<0.001$, p=0.002). However, there was a significant difference in favor of experienced

Table 1. Baseline characteristics of 305 respondents

Median age (years)	**36 (27-66)**
Academic title	**n (%)**
Resident	76 (24.9%)
Specialist	184 (60.3%)
Asst. Professor	20 (6.6%)
Assoc. Professor	18 (5.9%)
Professor	7 (2.3%)
Geographic location	n (%)
Marmara	88 (28.9%)
Aegean	43 (14.1%)
Central Anatolia	54 (17.7%)
Eastern Anatolia	18 (5.9%)
Southeastern Anatolia	12 (3.9%)
Black Sea	54 (17.7%)
Mediterranean	36 (11.8%)
Experience in urology (years)	n (%)
0-5	63 (20.7%)
5-10	110 (36.1%)
10-15	48 (15.7%)
15-20	32 (10.5%)
20 and more	52 (17%)

urologists who believe they can perform chemotherapy (p=0.018). Similarly, urologists in academic hospitals had better proportions of true knowledge about ABI-ENZ, PEM, and SUN (p=0.045, p=0.041, p=0.040). Also, there was a significant difference favoring this group in terms of feeling capable of managing chemotherapy complications (p=0.034).

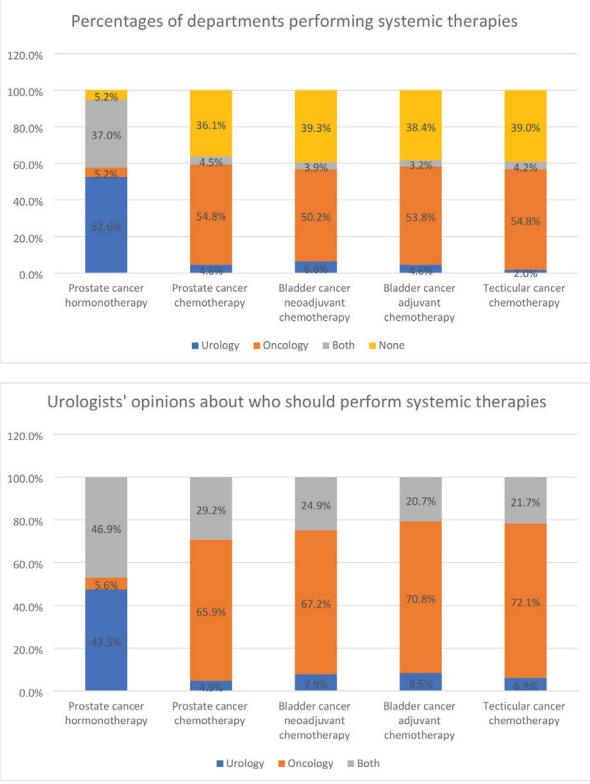

Figure 1. The involvement of urologist in systemic treatments and their perspectives

Discussion

The main finding of our study was that most urologists were uninterested in performing chemotherapy and supportive treatment for genitourinary malignancies. But respondents frequently use androgen deprivation therapy (ADT). According to the medical oncology status in Europe Survey, urologists are the primary physicians for screening, diagnosis, and surgery of genitourinary cancers; however, oncologists are on the chemotherapy side (8). There is a similar situation in our study. Inadequate training, lack of interest, and concerns about complications are the most common reasons for this (9). Since the outcomes of our study were similar, we believe the same reasons are valid. We also believe that the key source of motivation in the chemotherapy practice of the urologists is a desire to extend the field of urologic oncology research. Furthermore, in some clinics founded on a similar origin in our country, urologists insist on performing chemotherapy themselves. As a consequence, the residents who were trained in this manner will continue to perform chemotherapy in their future clinics. We think that the common factor among urologists who provide chemotherapy is training under similar environment.

A previous study showed that medical oncology is a well-established specialty in many countries, with 77% of patients receiving chemotherapy for genitourinary cancers in their international study. However, in Japan, only 39.4% of cancer care hospitals had medical oncology departments (10). In Korea, medical oncologists administered chemotherapy for only 24% of urological malignancies (11). Urological cancers were treated mostly by urologists, including chemotherapy, in both countries (12). In Turkey, there are 808 medical oncologists working in 240 different institutes. Furthermore, at least 1225

Table 2. Percentages of urologists performing systemic therapies and urologists' opinions

Variables	**Types of systemic therapies**				
Percentages of urologists performing systemic therapies (according to hospital type and academic title)					
Hospital type	Pca HT	Pca CT	Bca Neoad. CT	Met. Bca CT	Tca CT
Academic n=148	132 (89.2%)	15 (10.1%)	15 (10.1%)	15 (10.1%)	15 (10.1%)
State n=106	92 (86.8%)	10 (9.4%)	12 (11.3%)	4 (3.8%)	2 (1.9%)
Private n=51	49 (96.1%)	3 (5.9%)	5 (9.8%)	5 (9.8%)	2 (3.9%)
Academic title	Pca HT	Pca CT	Bca Neoad. CT	Met. Bca CT	Tca CT
Resident n=76	71 (93.4%)	14 (18.4%)	15 (19.7%)	14 (18.4%)	15(19.7%)
Specialist n=184	163 (88.6%)	14 (7.6%)	15 (8.2%)	8 (4.3%)	4 (2.2%)
Academician n=45	40 (88.9%)	0 (0%)	2 (4.4%)	2 (4.4%)	0 (0%)
Overall n=305	274 (89.9%)	28 (9.2%)	32 (10.5%)	24 (7.9%)	19 (6.2%)
Percentages of urologists thinking urologist should give systemic therapies (according to academic title)					
Academic title	Pca HT	Pca CT	Bca Neoad. CT	Met. Bca CT	Tca CT
Resident n=76	72 (94.7%)	27 (35.6%)	26 (34.2%)	23 (30.3%)	23 (30.3%)
Specialist n=184	173 (94%)	59 (32%)	60 (32.6%)	55 (29.9%)	48 (26.1%)
Academician n=45	43 (95.6%)	18 (40%)	14 (31.1%)	11 (24.4%)	14 (31.1%)
Overall n=305	288 (94.4%)	104 (34.1%)	100 (32.8%)	89 (29.2%)	85 (27.9%)

Pca: Prostate cancer, HT: Hormonotherapy, CT: Chemotherapy, Bca: Bladder cancer, Neoad.: Neoadjuvant, Tca: Testicular cancer, n: Number of urologists, Met: Metastatic

medical oncologists will be needed to provide comprehensive healthcare for cancer patients in Turkey by 2023 (13). We believe that achieving this goal will be difficult. On the other hand, there are 2223 urologists spread across 828 different institutes (14). Urologists should take a more prominent role in the field of chemotherapy by using the advantage of superiority in numbers. Thus, urologists will be able to offer more effective treatment options to patients suffering from urological cancer.

In terms of neoadjuvant chemotherapy (NAC) and adjuvant chemotherapy (AC), most German urology departments administer NAC (81.3%) and AC (85.7%) in bladder cancer, which is similar to Japan but differs from many other European countries (15,16). Regardless of whether they work in academic or nonacademic institutions, most Turkish urologists do not administer these therapies and have low interest in NAC and AC. Many of them are unaware that they can prescribe and administer NAC (76.7%) and AC (74.8%) without the approval of a medical oncologist. Additionally, referring patients to medical oncologists for NAC can result in a delay in treatment because rescheduling a medical oncology visit can take time. This may cause the optimal time for radical cystectomy (RC) to be delayed. Delays of more than 12 weeks between the diagnosis of bladder cancer and RC can lead to higher mortality and shorter progression-free survival (17,18,19). Urologists can prevent this delay by administering NAC themselves rather than referring patients to oncologists. But, first and foremost, urologists must be interested in and knowledgeable about chemotherapy and its complications.

According to the CHAARTED study, in addition to ADT, chemotherapy is recommended for first-line treatment of metastatic PCa (20). Turkish urologists outperform oncologists in administering hormonotherapy of PCa. However, a minority of urologists perform chemotherapy in PCa with similar percentages to an American study involving the role of the urologist (4). Administering the treatment in two different departments can lead to loss of time and a decrease in treatment effectiveness. If urologists provide both hormonotherapy and chemotherapy

Table 3. Percentages of urologists feeling confident to perform chemotherapy and manage complications

Hospital type	Overall	Feeling confident to perform CT	Feeling capable of managing CT complications
Academic	148	38 (25.7%)	30 (20.3%)
State	106	20 (18.9%)	11 (10.4%)
Private	51	15 (29.4%)	10 (19.6%)
Academic title			
Resident	76	13 (17.1%)	11 (14.5%)
Specialist	184	42 (22.8%)	25 (13.6%)
Academician	45	18 (40%)	15 (33.3%)
Overall	305	73 (23.9%)	51 (16.7%)
CT: Chemotherapy			

Table 4. Percentages of urologists' true knowledge about systemic therapies' approval requirement**

Variables	Therapies not requiring oncology approval						Therapies requiring oncology approval			
Hospital type	BEP	Neoad. C-G	Adj. C-G	DOC	G-B	ZA	ABI-ENZ	DEN	SUN	PEM
Academic n=148	30.4%	24.3%	23.6%	33.1%	71.6%	76.4%	66.9%	59.5%	83.8%	83.1%
State n=106	38.7%	22.6%	25.5%	37.7%	80.2%	79.2%	58.5%	68.9%	71.7%	75.5%
Private n=51	25.5%	21.6%	29.4%	41.2%	78.4%	84.3%	49.1%	56.9%	64.7%	66.7%
Academic title										
Resident n=76	30.3%	22.4%	23.7%	34.2%	72.4%	76.3%	64.5%	67.1%	80.3%	78.9%
Specialist n=184	34.2%	22.8%	26.6%	38.6%	77.2%	79.3%	60.3%	71.2%	76.1%	78.3%
Academician n=45	28.9%	26.7%	22.2%	28.9%	75.5%	80%	57.8%	66.7%	71.1%	73.3%
Experience										
0-5 years n=63	31.7%	25.4%	25.4%	34.9%	68.3%	81%	60.3%	66.7%	76.2%	74.6%
5-10 years n=110	32.7%	24.5%	27.3%	35.5%	80%	76.4%	69.1%	75.5%	85.5%	89.1%
10-15 years n=48	22.9%	20.8%	25%	41.7%	75%	81.3%	58.3%	77.1%	77.1%	81.3%
15-20 years n=32	28.1%	25%	18.8%	34.4%	78.1%	84.4%	43.8%	56.3%	59.4%	59.4%
>20 years n=52	44.2%	19.2%	25%	34.6%	75%	75%	57.7%	61.5%	67.3%	65.4%
Overall n=305	32.5%	23.3%	25.2%	36.1%	75.7%	78.7%	61%	69.5%	76.4%	77.7%
Feeling confident to perform CT n=73	52.1%	43.8%	42.5%	56.2%	75.3%	80.8%	49.3%	63%	71.2%	71.2%
Feeling capable of managing CT complications n=51	49%	39.2%	37.3%	52.9%	78.4%	88.2%	49%	60.8%	74.5%	70.6%

*ABI-ENZ: Abiraterone-enzalutamide, Neoadj. C-G: Neoadjuvant cisplatin-gemcitabine, Adj C-G: Adjuvant cisplatin-gemcitabine, DEN: Denosumab, SUN: Sunitinib, PEM: Pembrolizumab, G-B: Goserelin-bicalutamide, DOC: Docetaxel, ZA: Zoledronic acid, BEP: Bleomycin-etoposide-cisplatin
**The first six columns of the table are the percentages of the respondents who state that medical oncology approval is not mandatory. The last four columns of the table are the percentages of the respondents who state that medical oncology approval is mandatory

themselves, these risks can be minimized. According to a previous study involving characteristics of physicians treating castration-resistant prostate cancer (CRPC) by country, urologists treated CRPC in Japan, Germany, the USA, the UK, and France with percentages of 98.7%, 92.9%, 74%, 73.4%, and 56.7%, respectively (3). On the other hand, another study in the USA found that oncologists used chemotherapy more frequently than urologists for CRPC (21). In both studies, higher percentages of urologists believe that urologists should perform chemotherapy in PCa than the percentages of urologists who actually perform it. Nonetheless, the majority of urologists think that chemotherapy is a subject for medical oncology. Therefore, the training and perspective of urologists should be investigated. Previous research has shown that urologists can quickly adapt to other systemic treatments for PCa, as they did for hormonotherapy (22,23).

For the first decade after introducing BEP chemotherapy for testicular cancer, urologists administered these therapies in many hospitals until the drawbacks of drug toxicity were discovered. Similar reservations were expressed regarding the systemic treatment of kidney tumors (24). Nowadays, more than 70% of Turkish urologists say they would refer testicular cancer patients to medical oncologists for even first-line chemotherapy because the majority do not believe they are capable of managing chemotherapy complications (83.3%). Furthermore, 70% of respondents think that medical oncology approval is necessary for BEP treatment, although it is not. Even many urologists who are confident in their ability to perform chemotherapy had low percentages of true knowledge about oncology approval requirements for certain types of systemic therapies.

For many years, urologists have used systemic therapies such as ADT, intravesical chemotherapy, and bacillus Calmette-Guerin therapy. These therapies can have life-threatening side effects (25). Nowadays, many urologists can manage complications of these therapies through training in residency and experience over the years. With education, practice, and a strong interest, similar competency can occur over time for intravenous (iv) chemotherapy of urologic cancers.

If urologic oncologists want to become comprehensive care providers for genitourinary cancers, they should be active beyond the operating room. Performing all systemic therapies themselves would provide increased patient satisfaction and professional satisfaction of urologists, avoid delays in treatment, and add a significant field of research in urology (9). Additionally, we hope that urologic oncology will be recognized as an official subspecialty of urology, allowing urologic oncologists to provide comprehensive healthcare to patients.

Study Limitations

Our study is the first nationwide research that shows the current status of systemic urologic cancer treatment among Turkish urologists. There were several limitations to this study. First, as with any survey study, there is a possible selection bias. The respondents may or may not be interested in the systemic treatment of urologic cancers. Due to demographic bias, the findings cannot be expanded. The overall response rate represents a small proportion of all urologists, but it reveals the general situation. Academic participation rate in the survey was lower than that of specialists and residents. Another point to consider is that cancer treatment is rapidly evolving due to the newly-introduced drugs. The systemic therapies mentioned in this study may become obsolete in the near future. Nevertheless, we found a lack of interest in current medical treatments for urologic cancers among urologists.

Conclusions

Turkish urologists have a lack of performance and interest in administering systemic therapies for urologic cancers. Training in urologic oncology should include not only operations but also systemic treatments. Currently, treatment of genitourinary cancers requires a multidisciplinary approach between urologists, medical oncologists, radiation oncologists, and other specialists. Urologists, on the other hand, should be aware that they are the primary physicians for urologic cancers and are legally competent to manage urologic oncology patients at all stages.

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Ethics

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Informed Consent: Because the study was not based on patient groups, informed consent was not necessary.

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Authorship Contributions

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

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Case Report
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Isolated Pulmonary Metastasis Metastasectomy After Curative Prostate Cancer Treatment in Oligometastatic Disease

Hakan Gemalmaz[1], Abdullah Akdağ[1], Mehmet Dündar[1], Nil Çulhacı[2]

[1]Adnan Menderes University Hospital, Clinic of Urology, Aydın, Turkey
[2]Adnan Menderes University Hospital, Clinic of Pathology, Aydın, Turkey

Abstract

Isolated pulmonary metastasis is observed in 2%-3% of prostate cancer cases but a complete treatment algorithm was not established for these patients. This study aimed to present a case of isolated pulmonary metastasis during the follow-up after radical prostatectomy, in which recurrence was not detected for 2 years after metastasectomy. The patient was on follow-up without any treatment for 22 months, with an unobservable prostate-specific antigen value. Metastasectomy in oligometastatic disease has emerged as a treatment option in recent years but is not considered a standard treatment. Literature contribution is necessary for oligometastatic disease definition to clarify its nature and compare treatment options.
Keywords: Prostate cancer, metastasis, recurrence, metastasectomy

Introduction

Isolated lung metastasis is observed in 2%-3% of prostate cancer (PCa) cases, without an established complete treatment algorithm for these patients (1). The lymph nodes and bones are the most common metastatic sites of PCa; however, visceral metastasis rates are not negligible. In addition, visceral involvement represents a more aggressive disease (2). A recent prospective study revealed beneficial imaging-guided metastasis-based therapies in patients with recurrent PCa after primary treatment (3). Most metastases have nodal and bone involvement, thus salvage therapies are directed. The role of resection in pulmonary metastases is still unclear. This study aimed to present a case of isolated pulmonary metastasis during the follow-up after radical prostatectomy, in which recurrence was not detected for 2 years after metastasectomy.

Case Report

A 60-year-old male patient presented with penile deviation and pain. Rectal examination revealed a 5 mm rigid nodule in the right lobe of the prostate. Prostate-specific antigen (PSA) and free PSA were 2.6 ng/mL and 0.35 ng/mL, respectively. Systematic ten quadrant biopsies with transrectal ultrasonography were performed, and Gleason 3+3=6 (15%-30%) prostate adenocarcinoma was diagnosed in two samples. In November 2010, a radical prostatectomy was performed. The final pathology revealed a Gleason 3+4=7 prostate adenocarcinoma located in the posterior right lobe and anterior left lobe. The lesion was located in 20% of the prostate with the largest size of 1.5 cm. The tumor reached the capsule, with lymphovascular and perineural invasion in the tumoral areas and high-grade prostatic intraepithelial neoplasia in the adjacent areas. The tumor continued in the anterior surgical margin area. Immunohistochemical high molecular weight keratin staining of the anterior surgical margin had no staining. Posterior surgical margin, ductus deferens, and seminal vesicle were intact. The pathological TNM stage was reported as pt2c.

The first-month postoperative PSA was 0.03 ng/mL. Upon PSA detection of 0.052 ng/mL in November 2012, 0.089 ng/mL in March 2013, and 0.18 ng/mL in June 2013, the patient underwent abdominal computerized tomography and total body bone scintigraphy for metastasis screening. Metastasis signs were not found. Between June and August 2013, 72cGy salvage radiotherapy was given. Thereafter, PSA

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Address for Correspondence: Abdullah Akdağ, Adnan Menderes University Hospital, Clinic of Urology, Aydın, Turkey
E-mail: aakdag90@gmail.com **ORCID-ID:** orcid.org/0000-0001-9281-0913
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decreased to 0.003 ng/mL. When the PSA value was 0.4 ng/mL in February 2017, metastasis screening was performed with F-18 fluorodeoxyglucose positron emission tomography. A hypermetabolic 2 cm nodule was detected in the middle lobe of the right lung (Figure 1). The patient was evaluated for second, primary, or metastasis, thus segmental lobectomy was decided. In October 2017, right lung middle lobectomy and lymph node dissection pathology were reported as adenocarcinoma metastasis, without lymph node involvement (Figure 2). The patient was on follow-up for 22 months without any treatment. The PSA value is unobservable (0.003 ng/mL, July 31, 2019). The patient's information was presented as a case report after obtaining patient consent.

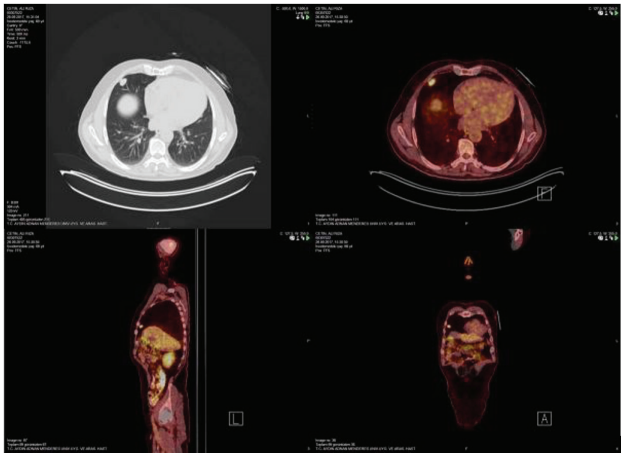

Figure 1. Pulmonary metastasis

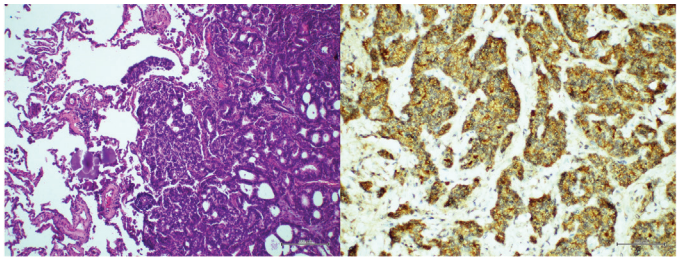

Figure 2. Segmental lobectomy

Discussion

PCa metastasis mechanism was not fully revealed. Paget (4) proposed the theory of seed and soil, which assumes that metastasis development depends on the interaction between the properties of the metastatic cells (seed) and the characteristics of the target organ microenvironment (soil). The seeds of the PCa metastatic cells are preferably located in the soil of the bone matrix. In addition, the specific target organ attracts cancer cells through the release of chemotactic factors (homing theory) (5). Batson (6) suggested that PCa cells frequently migrate to the skeleton, especially the lower spine, due to a portal-like venous system between the prostate and lower vertebrae. The second most common metastasis site of PCa is the lymph nodes. PCa lymphatic spread always ascends from the pelvis to the retroperitoneum via the common iliac lymph nodes (7). Bubendorf et al. (8) hypothesized that visceral metastases without bone involvement are related to the spread of PCa cells directly through the inferior vena cava, called a cava-type pathway. Recent studies revealed that circulating tumor cells and their count are important in PCa metastasis (9). Tumor cells leading to oligometastatic lesions have not fully achieved their metastatic potential, as the metastatic niche was not fully prepared (10). PCa metastases are seeded not only from the primary tumor but also from other metastatic sites (11). This suggests that curative local treatments are effective in oligometastatic disease.

Immediate or delayed androgen deprivation therapy (ADT) with initial surveillance is preferred for recurrent PCa after curative treatment options (12). Literature has limited high-level evidence comparing survival rates of metastasectomy and ADT (13). In the late 1990s, the hypothesis that metastasis-targeted therapy could increase survival rates was introduced (14). In 2017, Ost et al. (15) published a prospective, randomized multicenter study comparing metastasis-targeted therapy and surveillance in oligometastatic PCa recurrence. Their study started ADT as symptomatic progression, progression to more than three metastases, or local progression of known metastases. They stated that ADT-free survival was longer with metastasis-targeted therapy than surveillance alone for oligorecurrent PCa. Metastatectomy and stereotactic body radiotherapy were the most used treatment options for oligometastasis (13). The role of pulmonary metastases resection is still unclear, with few literature results (16,17). A case series by Ciriaco et al. (18) revealed that 1 of 20 patients with oligometastatic PCa, who underwent pulmonary resection, required hormone therapy. The median follow-up period was 23 months and PSA levels were not measurable during the follow-up. Some patients can benefit from this treatment strategy but should be considered only in highly selected patients. Our case preferred metastasis-targeted therapy after consulting thoracic surgery for segmental lobectomy, considering surgical complications, ADT-related side effects, and patient conditions.

In conclusion, in oligometastatic PCa, biochemical cure in 2 years follow-up without need for androgen deprivation treatment was evaluated in this case. Visceral metastasis without bone and lymph node involvement in PCa is rare and treatment options are unclear. Metastasectomy in oligometastatic disease has emerged as a treatment option in recent years but is not considered a standard treatment. Literature contributes to define the oligometastatic disease, clarify its nature, and compare treatment options is necessary.

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Ethics

Informed Consent: The patient's information was presented as a case report after obtaining patient consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Supervision: H.G., Concept: A.A., Design: A.A., Data Collection or Processing: A.A., M.D., N.Ç., Analysis or Interpretation: A.A., Literature Search: A.A., Writing: A.A.

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Case Report

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Recognizing A Low-Grade Oncocytic Renal Tumor

Zeynep Bayramoğlu[1], Avni Merter Keçeli[2], Murat Gönen[3], Muhammet İrfan Dönmez[3]

[1]*Konya Training and Research Hospital, Clinic of Pathology, Konya, Turkey*
[2]*Konya Training and Research Hospital, Clinic of Radiology, Konya, Turkey*
[3]*Konya Training and Research Hospital, Clinic of Urology, Konya, Turkey*

Abstract

Oncocytic renal tumors are sometimes challenging since oncocytic morphology found in several renal tumors due to the lack of a standardized diagnosis. Some tumors with "borderline or intermediate" features are descriptively reported as "oncocytic" and/or "unclassified". This case report highlights a low-grade oncocytic renal tumor.

Keywords: Chromophobe, renal cell carcinoma, hybrid tumor, low-grade, oncocytic tumor

Introduction

Oncocytic renal tumor diagnosis is sometimes challenging due to the oncocytic morphology in several renal tumors. The most common problem is the distinction between eosinophilic variant of chromophobe renal cell carcinoma (ChrRCC) and oncocytoma. Tumors with "borderline or intermediate" features are often descriptively reported as "oncocytic" and/or "unclassified" as main descriptive diagnosis terms preferring one or the other (1). However, some oncocytic tumors still do not fit into any available "oncocytic" tumor categories (2,3). Therefore, a comprehensive morphology, immunohistochemistry, and genetic profile research to precisely define and classify tumors with oncocytic morphology is important (2). This case report highlights a low-grade oncocytic renal tumor.

Case Report

All procedures performed in this study involving human participant were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Consent was obtained from the patient.

A 73-year-old female patient was admitted to the department of pulmonology due to extreme coughing. She had chronic renal failure and hypertension for 10 years. The computed tomography of the chest detected a solid mass in the lower pole of the right kidney (Figure 1). Irregularity was observed in its contour compatible with fibrotic sequela in the middle pole of the ipsilateral kidney. The left kidney was atrophic. A dynamic enhanced magnetic resonance imaging evaluated the renal mass since the patient had compromised renal functions. The right renal mass was well limited and separated from the normal kidney parenchyma. It was overflowing from the kidney contour, but not exceeding the kidney capsule. A pseudocapsule appearance was observed around the mass. The internal lesion

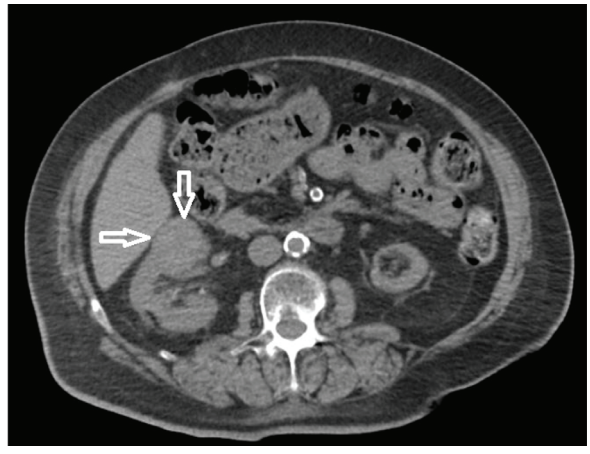

Figure 1. Non-enhanced axial plan CT image showing the right kidney mass (arrows). The mass is well-circumscribed with similar density to the kidney parenchyma. The left kidney is atrophic in size

CT: Computer tomography

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Address for Correspondence: Muhammet İrfan Dönmez, Konya Training and Research Hospital, Clinic of Urology, Konya, Turkey
Phone: +90 312 305 19 69 **E-mail:** m_irfan83@yahoo.com **ORCID-ID:** orcid.org/0000-0002-2828-7942
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structure was close to the kidney tissue in T1 and T2 weighted images, without significant fat contents. The enhanced image series enhanced the early phase, without contrast washout in the late phase. Pathological lymph node, solid organ metastasis, or renal vein thrombosis were not observed (Figures 2a-c). Radiological findings were compatible with low-grade RCC.

Pathological Findings

The patient underwent an open partial nephrectomy with pre-diagnosis of RCC based on radiological findings. The macroscopic examination revealed a partially well-circumscribed, non-encapsulated, solid, and tan-brown lesion in 35×32×21 cm diameter. Central scar was not observed. The microscopic examination revealed tumor cells with oncocytic cytoplasm, irregular nucleus, nucleolus, and focal perinuclear halo in some areas in solid pattern (Figure 3a-b). Thus, differential diagnoses included oncocytoma, ChrRCC, low-grade oncocytic tumor (LOT), eosinophilic clear cell RCC, epithelioid hemangioendothelioma, succinate dehydrogenase-deficient RCC, and hybrid oncocytoma-chromophobe tumor. The immunohistochemical examination found a diffusely positive reaction for EMA, cytokeratin (CK) 7, and PAX8. A negative reaction for immunohistochemical cluster of differentiation (CD) 10, CD117, alpha methyacyl CoA racemase, RCC, HMB45, Melan A, and CK20 was recorded (Figure 4a-d). Therefore, the patient was diagnosed with LOT.

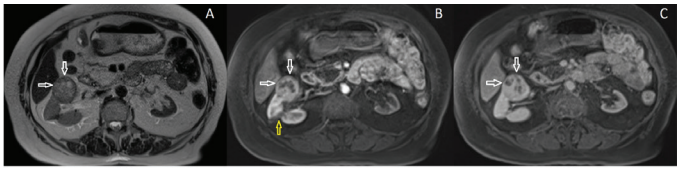

Figure 2. Dynamic enhanced MRI obtained in axial plan; T2W (a), arterial phase T1W (b), late phase T1W (c) images. The lesion is clearly seen in all images (white arrows). The mass without destruction is rapidly enhanced in the early arterial phase (b). Contrast washout is not observed in the late phase (c). Non-enhanced areas within the lesion are compatible with necrosis. The contour irregularity and notching seen in the right kidney middle section are compatible with the sequelae changes (b, yellow arrow). Radiological findings were found compatible with renal cell carcinoma

MRI: Magnetic resonance imaging

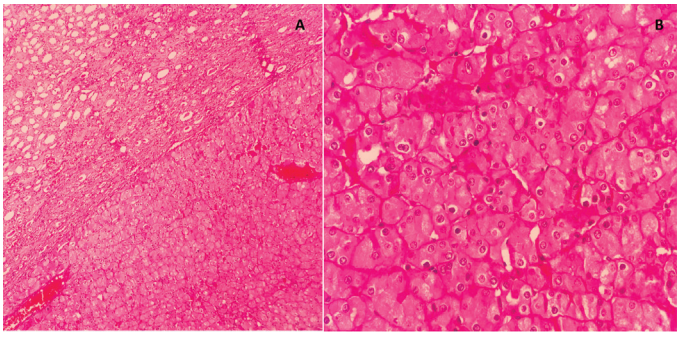

Figure 3. Microscopic features. Low-grade oncocytic tumor lacked a peripheral capsule and showed solid growth (H&E, 40X) (a), the cells demonstrated solid and compact acinar growth. The tumor cells had homogeneous oncocytic cytoplasm, uniformly round to oval nuclei (b) (H&E, 400X)

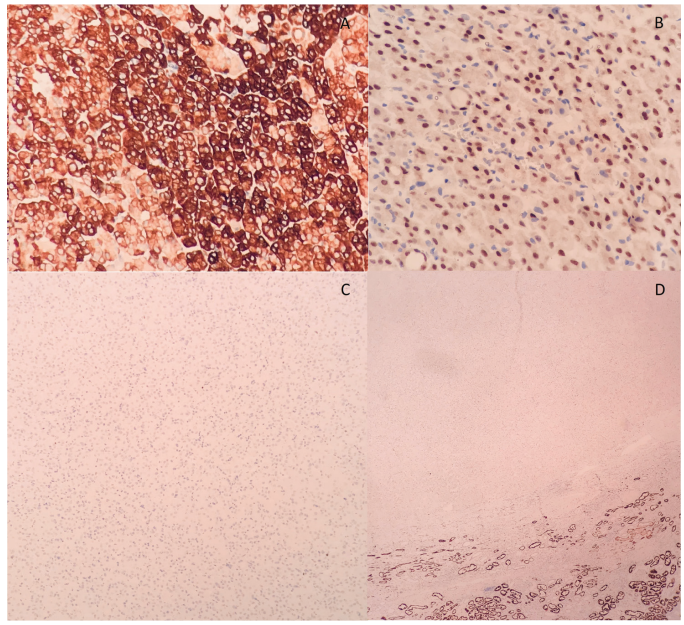

Figure 4. Immunohistochemical examination showing a positive reaction with CK7 (a) and PAX8 (b) and negative reaction with CD117 (c) and CD10 (d)

Discussion

Renal oncocytoma and ChrRCC were accepted as histological subtypes of renal tumors for years. ChrRCC is a malignant tumor, whereas renal oncocytoma is benign (4). A very little similarity was found between the classical histopathological appearance of ChrRCC and oncocytoma. However, serious problems are encountered in the eosinophilic variant differentiation of ChrRCC and oncocytoma. A great number of techniques, such as histochemical examinations, immunohistochemical examinations, chromosomal changes, molecular analyses, and electron microscopy were investigated to differentiate these two tumors for years, wherein immunohistochemical CD117 (KIT) and CK7 are most commonly used. CD117 and CK are positive in eosinophilic ChrRCC and oncocytoma. Moreover, CD117 and CK are positive in some oncocytomas with hybrid features. Using CD117 is helpful in differentiating typically CD117-negative tumors. Prevalent CD117 positivity supports ChrRCC. CK7 is generally negative in oncocytoma or typically positive in <5% of tumor cells (2). The oncocytic renal tumor differential diagnosis is presented in Table 1.

A study of 28 cases reported that LOTs showed a solid or compact nested growth pattern and the tumor cells had oncocytic cytoplasm with round to oval nuclei and focal perinuclear halo in microscopic examination. This study found CD117-/CK7+ in all cases. In addition, a negative reaction for CA9, CK20, vimentin, CK5/6, HMB45, Melan A, and CD15 was found. Frequent deletions detected at 19p13.3, 1p36.33, and 19q13.11 on array comparative genomic hybridization and disomic status was recorded in 2 out of 9 cases (3). Moreover, "high-grade oncocytic tumors" showing different morphology and immunoprofile from LOTs are defined in literature (5).

In conclusion, LOTs are tumors with oncocytic morphology, CD117-/CK+ immunoprofile, lacking multiple chromosomal

Table 1. Differential diagnosis of low-grade oncocytic renal tumor

Diagnosis	Pathological findings	Immunohistochemistry
Low-grade oncocytic tumor	-Solid sheets and compact nests with gradual transition to trabecular areas -Sharply delineated edematous stromal areas with loose cell growth	CD117-, CK7+, PAX8+
Chromophobe RCC, eosinophilic	-Solid growth -More prominent cell membranes, irregular (raisinoid) nuclei, perinuclear halos	CD117+, CK7+, CD10-
Oncocytoma	-Tubulocystic growth -Lacks perinuclear halos, central stromal "archipelaginous" areas are present	CD117+, CK7-/+
Clear cell RCC, eosinophilic	-At least focal clear cell areas, delicate vasculature in the background	CA9+, CD117-, CD10+
Epithelioid angiomyolipoma	-Epithelioid cells, pleomorphic, lacks perinuclear halos	PAX8-, MelenA+, Desmin+, HMBE45+, PANCK-, CK7-
SDH- deficient RCC	-Flocculent cytoplasm and vacuoles -Lacks perinuclear halos	CD117-, SDH-, PANCK-

RCC: Renal cell carcinoma

losses and gains, and exhibiting indolent clinical behavior. LOT shows oncocytic morphology in histopathological examination; however, its morphology does not completely fit into oncocytoma or eosinophilic ChrRCC. Therefore, the pathologist should support his diagnosis with immunochemistry. Estimating the actual LOT incidence is hard because these cases are previously reported as "eosinophilic ChrRCC," "oncocytic renal tumor/NOS," "unclassified/LOT," or "hybrid oncocytoma-chromophobe tumor." This study aimed to present LOT among newly defined oncocytic tumors to increase awareness.

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

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Ethics

Informed Consent: Consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Z.B., A.M.K., M.G., M.İ.D., Design: Z.B., A.M.K., M.G., M.İ.D., Data Collection or Processing: Z.B., A.M.K., M.G., M.İ.D., Analysis or Interpretation: Z.B., A.M.K., M.G., M.İ.D., Literature Search: Z.B., A.M.K., M.G., M.İ.D., Writing: Z.B., A.M.K., M.G., M.İ.D.

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Case Report

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Spontaneous Wilms Tumor Rupture: A Preoperative Clinical Diagnosis

Rahul Gupta, Praveen Mathur, Vinayak S. Rengan, Gunjan Sharma, Punit Singh Parihar, Priyanka Mittal

Department of Paediatric Surgery Sawai Man Singh Medical College, Jaipur, Rajasthan, India

Abstract

We report a rare case of a spontaneous Wilms tumor rupture in a 13-month-old male who presented with a rapidly increasing abdominal distension. The child had acute exacerbation of symptoms which precipitated an emergency left radical nephrectomy and renal venectomy (due to densely adherent tumoral embolus in left renal vein and Inferior Vena Cava) indicated for intraperitoneal tumor rupture. Postoperative histopathology confirmed a Wilms tumor; classified as stage IIIc. He is on a three-drug chemotherapy and doing well on follow-up. Preoperative spontaneous Wilms tumor rupture is a clinico-radiological challenge. A high index of suspicion is a prerequisite for diagnosis. However, an upfront emergency radical nephrectomy should be discussed.

Keywords: Emergency, preoperative, radical nephrectomy, rupture, spontaneous, Wilms tumor

Introduction

Wilms tumor rupture is rare, constituting 3% of all the cases of Wilms tumor (1,2). Preoperative rupture is rarer and could either be post-traumatic or spontaneous in nature (1,2). Diagnosis of preoperative rupture is based on clinico-radiological signs (1,3). Confirmation is either intraoperative and subsequently on histopathological evaluation (1,4,5). We report a very rare case of spontaneous Wilms tumor rupture in a child who was diagnosed clinically and then confirmed intraoperatively (6). A mini review of preoperative Wilms tumor rupture is contemplated.

Case Presentation

A thirteen-month-old male, weighing 8,200 g, second in birth order, and a product of non-consanguineous marriage presented with a rapidly increasing abdominal distension evolving for the last two months. There were episodes of low-grade fever, loss of appetite, and crying episodes for similar duration. On examination, the child was conscious, hemodynamically stable, but in agony due to pain. He was pale, a pulse rate of 116/min, respiratory rate of 36/min with mild-to-moderate dyspnea. Per-abdominal examination revealed a firm-to-hard, large, tender lump occupying left half of abdomen and reaching the midline; genitalia were normal.

Baseline blood investigations (inv.) revealed anemia (hemoglobin-6 g/dL), and leukocytosis (total leucocyte count-14.800/mm^3); rest of the inv. were normal. Abdominal ultrasonography (USG) confirmed a large (13 × 11 cm), heterogeneous, solid-cystic left kidney tumor with vascularity (on color Doppler) and tumor thrombus extending in left renal vein (19 mm).

Patient was optimized; three-packed RBC transfusions were administered. Patient was planned for further evaluation with preoperative abdominal contrast-enhanced computerized tomography, fine needle aspiration cytology, and neo-adjuvant chemotherapy. However, the child had acute exacerbation of pain with marked abdominal distension. A moderate respiratory distress and nasal flaring which was suggestive of splinting of diaphragm was also observed. On palpation, there was a sudden increase in size of lump, marked tenderness and abdominal wall induration on the left half of the abdomen, suggestive of tumor rupture necessitating emergency laparotomy. The patient was transferred to the operation room after obtaining informed written consent from the parents.

Exploratory laparotomy revealed a large ruptured left renal tumor causing antero-medial displacement and compression of the descending colon as shown in the diagrammatic representation (Figure 1). The tumor had ruptured (eroded) intra-peritoneally through a large, 4 × 4 cm size rent in the descending mesocolon (Figure 2) with tumor fragments, necrotic material and hemorrhagic fluid in the pelvic cavity and Morrison's pouch. Dissection of the tumor from the renal fossa

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Address for Correspondence: Rahul Gupta, Department of Paediatric Surgery Sawai Man Singh Medical College, Jaipur, Rajasthan, India
Phone: +9079206062 **E-mail:** meetsurgeon007@gmail.com **ORCID-ID:** orcid.org/0000-0002-6487-5549
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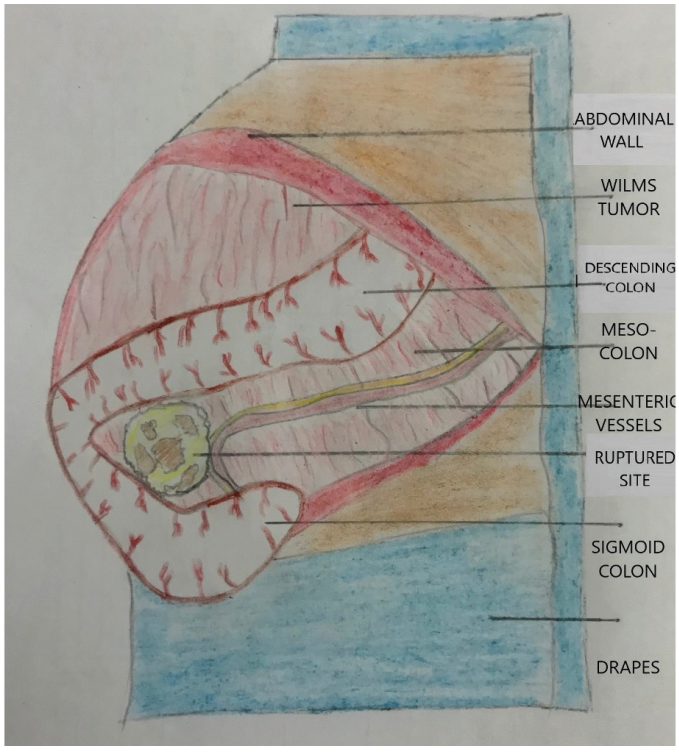

Figure 1. Diagrammatic representation (by RG) of a large left renal tumor causing antero-medial displacement of the descending colon; tumor is ruptured intra-peritoneally through a large, 4 × 4 cm size rent in the descending mesocolon with tumor fragments and necrotic material seen coming out of the surface

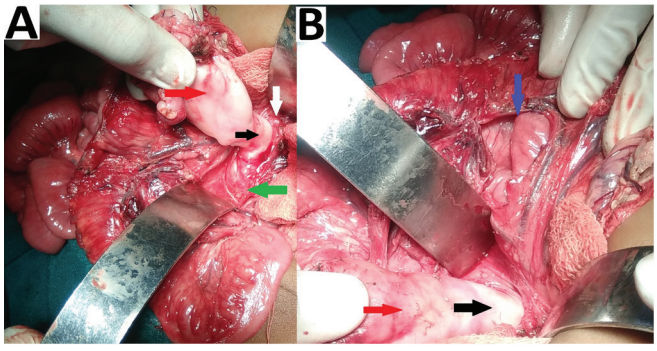

Figure 2. Intraoperative photographs showing (A) tumor embolus (red arrow) extending into the left renal vein (black arrow) and IVC (green arrow); the tumor embolus is extending into the IVC superiorly (white arrow); (B) a large, 4 × 4 cm size rent in the descending mesocolon (blue arrow) through which the tumor had ruptured (eroded) intra-peritoneally

IVC: Inferior Vena Cava

and adherent mesocolon was performed. The tumor extended into the left renal vein and Inferior Vena Cava (IVC) (Figure 2). Radical left-sided nephrectomy (Figure 3) with the removal of para-aortic and aorto-caval lymph nodes was performed. Left renal venotomy was performed to remove the densely adherent tumor embolus in the renal vein and IVC, which was unsuccessful. Renal venectomy was performed at its junction with the IVC (Figure 4). Postoperative recovery was satisfactory, except for a few episodes of fever spikes.

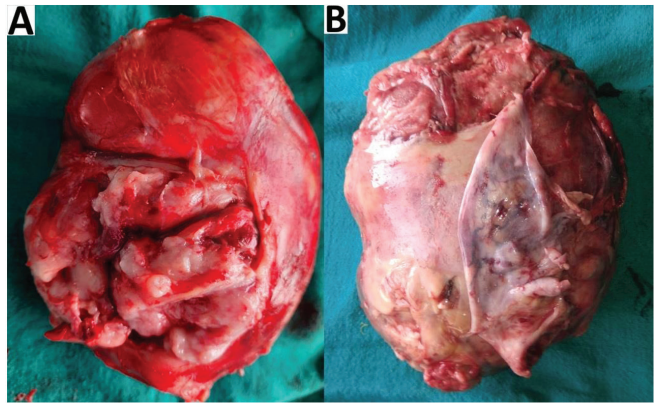

Figure 3. Radical nephrectomy specimen showing (A) peritoneal surface with ruptured area; (B) retroperitoneal surface

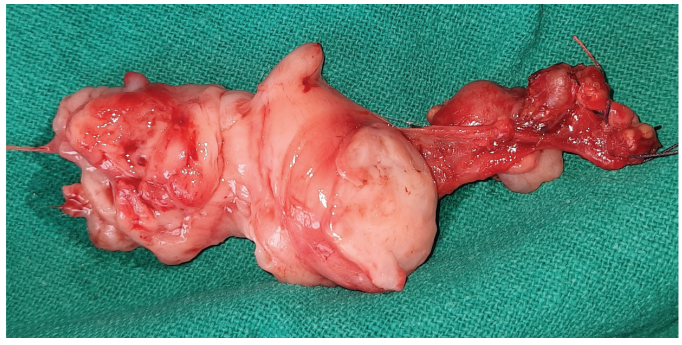

Figure 4. Renal venectomy specimen with densely adherent tumor embolus

Histopathology confirmed the diagnosis of triphasic nephroblastoma (Wilms tumor) with favorable histology; tumor embolus in the renal vein. There were no tumor cells in lymph nodes samples. The pathologist confirmed the rupture of the tumor. Pediatric oncology opinion was sought; the stage of the tumor was classified as IIIc on the basis of the radiological, intraoperative findings, and pathological evaluation. The patient is on 3 drug chemotherapy treatment protocol/regimen [recommended as per International Society of Pediatric Oncology (SIOP) 2001] with us and is under 3 months follow-up.

Discussion

Wilms tumor constitutes 6% of all pediatric malignant tumors (5). The most affected age group is 2-3 years, though it may present in early infancy to 10 years and beyond in the adults (7,8). Wilms tumor is a rapidly growing tumor, and usually attains an enormous size before it is diagnosed (9). Also, its doubles after 11 days, making it prone to rupture, either preoperatively or intraoperatively (spill) (9). Tumor rupture is a potentially significant event triggering tumor dissemination, both locally (through lymphatics) and remotely (through blood stream) (2). Tumor spillage is considered if there is preoperative tumor rupture, intraoperative tumor spill, or a tumor biopsy. Intra-operative tumor spill and tumor biopsy are intervention-related events (3). The SIOP Nephroblastoma Trial Group recommends neo-adjuvant chemotherapy for prevention of tumor rupture (10). In our case, the tumor ruptured before chemotherapy was initiated.

Tumors greater than 12 cm in size have a two-fold risk of intraoperative rupture than smaller lumps (11). Intraperitoneal rupture (our case) is less common than retroperitoneal type (4,5). Rupture is common in males than females; right side is greater than left side (4,5).

Preoperative Wilms tumor rupture could either be post-traumatic or spontaneous in type. Spontaneous ruptures (as appreciated in our case) are rarer than the former (1,2). In a large series of 1853 Wilms tumors, preoperative rupture was appreciated in 5% (88) of patients (1). Preoperative rupture ranged from 2.1% to 23% in different studies (4,12). A study in Europe reported it to be 3% Wilms tumor (1). During a 9 year period from 2012 to 2020, 152 patients with Wilms tumor were surgically managed in our institute. Among these, this is the first (index) case of preoperative spontaneous Wilms tumor rupture. It is due to delay in seeking treatment, large tumor size (13 cm), rapid growth with involvement of renal vein and IVC by densely adherent large tumor thrombus (Figure 2 and Figure 3) (by senior author, RG).

Consequences of preoperative Wilms tumor rupture are: upstaging (IIIc), tumor spillage, surgery without neo-adjuvant chemotherapy, alteration in treatment (intensive chemotherapy with abdominal radiotherapy), and altered prognosis with adverse effects due to tumor dissemination (4,5,13). Wilms tumor spillage increases the risk of abdominal recurrence to 20% (14).

Clinical signs suggestive of preoperative Wilms tumor rupture include: acute exacerbation of abdominal pain, history of trauma, retroperitoneal or intraperitoneal hemorrhage, and sudden drop in Hb requiring blood transfusion (5).

Radiological signs [computerized tomography (CT) or USG findings] suggestive of preoperative rupture are: (a) poorly circumscribed mass with a non-delineated mass (b) fat stranding around tumor with linear areas of soft-tissue attenuation in peri-tumoral fat suggestive of capsular breech, (c) retroperitoneal hemorrhage or fluid in the sub-capsular (crescent-shaped fluid collection following the contour of the kidney), perirenal, or pararenal space, (d) hemorrhagic ascites or ascites beyond the cul-de-sac, (e) peritoneal implants, (f) retroperitoneal tumor nodules separate from primary tumor (g) mesenteric infiltration (h) ipsilateral pleural effusion, (i) tumoral fracture communicating with peritoneal effusion and (j) intra-tumoral hemorrhage. CT has high specificity but relatively low sensitivity in the detection of preoperative Wilms tumor rupture (1,3,4,5). The most consistent CT sign is the presence of ascites beyond the cul-de-sac, irrespective of attenuation (3).

Management of preoperative Wilms tumor rupture is divided into either immediate or delayed group on the basis of timing of radical nephrectomy (5). Emergency surgery for preoperative Wilms tumor rupture range from 1.8% and 3% (4). The decision is based on clinico-radiological findings (1,3,4,5). In the immediate group, upfront surgery is performed, followed by adjuvant chemotherapy. In the delayed group, upfront chemotherapy followed by surgical intervention is achieved (5,10). The criteria for immediate surgery include localized rupture, completely resectable forms, tumor not crossing the midline and without IVC thrombus. Delayed surgery after preoperative chemotherapy has been recommended with non-localized rupture, large tumors that cannot be completely resected, tumors infiltrating to surrounding organs and long IVC tumor thrombus (5,10).

They were more cases of metastasis and recurrence in immediate group (2/13) than delayed group (8/28) in a large series of Wilms tumor, though not significant (41) (5). Survival outcomes were better in immediate than in the delayed group (5,14).

Conclusion

Preoperative spontaneous Wilms tumor rupture is a clinico-radiological challenge. A high index of suspicion is a prerequisite for diagnosis. Therefore, an upfront emergency radical nephrectomy should be discussed.

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Ethics

Informed Consent: The patient was transferred to the operation room after obtaining informed written consent from the parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Supervision: R.G., Concept: R.G., Design: R.G., Data Collection or Processing: R.G., V.S.R., G.S., P.S.P., Mi., Analysis or Interpretation: P.M., Literature Search: R.G., V.S.R., G.S., Critical Review: P.M., Writing: R.G., V.S.R., G.S., P.S.P., Mi.

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Case Report

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Safety of Robotic Surgery in Urological Cancers in Patients with Ventriculoperitoneal Shunt: A Report of Two Cases

Varun V Agarwal[1], T.B Yuvaraja[1], Santosh S Waigankar[1], Preetham Dev[1], Abhinav P Pednekar[1], Abhijit A Raut[2]

[1]*Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Department of Urology, Mumbai, India*
[2]*Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Department of Radiology, Mumbai, India*

Abstract

Patients with a ventriculoperitoneal shunt (VPS) are at risk for shunt infection and failure during laparoscopic and robotic abdominal surgeries due to pneumoperitoneum. Herein, we present the first-ever report of robotic surgery in two uro-oncological cases with VPS *in situ*.

The first patient underwent robotic radical cystectomy with intracorporeal ileal conduit formation for bladder cancer, whereas the second underwent radical prostatectomy for localized prostate carcinoma. Surgeries were performed in Trendelenburg position and intra-abdominal pressure of 10-12 mm Hg. Pneumoperitoneum time was 210 and 165 min, respectively. Both patients had an uneventful intraoperative and postoperative course, without any urological or neurological sequelae at 1 and 7 years follow-up, respectively.

Prolonged robotic surgeries were safely performed with less insufflation pressure in the Trendelenburg position in patients with VPS. The shunt did not affect the oncological outcomes, operative time, blood loss, or rates of conversion to open procedure during robotic surgeries.

Keywords: Robotic surgery, ventriculoperitoneal shunt, urological cancers, radical prostatectomy

Introduction

Ventriculoperitoneal shunt (VPS) was described as a treatment for increased intracranial pressure (ICP), resulting from different causes, such as trauma, tumors, infections, and hemorrhage (1). Contamination during abdominal surgeries is possible in patients with VPS, thus various techniques are used, such as shunt externalization or conversion to ventriculoatrial shunt (2). More concerns are noted in laparoscopic/robotic cases due to the retrograde travel of carbon dioxide to the central nervous system, shunt infection, and malfunction due to a high-pressure pneumoperitoneum (3). Published literature described robotic surgeries in patients with VPS (4), but none for urological malignancies. To the best of our knowledge, this is the first-ever case report about robot-assisted uro-oncology cases, namely radical cystectomy with intracorporeal ileal conduit (RCIIC) and radical prostatectomy (RP) in patients with VPS.

Case Presentation

Case 1: A 76-year-old male patient, with a history of VPS surgery in 2006 for obstructive hydrocephalus secondary to arteriovenous malformation, presented with a large bladder mass and biopsy report of muscle-invasive transitional cell carcinoma. In 2012, he underwent an open extraperitoneal RP with pelvic lymph node dissection (PLND) for prostate cancer. Now, RCIIC was performed with care to reduce the contamination from bowel and urine spillage. The total console time was 210 min, which is the average time in our institution for this surgery. Postoperatively, the abdominal drain was removed on day 5, when its output reduced to <50 mL. All blood parameters and biochemical investigations were within normal range. At the 1year follow-up, the patient has no recurrence on positron emission tomography (PET) scan.

Case 2: A 64-year-old male patient presented to us in 2014 with localized prostatic adenocarcinoma (cT2b) and Gleason's score of 4+3=7. He had VPS inserted for traumatic hydrocephalus 5 years ago. The patient underwent robotic RP with PLND. Urinary contamination was experienced upon bladder neck incision during prostatectomy. The total console time was 165 min and surgery was uneventful. The latest prostate-specific membrane antigen PET scan at 7 years follow-up was normal.

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Address for Correspondence: T.B Yuvaraja, Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Department of Urology, Mumbai, India
Phone: +91 9321322505 **E-mail:** tb.yuvaraja@gmail.com **ORCID-ID:** orcid.org/0000-0001-9103-8124
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Preoperatively, neurosurgeon's opinion was sought for both patients. They were fully conscious and obeyed commands with normal higher mental functions, without any focal neurological deficit. Intraoperatively, patients were placed in Trendelenburg position at 30°-35° and the pneumoperitoneum pressure was maintained at 10-12 mm Hg. In both cases, shunts were visualized in the right pelvic region (Figure 1) and placed away from the operative field in the upper abdomen. Signs of increased ICP, such as hypertension or bradycardia, were not noted intraoperatively. Minimal intestinal adhesions from the previous VPS surgery required adhesiolysis. Blood loss was minimal. In the end, the shunt was placed back in the pelvic cavity. As per hospital protocol, second-generation cephalosporin was administered. Both patients had a normal postoperative hospital stay, without any neurological or urological sequelae.

As this was a retrospective study, informed consent for study participation was not obtained. However, both participants provided written informed consent for undergoing the surgery.

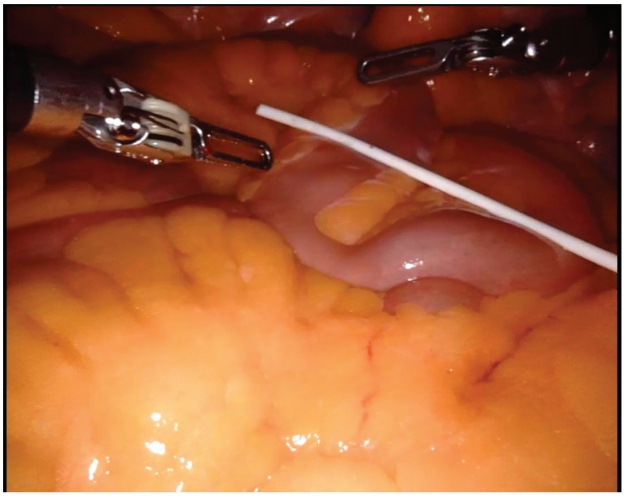

Figure 1. Intraoperative photo of the shunt

Discussion

Laparoscopic and robotic surgeries are well-accepted modalities in managing different abdominal surgical conditions. Traditionally, these are associated with carbon dioxide absorption from the peritoneum, leading to hypercapnia. It causes cerebral vasodilatation and increased ICP. Patients with an incompetent valve in the VPS can experience cerebrospinal fluid backflow in the shunt, thus further increasing ICP (3).

Schwed et al. (5) first reported the case of laparoscopic procedure in a patient with VPS. Their patient underwent laparoscopic cholecystectomy and had massive subcutaneous emphysema intraoperatively, which was attributed to the shunt tract's inability to mature as it was inserted 10 days before surgery. They concluded that laparoscopy should be deferred until maturity and fibrosis of the VPS tract, although the exact timing was not decided. Our patients had VPS surgery 14 and 5 years before undergoing surgery for urological cancers. Li and Dutta (2) performed one of the most extensive case series of 39 abdominal surgeries in patients with VPS. Only seven patients underwent laparoscopic surgeries; however, they concluded that pneumoperitoneum did not pose added risk to the shunt. Bush et al. (4) reported about robotic hysterectomy and mentioned that a pressure up to 25 mm Hg can be safely used in patients with VPS. A French study, which used transcranial Doppler to monitor the intraoperative ICP, also mentioned pneumoperitoneum's safety as long as pressure was not abruptly increased (6). Due to the abdominal wall tenting with robotic arms, the abdomen was gradually insufflated up to a pressure of 10-12 mm Hg using the Airseal Insufflation system (ConMed), which was sufficient to maintain a good vision and working space. Intraoperatively, reflux through the shunt to the intraventricular space is possible. Therefore, various preventive maneuvers are performed, such as temporary clamping using a clip (7), placing the distal end of the shunt in an endopouch bag, placing it away from the operative field (8), or externalizing it in cases of gross purulent contamination (2). We placed away from the surgical field at the beginning of the surgery.

Another study documented the worsening of hydrocephalus, even pneumocephalus, due to carbon dioxide (9). However, our patients had a valved shunt, which was proven to be safe by *in vitro* studies at high pressures (3). Another study noticed a higher conversion to open rates due to adhesions resulting from previous shunt surgery (10). In the present study, the first patient had abdominal adhesions near the tip of the shunt, which was released, and surgery was uneventful, although the patient had undergone an open extraperitoneal RP. Studies mention that laparoscopic surgery of <30 min with low pressures in the Trendelenburg position up to 15° is safe for the shunt (6); however, we experienced no perioperative complications with a pneumoperitoneum time of 210 and 165 min in a Trendelenburg position at 30°-35°. In the past, concerns arose regarding port site metastasis and retrograde spread of cancer due to pneumoperitoneum; however, Emoto et al. (11) have laid to rest all such speculations. Both of our patients were free of any disease recurrence at 1 and 7 years follow-up, confirming the oncological safety of robotic surgery with VPS *in situ*. Literature was against the use of prolonged antibiotic treatment in clean and clean-contaminated surgeries. The shunt infection rates remain the same in intestinal and urological surgeries, even when both systems are breached (2). In the first patient, the antibiotic was administered for 5 days, without adverse effects even after urinary and gastrointestinal contamination.

Conclusion

Prolonged robotic uro-oncological surgeries are safely performed with less insufflation pressure in Trendelenburg position in patients with VPS by placing it away from the operative site. VPS did not affect oncological outcomes, operative time, blood loss, or rates of conversion to open procedure in our robotic surgeries. However, further studies with a greater number of patients are needed to validate these outcomes along with the safety of the Trendelenburg position in patients with VPS. This is the first case report highlighting the perioperative and long-term oncological safety of robotic management for urological malignancies in patients with VPS, which can be further ascertained by studies with a larger sample size.

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Ethics

Informed Consent: As this was a retrospective study, informed consent for study participation was not obtained. However, both participants provided written informed consent for undergoing the surgery.

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Authorship Contributions

Concept: V.V.A., T.B.Y., S.S.W., P.D., A.P.P., A.A.R., Design: V.V.A., T.B.Y., S.S.W., P.D., A.P.P., A.A.R., Data Collection or Processing: V.V.A., T.B.Y., S.S.W., P.D., A.P.P., A.A.R., Analysis or Interpretation: V.V.A., T.B.Y., S.S.W., P.D., A.P.P., A.A.R., Literature Search: V.V.A., T.B.Y., S.S.W., P.D., A.P.P., A.A.R., Critical Review: V.V.A., T.B.Y., S.S.W., P.D., A.P.P., A.A.R., Writing: V.V.A., T.B.Y., A.P.P., A.A.R.

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