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

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

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

All submitted manuscripts are committed to rigorous peer review.

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

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

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

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

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

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

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

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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:

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

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

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

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

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-Abbreviations:

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

-Units of Measurement:

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

-Statistical Evaluation:

All retrospective, prospective, and experimental research articles must be evaluated in terms of biostatics and should be stated together with an appropriate plan, analysis, and report. P values must be given clearly in the manuscripts (e.g., p=0.033). It is the authors' responsibility to prepare a manuscript that meets biostatistical rules.

-Language:

Accepted articles will be published in English online. It is the authors' responsibility to prepare a manuscript that meets spelling and grammar rules. Authors who feel their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English are encouraged to consult an expert. All spelling and grammar mistakes in the submitted articles are corrected by our redaction committee without changing the data presented.

5. Article Types

The Bulletin of Urooncology publishes articles prepared in compliance with the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals published by International Committee for Medical Journal Editors (ICMJE). Manuscripts that do not meet these requirements will be returned to the author for necessary revision prior to review.

The Bulletin requires that all submissions be submitted according to these guidelines: Manuscripts should be prepared as a word document (*.doc) or rich text format (*.rtf). Text should be double-spaced with 2.5 cm margins on both sides using 12-point type double spaced in Times Roman.

All manuscripts submitted must be accompanied by the "Copyright Transfer and Author Declaration Statement Form" (www.uroonkolojibulteni.com). The corresponding author must also provide a separate "Title Page" including full correspondence address including telephone, fax number, and e-mail address, list of all authors with The ORCID number. Contact information for the corresponding author is published in the Bulletin.

All manuscripts submitted must also be accompanied by an "Acknowledgements Form" (www.uroonkolojibulteni.com). Acknowledgements are given for contributors who may not be listed as authors. Any grants or financial support received for the paper should be stated in the "Acknowledgements Form". If presented as an abstract; the name, date, and place of the meeting should also be stated in this form. A statement of financial, commercial or any other relationships of a declarable nature relevant to the manuscript being submitted, (i.e. a potential conflict of interest) must also be included in "Acknowledgements Form".

Each section of the" Main Text" mentioned below should be started on a new page and be organized according to the following sequence:

1) First page: Title, abstract and keywords (without authors' credentials)

2) Manuscript text structured based on the article type (without authors' credentials)

3) References

4) Figure legends

5) Short Quiz for review articles.

Tables and figures should be uploaded separately.

Also, "Acknowledgements Form" should be uploaded separately.

A. Original Research Articles

Original prospective or retrospective studies of basic or clinical investigations in areas relevant to urologic oncology.

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

- First page: Title - Abstract (structured abstract limited to 300 words, containing the following sections: Objective, Materials and Methods, Results, Conclusions) - Keywords (List 3-5 keywords using Medical Subjects Headings [MeSH])

-Introduction

- Materials and Methods

- Results

- Discussion

- Study Limitations
- Conclusions
- References
- Figure Legends: These should be included on separate page after the references.

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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).

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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.

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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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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:

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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.

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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.

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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.

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The title page should include the following:

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-Running title

-Authors' names and institutions

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

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-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).

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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.

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-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

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Non-muscle Invasive Bladder Cancer: Identifying Patients to Consider Timely, Initial Cystectomy

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Abstract

Non-muscle invasive bladder cancer is a heterogeneous disease with widely varying risks of recurrence and progression to muscle invasion. Risk stratification within current treatment guidelines are an attempt to address this heterogeneity. This heterogeneity stems from a number of pathologic characteristics as well as recurrence status. Radical cystectomy, while the definitive, curative therapy for muscle invasive disease, is not often utilized for non-muscle invasive disease, even when it may be a superior option to bladder-sparing therapy. A majority of American Urologists have been reported to defer cystectomy for less invasive therapies when it is a guideline driven option. Both cystectomy and bladder-sparing therapy have excellent oncologic outcomes, but very different morbidity and mortality profiles. Timely, initial cystectomy provides improved oncologic outcomes for patients with high-risk non-muscle invasive bladder cancer, as opposed to delayed cystectomy following prolonged, failed bladder-sparing therapy. Patient selection is paramount when considering timely, initial cystectomy, given the increased rates of morbidity and mortality. The heterogeneity of non-muscle invasive pathologic characteristics includes a number of factors that may help differentiate patients who would benefit from a timely, initial cystectomy as opposed to bladder-sparing therapy. A rapidly evolving understanding of bladder cancer biology may help improve risk stratification and further aid in the selection of patients for timely, initial cystectomy.

Keywords: Early cystectomy, high-risk bladder cancer, non-muscle invasive bladder cancer, timely cystectomy

Introduction

Bladder cancer burdens the healthcare system as the sixth most commonly diagnosed cancer in the United States (US), with the highest per patient cost of any cancer in the US (1,2). These statistics are even more troublesome as the incidence and death rate of bladder cancer have remained remarkably unchanged from 1985 (20.7 and 4.7 per 100,000) to 2016 (19.4 and 4.4 per 100,000) based on the SEER Medicare Dataset (2).

Approximately 75% of bladder cancers are non-muscle invasive bladder cancer (NMIBC) at diagnosis (3). This predominance for non-muscle invasive disease complicates the treatment algorithm due to its heterogeneity of risk and treatment options. Treatment of NMIBC by the American Urological Association (AUA) Guidelines relies on risk stratification based on tumor characteristics and recurrence status. The applicability of these treatment algorithms has improved with the current guidelines by the introduction of, and emphasis on, risk re-stratification at every subsequent recurrence, treatment and transurethral resection of a bladder tumor (TURBT) (4).

Treatment of NMIBC and Early Cystectomy

Both recurrence and progression rates vary widely for low, intermediate and high-risk NMIBC, with the overall risk of recurrence as high as 70% within the first year, and the lifetime risk of progression to muscle invasive disease between 10-50% (5,6). This variability reflects the range of factors that contribute to the AUA risk stratification, namely the depth of tumor invasion, presence of lymphovascular invasion (LVI), concomitant carcinoma *in situ* (CIS), tumor size and location, tumor biology including a number of potential variants and recurrence status (5,7,8,9,10). However, these factors represent an incomplete list, as molecular and genetic factors will help determine more effective therapeutic strategies on an individual basis (11,12).

This heterogeneity within the NMIBC cohort, though complicating, emphasizes the need to categorize patients who may bear increased risk from bladder-sparing, intravesical therapy and thus may benefit from timely, initial, up front cystectomy. It should be noted that repeat TURBT, when indicated, is essential for appropriate risk stratification, and has been associated with decreased mortality and increased rates of tumor upstaging (13).

Guideline-directed treatment of NMIBC includes complete resection of all visible tumor and risk-guided surveillance, and may include intravesical instillation of immunotherapy [Bacillus Calmette-Guerin (BCG)] or chemotherapy, re-resection of the primary tumor site, or radical cystectomy (4,14). There is no argument that bladder-sparing techniques serve as the backbone

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of NMIBC therapy. Both induction and maintenance courses of intravesical BCG have been shown to decrease recurrence and progression of NMIBC when compared to TURBT alone or to TURBT plus intravesical chemotherapy (15,16,17,18).

Regarding BCG for patients with high-grade invasion into the lamina propria NMIBC (T1), multiple retrospective analyses have demonstrated BCG's efficacy. In a series of 126 patients with T1 disease, Brake et al. (19) reported a recurrence-free rate of 86% at 53 months following 1 or 2 cycles of induction BCG. These successes were re-demonstrated by Novotny in a group of 63 patients who underwent a combination of induction and maintenance BCG regimens showing a recurrence in 25% and progression in 13% of patients. Canter also showed a decrease in progression to 8.6% with the addition of adjuvant BCG (20).

Given these results for BCG, and realizing the morbidity of radical cystectomy, up front bladder removal, even for high-risk NMIBC patient, is not often considered (21). This holds true for BCG refractory NMIBC, which carries an approximately 80% chance of treatment failure or progression, as evidenced by one survey in which 80% of American Urologists would not recommend a radical cystectomy for a patient with NMIBC refractory to two induction courses of BCG (22). This lack of adoption is likely multifactorial, but worrisome given the excellent, albeit retrospective data, supporting upfront, timely radical cystectomy versus delayed cystectomy following failed bladder-sparing therapy. Herr and Sogani (23) reviewed 90 patients with high-risk NMIBC who underwent cystectomy. Of the patients whose cystectomy was within 2 years of BCG initiation, 15-year cancer-specific survival was 69%, versus 29% in those who underwent cystectomy more than 2 years after BCG initiation. While none of these patients underwent cystectomy prior to progression to muscle invasion, Jäger et al. (24) showed a similar result in strictly high-risk NMIBC patients, with a ten-year overall survival of 79% in patients who underwent cystectomy within 6-12 months of their initial TURBT as opposed to 62% for cystectomy after 12 months. Raj et al. (25) then compared Herr's original group to a more contemporary cohort that underwent early cystectomy for recurrent T1 disease, showing an improved disease-specific survival favoring early cystectomy, which was then echoed by Denzinger et al. (26) in a similar population. Denzinger et al. (26), Hautmann et al. (27) and Stöckle et al. (28) have all reported similar findings in patients who either underwent early radical cystectomy for high-risk non-muscle invasive disease versus delayed cystectomy following failure of bladder-sparing therapy, showing five-year disease-specific survivals of 90% compared to 62% and ten-year disease-specific survivals of 78-79% compared to 51%-65%, favoring early cystectomy.

Given the excellent outcomes from both bladder-sparing BCG, and from timely, initial cystectomy, it is unsurprising that a recent meta-analysis showed mixed results regarding the differences in cancer-specific survival for bladder-sparing therapy versus timely cystectomy for patients with high-risk T1 NMIBC (29). In this analysis, cancer-specific survival showed no significant difference between upfront cystectomy versus intravesical therapy at 2, 5 and 10-years; it favored cystectomy at 15-years, however with significant variability of the data. Overall survival on the other hand favored bladder-sparing intravesical therapy at 2, 5 and 10-years, with insufficient data for 15 years. It should be noted that these results reflect both a heterogeneous group of studies, and include complete responders to intravesical therapy, thus decreasing the power of the meta-analysis to detect differences between immediate versus delayed cystectomy. The true denominator of those who never received cystectomy and instead received alternative, likely ineffective, intravesical therapies is unknown and likely underestimated.

Outside of oncologic outcomes, any discussion of radical cystectomy should also take into account both the advantages of cystectomy's improved staging and the disadvantages of its increased morbidity and mortality. Accurate staging is paramount when discussing the potential treatment options available for bladder cancer given the strong evidence for radical cystectomy for muscle invasion (30). Unfortunately, staging is often not as technically straightforward as the dichotomy of "muscle invasive or not". More than 20% of patients initially diagnosed with T1 NMIBC have been found to be incorrectly staged on repeat TURBT (31). This is echoed by the rates of pathologic upstaging at the time of radical cystectomy, which have found previously T1 NMIBC patients to be reclassified as muscle-invasive in 25-50% of cases, with 15% of patients found to harboring lymph-node positive disease at the time of cystectomy for NMIBC (32,33).

Radical cystectomy is not without risk, which may account for the reported reluctance to recommend extirpative therapy, even when indicated (22). Contemporary series have reported the 90-day morbidly of radical cystectomy to be between 27-60% when genitourinary, gastrointestinal, infectious and wound related complications are considered, regardless of an open versus robotic surgical approach, with mortality often cited between 3-5% (21,34,35). Outside of the perioperative risk, there has been controversy regarding quality of life outcomes after radical cystectomy. Yang et al. (36) found both genitourinary and sexual outcomes to be negatively impacted by radical cystectomy over bladder-sparing therapy. Interestingly, these results were significant regardless of continent versus incontinent urinary diversion. On the other hand, Kulkarni et al. (37) examined quality-adjusted life expectancy and found upfront radical cystectomy to have better outcomes than radical cystectomy following failure of bladder-sparing therapy.

Considering both the advantages and disadvantages of radical cystectomy weighed against the effectiveness of bladder-sparing therapy, discussing the criteria for choosing the NMIBC patient appropriate for a timely, upfront cystectomy is essential. This patient may be chosen before or following re-staging TURBT. Unsurprisingly, this question has long been the focus of multiple research groups in an attempt to optimize the NMIBC treatment pathway. Risk stratification and predictive modeling have both been employed to this end. AUA Guidelines serve as a framework for this discussion, categorizing patients based on the pathologic features of TURBT specimens and conferring "high risk" status on any specimen with high-grade lamina propria invasion, variant pathology, CIS, multifocality or large size of a high-grade tumor, high-grade recurrences/BCG failure or prostatic specimens and LVI (4). Both the European Organization for Research and Treatment of Cancer (EORTC) and the Club Urologico Español de Tratamiento Oncologico have devised predictive models to help improve risk stratification and thus

guide treatment decisions for NMIBC. Unfortunately, neither of these have shown much practical use for the modern patient, as both cohorts included patients without routine re-staging TURBT, did not categorize based on LVI or variant histology, and overall did not follow current treatment algorithms (6,38). These shortcomings were demonstrated in a multi-institutional external validation study showing both prediction tools to have poor discrimination between progression and recurrence, with low positive predictive values and a tendency to overestimate the risk of disease progression for high-risk NMIBC (39).

Lacking a contemporary tool to aid in the decision for timely, upfront cystectomy, tumor characteristics must be taken in turn. Substaging the level of invasion of the lamina propria, as defined by the current American Joint Committee on Cancer Staging (AJCCS), has been a focus of much research. Both identification of muscularis mucosa involvement as well as the depth of lamina propria invasion have been identified to carry prognostic value (40). When T1 disease is subclassified into "superficial" versus "deep" invasion, Holmang et al. (8) showed a significant difference in both progression (36% vs 58%) and disease-specific mortality (23% vs 45%). Rouprêt et al. (41) reported a similar finding, showing improved recurrence-free, progression-free and cancer-specific survival for T1a over T1b NMIBC. Further subdividing T1 tumors into T1a, T1b, or T1c depending on the depth of invasion above, into, or beyond the muscularis mucosa, respectively, has also been consistently associated with increased progression and decreased survival for deeper T1 subclasses (5,42). Extent of muscularis mucosa invasion has also been proposed as a subclassification of T1 disease, although the exact definition of "extent" has not yet been standardized. Indeed, the most recent update to the AJCCS guidelines recommends an attempt at quantification of lamina propria invasion, although no specific strategy or metric is defined (43). Even though muscularis mucosa involvement has previously been discussed as a potentially useful measurement to subcategorize T1 NMIBC, its adoption has not been widely implemented, as its identification is extremely inconsistent. Muscularis mucosa is often scattered and discontinuous, and its reported detection rate ranges from 6 to 76% (44,45). Using depth of invasion with a tangible, easily defined cutoff for microinvasion has been more readily adopted and shown improved prediction of progression, over the EORTC calculator, and an association with progression-free survival, depending on the cut-off used (10,40). Even more recently, aggregate linear length of invasive carcinoma has been reported as an independent predictor of progression to muscle invasion in a recent study by Leivo et al. (46). While it is clear that sub-classification of lamina propria invasion has prognostic value, and will likely someday factor more directly into the decision to recommend timely cystectomy over bladder-sparing therapy, the lack of widespread validation and adoption of a single, definitive strategy for sub-classifying pure T1 NMIBC limits its current clinical application.

LVI provides another pathologic characteristic with the potential to help differentiate the patient who may benefit from a timely, initial radical cystectomy for non-muscle invasive disease. For MIBC, the presence of LVI is well established as a poor prognostic factor, and has been associated with advanced stage, grade and lymph-node involvement as well as decreased recurrence-free survival, cancer-specific survival and overall survival (47,48,49). For NMIBC, large, multicenter cohorts have also shown independent associations with recurrence-free survival, progression-free survival and cancer-specific survival, and have been further confirmed by a 4.000 patient meta-analysis (50,51,52). Unfortunately, LVI proves difficult to implement as a widespread metric due to technical challenges. Certain tissue processing artifacts like tissue retraction can complicate the identification of LVI (53). Furthermore, LVI in TURBT specimens only represents a small sample of the total tumor burden and thus it may be missed, or conversely overestimated in the overall tumor burden. Accordingly, concordance between TURBT and cystectomy specimens ranges from 18-79% with a negative predictive value of 50-70% (54,55,56). However, even considering these technical barriers to standardization, a recent meta-analysis and systematic review found that LVI in NMIBC tripled the risk of progression to MIBC and doubled the risk of disease recurrence. Furthermore, this evidence was so strong that the authors recommended LVI for inclusion in the TNM staging criteria for bladder cancer (57).

At diagnosis, approximately 10% of bladder cancer patients are found to have CIS, which represents a high-risk form of NMIBC, regardless of whether it presents as a discrete lesion, or synchronous with other non-muscle invasive lesions (4). At the time of cystectomy, specimens with CIS are understaged in up to 48% of non-muscle invasive cases, and the risk of pathologic upstaging in T1 NMIBC with synchronous CIS is 55% compared to 6% in high-risk T1 disease without CIS (58,59). The rate of progression in the presence of CIS also poses a major risk for NMIBC patients. In one study of NMIBC patients undergoing BCG therapy, 81% of whom had CIS, 53% of patients showed disease progression while on BCG therapy (60). This has been reproduced multiple times, demonstrating a strong association between CIS and progression to muscle invasion in 40-80% of cases (61,62). CIS has also been associated with nodal metastases in 4-6% of patients, along with risk of development of nodal metastases in up to 12% of patients when followed out to 3 years after cystectomy (63,64). Considering the high risk of both understaging and progression, the outcomes for radical cystectomy in patients with CIS-only disease are promising, with 3-year disease-free survival reported as high as 88% (63). Furthermore, Masood et al. (58) found 5-year cancer-specific survival to be 82% for CIS with concomitant T1 NMIBC. However, these results have been challenged in the era of neoadjuvant chemotherapy with Amini et al. (65) reporting no difference in oncologic outcomes for patients with CIS versus those without CIS, when adjusted for stage.

Variant histologies of NMIBC represent pathologic subsets that fall into the high-risk category in the AUA risk stratification table, accounting for 7-10% of new bladder cancer diagnoses (4,66). These include micropapillary, nested, plasmacytoid, neuroendocrine and sarcomatoid variants, each of which is thought to have its own tumor biology (67). One of the major concerns regarding variant histology is the relative rarity with which they are encountered as compared to pure urothelial carcinoma, and thus the lack of consistency regarding their identification and staging. Variant histologies go unrecognized in up to 44% of cases in one study of community pathologists

(68). This may also play a factor in the 30-60% rate of understaging in variant histology, which represents up to triple the rate of pure urothelial carcinoma understaging (69,70). Irrespective of difficulties with identification, variant histologies are considered more aggressive than pure urothelial carcinoma. Variant histologies present as muscle-invasive disease in up to three quarters of cases, as opposed to urothelial carcinoma that presents as non-muscle invasive in 70% of cases (71). Furthermore, variant histologies are associated with higher rates of locally advanced disease (72). The presence of a histologic variant has also been shown to be an independent predictor of nodal metastatic disease and decreased survival (73). Nested variant urothelial carcinoma has a propensity to progress to muscle-invasive disease more quickly than pure urothelial carcinoma, with a 54% rate of upstaging to muscle-invasive or metastatic disease after early cystectomy, even after thorough restaging TURBT showing cT1 disease (74). Regardless of the increased aggressiveness of variant histologies, it is important to note that intravesical therapy shows reduced effectiveness when compared to pure urothelial carcinoma, although this should be considered on a variant by variant basis. Kamat et al. (69) reported that up to 89% of patients with variant histology do not respond to intravesical therapy, with 67% actually progressing on BCG. This same cohort was then updated, showing that in patients with micropapillary variant, 5-year disease specific survival was 100% following upfront radical cystectomy versus 60% with BCG (75). A larger review of almost 900 patients with cT1 micropapillary bladder cancer showed no significant survival benefit for early cystectomy over bladder preserving therapy (76). It should be noted as well that the benefit of neoadjuvant chemotherapy is not quite clear, with a Vetterlein et al. (77) demonstrating improved rates of non-organ confined disease for many common histologic variants, but a survival benefit for only neuroendocrine variant.

As mentioned previously, in this age of personalized medicine, molecular and genomic classifications of bladder cancer are becoming critical in the considerations of potential patient management, although they have not yet been included in current risk stratifications. Biomarkers including p53, pRB and Ki-67 have all been associated with both increased recurrence and decreased survival for MIBC after radical cystectomy (78,79). For NMIBC, while early trials had conflicting results, newer evidence is emerging that suggests that recurrence may be predicted, and prognostic models improved, by molecular marker data (53,80,81,82,83,84).

Epigenetics, including oncogene activation, chromosomal alterations, tumor suppressor loss and cell-cycle regulation, has been associated with non-invasive tumor progression, which may serve as an indicator of patients who would benefit from timely, initial cystectomy (85,86,87). Mutation of the tumor suppresser gene p53 has been shown in many studies to be associated with tumor progression, although there is some conflicting evidence (88,89). Fibroblast growth factor receptor 3 (FGFR3) mutations, found to be present in up to 88% of low-grade papillary lesions but only 16% of high-grade T1 tumors, have been associated with a lower rate of progression, recurrence and disease-specific survival (90). RNA sequencing has also be implicated as a possible classifier of NMIBC, showing the ability to predict progression and recurrence (91). Furthermore, combining panels of molecular markers has further improved risk stratification for NMIBC. Combinations of FGFR3 mutation status with Ki-67 expression have been associated with progression, as well as shown significant improvement in the accuracy of the EORTC risk calculator (92,93). Tissue microarrays using a large number of genetic markers including p53, pRB, p21 and p27, as well as one using cyclin D1, MCM7, TRIM29 and UBE2C, have not only shown an association with tumor progression, but have also provided a continuum on which the number of marker alterations correlates with the probability of progression (86,94). While these various biomarkers have been shown to improve prognostication, they are not yet widely available in clinical practice.

The highest yield application of the increasing genetic and epigenetic knowledge base of bladder cancer may be the identification of two distinct molecular subtypes of NMIBC, namely the basal and luminal subtypes (11,12,95). The luminal subtype tends to have more papillary features, rich in FGFR3, whereas the basal subtype are often associated with squamous and sarcomatoid features and are often found to be metastatic at diagnosis (11,95). These new classifications may provide not only a more robust risk stratification model, but also a framework for increasingly targeted therapeutic algorithms (96).

Furthermore, bladder-sparing therapy is also likely to expand beyond the current intravesical options based on the increasingly deepening understanding of the basal and luminal subtypes (97,98). Basal type tumors, for example, respond well to immunotherapy given their concentration of programmed death ligand-1 T-cells as well as EGFR inhibitors (12,99,100). The potential for both improved risk stratification, as well as individualized patient care, could signal a paradigm shift in the approach to both MIBC and NMIBC. This is most clearly evidenced by the 25 ongoing clinical trials in the US for NMIBC (101).

Conclusion

The evidence for the oncologic benefit of cystectomy in the NMIBC setting is quite clear. However, the morbidity of cystectomy, both in the short-term perioperative period and in the long-term follow-up period, must be considered. Unfortunately, the data suggests that radical cystectomy for NMIBC is not as effective following ineffective, prolonged intravesical therapy. When choosing appropriate candidates, decisions about their treatment plans should follow repeat transurethral resections, when indicated, and their surgical fitness should be considered. Patients with non-invasive tumors not amenable to transurethral resection, regardless of risk stratification, should be considered for initial cystectomy. Those with tumors amenable to complete visual transurethral resection in patients fit for surgery, with tumor pathology reflecting pure urothelial carcinoma with high-risk characteristics like lamina propria invasion on repeat resection, deeper or more extensive lamina propria invasion, LVI, CIS or patients with histologic variants should all strongly be considered for a timely, initial cystectomy. As patients accumulate more of these risk factors, they should be considered increasingly stronger candidates

for timely, initial cystectomy. Genetic, epigenetic and genomic risk factors are paramount to the future of bladder cancer risk stratification and treatment, for both NMIBC and MIBC, and will likely add more variables to consider in the decision for bladder-sparing therapy versus timely, initial cystectomy for NMIBC.

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Authorship Contributions

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Short Quiz

1- Which of the statements below <u>is not</u> correct.

A) Contemporary series have reported the 90-day morbidly of radical cystectomy to be between 27-60%

B) More than 20% of patients initially diagnosed with T1 NMIBC have been found to be incorrectly staged on repeat TURBT.

C) Both genitourinary and sexual outcomes are equally impacted by radical cystectomy and bladder-sparing therapy.

D) Muscularis mucosa is often scattered and discontinuous, and its reported detection rate ranges from 6 to 76%.

E) For NMIBC, large, multicenter cohorts have also shown independent associations with recurrence-free survival, progression-free survival and cancer-specific survival

Answer: C

2- Which of the genetic factors below <u>has not</u> a study showing its effect on NMIBC

A) p53

B) pRB

C) p21

D) p27

E) p99

Answer: E

3- Which of the factors below <u>does not</u> contribute to the AUA risk stratification

A) Lymphovascular invasion (LVI),

B) Concomitant carcinoma in situ (CIS),

C) Tumor size

D) Cystoscopic appearance of the tumor

E) Tumor location

Answer: D

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Mini Review

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Efficacy of Chemotherapy Combinations in Metastatic Castration-Resistant Prostate Cancer Patients - Do Homologous Recombination Deficiency Affect the Outcomes?

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Abstract

Homologous recombination (HR) is a major repair mechanism of DNA damage. Platin-based agents are known to be more effective in patients with impaired HR mechanism. Previous studies combined platin compounds with docetaxel, but most of these studies did not perform subgroup analysis for HR-deficient patients. Aggressive variant prostate cancer (AVPC) is considered more susceptible to carboplatin. Furthermore, prostate cancers with a higher rate of small cell or anaplastic carcinoma components are more susceptible to carboplatin plus etoposide. We thought that the effect of cabazitaxel plus carboplatin on the progression-free survival might be related to carboplatin alone. In a study that evaluated the effect of cabazitaxel plus carboplatin, the proportion of AVPC patients was higher in the combination group than in the cabazitaxel group. Additionally, the combination of cabazitaxel and carboplatin led to increased toxicity.
Keywords: Chemotherapy, homologous-recombination deficiency, prostate cancer

Several clinical trials investigated the efficacy of combination chemotherapy for metastatic castration-resistant prostate cancer (mCRPC). In most of these trials, combination regimens are not superior to single-agent regimen (e.g., docetaxel or cabazitaxel). Hence, docetaxel and cabazitaxel (especially in the second-line setting) are the standard chemotherapeutic agents for mCRPC (1,2).

Homologous recombination (HR) is a major repair mechanism of DNA damage. In a previous study, 20%-25% of CRPC patients had a defect in the HR repair genes (3). Particularly, BRCA2 mutations were more frequent than mutations of other HR repair genes (4,5). Platin-based agents are known to be more effective in patients with impaired HR mechanism. In previous studies, platin compounds were combined with docetaxel, but most of these studies did not perform subgroup analysis for patients with HR repair mechanism deficiency. However, a prospective analysis of mCRPC patients with BRCA2 mutations revealed the efficacy of docetaxel plus carboplatin (6).

Aggressive variant prostate cancer (AVPC) is defined based on the clinicopathological or molecular features of prostate cancer. Prostate cancer characterized by small cell or anaplastic carcinoma morphology and atypical features or mutations of *TP53*, *PTEN*, or *RB1* genes are considered as AVPC (7). Furthermore, BRCA mutation carriers have more aggressive prostate cancer (8). Therefore, mutations of BRCA and other DNA repair genes were seen commonly among patients with AVPC (9). Prostate cancers with these aspects are considered more susceptible to carboplatin (10). Furthermore, prostate cancers with a higher rate of small cell or anaplastic carcinoma components are more susceptible to carboplatin plus etoposide (11). In patients with mCRPC, *HR* gene defects (e.g., *PTEN* gene defect) cause aggressive prostate cancer and taxane resistance (12).

Corn et al. (13) showed that cabazitaxel plus carboplatin improved the survival outcome in patients with mCRPC. In this study, the effect of cabazitaxel plus carboplatin on the progression-free survival might be related to carboplatin alone. In this study, the proportion of patients with AVPC was also higher in the combination group than in the cabazitaxel group (the AVPC-clinicopathological criteria was 56% versus 52% and the AVPC-molecular signature was 52% versus 36% in the cabazitaxel and cabazitaxel plus carboplatin groups, respectively). Furthermore, the authors mentioned that the benefit from the combination therapy was greater in the AVPC group than in the non-AVPC group. Consequently, the results were consistent with the effect

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of carboplatin in AVPC. Additionally, combination of cabazitaxel and carboplatin led to increased toxicity in this trial.

To our knowledge, no clinical trial has compared the effect of carboplatin as a single agent with docetaxel or cabazitaxel among patients with *HR* gene mutations. An ongoing phase 2 trial compares the effectiveness of carboplatin and docetaxel among patients with BRCA1, BRCA2, or PALB2 mutations (NCT04038502). The results of this trial will clearly present the effect of carboplatin alone versus docetaxel among patients with who have *HR* gene mutations.

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Original Article

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Role of Tissue Markers on Predicting the Prognosis of Intermediate and High-risk Non-muscle Invasive Bladder Cancer

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Abstract

Objective: Investigating the recurrence of high-risk non-muscle invasive bladder cancer patients with the phosphohistone H3 (PPH3), P53, and Ki-67 as a predictive markers.

Materials and Methods: A total of 46 patients with high-risk non-muscle invasive bladder cancer patients were included. All the patients treated with bacillus Calmette-Guérin instillation. Patients were divided into two groups consisted of the with recurrence (group 1) and without recurrence (group 2). Assessment of mitotic cells only in metaphase that are stained with PPH3 immunhistochemically counted separately at 20 and 40 magnification in most intense areas under microscope. Immunhistochemically stained urothelial cells with P53 evaluation was based on 3 different scoring categories that are intense, extent, and the total score. Ki-67 immunhistochemical stained cells were calculated with ratio of counted positive stained cells in intense area to the total cells. Mann-Whitney U test was used.

Results: There is no significant differences between the median value of PPH3 at 20 and 40 magnification in the two groups (p=0.620, p=0.241). P53 that was assessed with median values of the extent, intense, and total score had no significant findings between the two groups (p=0.377, p=0.102, p=0.380). Also, no significant results in median values of Ki-67 between the two groups found.

Conclusion: These markers could not predict recurrence in our study, but in our opinion, significant results will be found if increasing case numbers and standard immunhistochemichal staining and assessment methods are used.

Keywords: Bladder cancer, marker, recurrence

Introduction

Approximately 80% of transitional epithelial cell cancers of the bladder are limited to the mucosa and submucosa at the time of diagnosis. This condition is called superficial bladder tumor or non-muscle invasive bladder cancer (NMIBC). NMIBC is a very heterogeneous group, with papillary urothelial tumors confined to the mucosa, defined as low grade Ta on one side of the spectrum, and high grade T1 tumors with carcinoma *in situ* (CIS) on the other. Approximately 70% of NMIBCs are Ta, 20% T1, and 10% CIS lesions. The prognosis of NMIBC is generally good, but recurrence is seen in 30-80% of patients, while muscle invasive disease develops within 5 years in 1-45% of patients (1,2,3).

NMIBC is a lifelong chronic disease that often tends to relapse, and sometimes progresses. The aim of its treatment is to eliminate the disease, to prevent relapse and progression. There have been many studies on prognostic factors to predict the likelihood of relapse and many studies continue to be done. Currently, the two most important prognostic factors in this regard are tumor stage and grade, but these two prognostic factors alone are insufficient to determine the prognosis of NMIBC. Therefore, the investigation of tissue markers that can be used to predict the recurrence of bladder cancer comes to the fore.

Histone H3 is one of the histone proteins that make up the chromatin, and it has recently been reported that it is closely related to mitosis and that the anti-phosphohistone H3 (PPH3)

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antibody is a mitosis specific antibody. In the literature, it has been shown that PPH3 is used in grading of other cancer types such as brain and breast (4,5,6,7,8). Ki-67 protein expression is highly associated with cell proliferation and is present in all phases of the cell cycle (G1, S, G2 and mitosis) except G0. It is an excellent marker that determines the growth fraction of the cell population of the Ki-67 protein. In the literature, fractions of Ki-67 positive tumor cells have been associated with clinical progression, and it has been shown to have prognostic value in terms of survival and tumor recurrence in prostate and breast cancer (9).

P53 tumor suppressor gene has been shown in previous studies to play an important role in carcinogenesis. The most common genetic abnormality in other malignancies, including bladder cancer, is the P53 mutation. It has been found in the literature that changes in P53 are associated with bladder cancer progression, and it has been shown in recent studies that it can be used as a predictive factor for disease-related survival and disease-independent survival (10).

In this study, we aimed to investigate whether PPH3, Ki-67 and P53 are predictive markers in determining recurrence in patients with high-risk NMIBC.

Materials and Methods

In the study, the data of patients who underwent transurethral tumor resection for NMIBC between 2008 and 2015 in İstanbul University-Cerrahpaşa, Faculty of Medicine, Department of Urology were retrospectively reviewed. Risk stratification was made according to the European Association of Urology guidelines (2). Accordingly, 46 patients diagnosed as having high-risk NMIBC were included in the study. The first resection preparations of all patients were evaluated. The cystoscopic follow-up protocol of the patients was applied every three months for the first 2 years, every six months for the next 3 years, and then annually, if there was no recurrence after the first resection. Recurrence at least once in the follow-up of the patients was accepted as recurrence. Bacillus Calmette-Guérin treatment was applied to all patients. Patients who received 6 months of induction and at least 1 year of maintenance therapy were included in the study. The patients included in the study were divided into two groups according to their recurrence status as the group with recurrence (group 1) and the group without recurrence (group 2).

PPH3, Ki-67 and P53 results were re-evaluated by a single pathologist by performing manual immunohistochemical staining in the first resection pathology specimens of both groups. The slides of the specimens stained immunohistochemically with PPH3 were evaluated under the microscope by counting only mitosis cells in the metaphase phase at 20 and 40 magnifications under the microscope. Urothelial cells immunohistochemically stained with P53 were evaluated in three different scoring categories as intensity, prevalence and total score. Intensity evaluation according to the staining intensity of the cells were: No staining (score 0), weak staining (score 1), moderate staining (score 2), and severe staining (score 3). The prevalence scoring according to the proportion of positive cells stained were: 0% (score 0), 1-10% (score 1), 10-25% (score 2), 25-50% (score 3), 50-75% (score 4), >75% (score 5). The total score of the patients was calculated by multiplying the extent and intensity scores (lowest score: 0 and highest score: 15). Ki-67 immunohistochemical staining, also known as proliferation marker, was determined by calculating the ratio of positive cells stained in the most intensive area to total cells.

The results of both groups were compared by applying the Mann-Whitney U test. A p-value of less than 0.05 was considered significant. The study was approved by the Ethics Committee of Cerrahpaşa Medical Faculty.

Statistical Analysis

Statistical analyzes were performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 software (IBM SPSS Statistics for Windows, version 21.0. Monk, NY: IBM Corp., Armonk, NY). Pearson chi-square and Fisher's Exact tests were used to search for the difference between categorical variables, and Kruskal-Wallis and Mann-Whitney U tests were used to search for the difference between means. A p-value of less than 0.05 was considered statistically significant. The study protocol was approved by the Cerrahpaşa Medical Faculty Ethics Committee (83045809/604.01/02-218946). The consent form was filled in by all participants and their families.

Results

A total of 46 patients were included in the study and 23 of these patients were included in group 1, while the other 23 were included in group 2.

Three (13%) of the patients belonging to group 1 were female and 23 (87%) were male. Mean age was determined as 72.1±11.6 (53-85). Average follow-up period was calculated as 43.2±8.6 months. Ten of the patients (43.4%) had Ta high grade, 13 (56.6%) had T1 high grade pathology. CIS Ta was found in the pathological diagnosis of 2 patients with high grade.

Three (13%) of the patients belonging to group 2 were female and 23 (87%) were male. Mean age was determined as 66.8±4.9 (40-81). Mean follow-up period was calculated as 56.5±11.4 months. The number of patients with a diagnosis of Ta high grade was 14 (60%), and the number of patients with a diagnosis of T1 high grade was 9 (40%). Three patients (13%) with Ta high grade were diagnosed as having CIS (Table 1).

In group 1, the mean values of PPH3 of mitosis cells counted at 20 and 40 magnification were determined as 11.5 (1-27) and 6.1 (1-12). The mean P53 intensity value was 2 (1-3), the mean prevalence value was 1.7 (1-5), and the total score mean value was 4.1 (1-15). Finally, the average result of Ki-67 was calculated as 13% (3-30%).

In group 2, the mean values of PPH3 of mitosis cells counted at 20 and 40 magnification were found as 14.3 (1-48) and 7.6 (1-20). The mean P53 intensity value was 1.6 (0-3), the prevalence mean value was 2.6 (0-59), and the total score mean value was 6.1 (0-15). The mean value of Ki-67 was found to be 13% (2-30%) (Table 2).

When the mean values of both groups were compared, no significant difference was found in PPH3 at magnification of 20

Table 1. Demographic data			
	Group 1	**Group 2**	**p**
Mean age	72.1±11.6	66.8±4.9	0.11
Gender			
Female	3 (13%)	3 (13%)	>0.999
Male	20 (87%)	20 (87%)	-
Mean follow-up (months)	43.2±8.6	56.5±11.4	0.55
T stage			
Ta	10 (43.4%)	14 (60%)	>0.99
T1	13 (56.6%)	9 (40%)	>0.99
Ta + CIS	2 (8.6%)	3 (13%)	>0.99
CIS: Carcinoma *in situ*			

Table 2. As a result of statistical analysis, it was determined that PPH3, Ki-67, P53 could not be used as predictive molecular markers to determine recurrence			
	Group 1	**Group 2**	**p**
PPH3			
x20 magnification	11.5 (1-27)	14.3 (1-48)	0.620
x40 magnification	6.1 (1-12)	7.6 (1-20)	0.241
P53			
Intensity	2 (1-3)	1.6 (0-3)	0.377
Prevalence	1.7 (1-5)	2.6 (0-5)	0.102
Total score	4.1 (1-15)	6.1 (0-15)	0.380
Ki-67	13% (3-30)	13% (2-30)	0.757
PPH3: Phosphohistone H3			

and 40 (p=0.620, p=0.241). P53 prevalence, intensity and total score mean value were not significantly different between both groups (p=0.377, p=0.102, p=0.380). Ki-67 mean values were not significantly different between the two groups (p=0.757).

Discussion

Bladder cancers are a heterogeneous group of diseases and there are many factors affecting recurrence, progression and survival. Routinely used tumor characteristics such as tumor stage and grade have limited effects on routine clinical practice, therefore, it has prompted the investigation of molecular markers to predict tumor recurrence and progression (11). In this study, we investigated whether PPH3, P53 and Ki-67, which were molecular markers each in patients with NMIBC, could be used as a predictive marker to predict recurrence.

In the statistical analysis, when the average values of group 1 and group 2 were compared, no significant difference was found in PPH3 at 20 and 40 magnification (p=0.620, p=0.241). P53 prevalence, intensity and total score mean value were not significantly different between both groups (p=0.377, p=0.102, p=0.380). Ki-67 mean values were not significantly different between the two groups (p=0.757). As a result of the study, it was concluded that these markers could not predict recurrence.

PPH3 is the core histone protein of eukaryotic cell chromatin. While PPH3 is not seen at all in the intraphase phase, it reaches its maximum levels in the chromatin condensation phase of mitosis. Anti-PPH3 is specific for phosphorylated H3 and is used as a mitosis marker. Its use as a marker of mitosis in many different tumor types such as breast cancer, malignant melanoma, meningioma, and lung cancer has been validated (6,7,8,9,10). Related to this, there is 50-60% disagreement between pathologists in the grading of upper urinary tract and bladder urothelial cancers. Therefore, Solomides et al. (12) investigated whether PPH3 can be used as a molecular marker that could eliminate this variability in the grading of upper urinary system urethral cancers in their study conducted in 2012. Sixty one patients with upper urinary tract urothelial cancer were included in that study. Pathology specimens of the patients were stained with both Hematoxylin & Eosin (H&E) and PPH3 immunohistochemical staining with H&E. Tumor grades were compared with the 1973 World Health Organization (WHO) classification (1: well differentiated, 2: moderately differentiated, 3: poorly differentiated) used in the grading of tumors with this method. The results were evaluated by three pathologists. Eighty percent consensus was achieved in the grading of tumors after staining the cell blocks with PPH3 together with H&E, while this ratio was found to be 55% with the use of the 1973 WHO classification. In another study, Gunia et al. (13) compared Ki-67 and PPH3 values in the differentiation of CIS and carcinoma non-superficial tumors. The study included 32 CIS, 31 non-CIS superficial lesions (low grade dysplasia and reactive atypia). Differentiation of superficial lesions with and without CIS was made according to the 2004 WHO classification. As a result of that study, it was found that the rate of cells stained positive with Ki-67 was higher in patients with CIS. It was shown that it could be used as an important marker in the differentiation of patients with and without CIS. When looking at PPH3 values, another molecular marker used to differentiate superficial bladder tumors with and without CIS, no significant difference was found between the two groups (p>0.25). Parallel to this, when the mean values of both groups were compared in our study, no significant difference was found in terms of PPH3 at magnification of 20 and 40 (p=0.620, p=0.241).

Mangrud et al. (14) investigated whether Mitotic Activity index (MAI), Ki-67 and PPH3 markers had superiority over the 1973-2004 WHO classification in predicting prognosis in NMIBC in a study conducted in 2013. Two hundred forty nine patients were included in that study, 125 of those patients had high-risk NMIBC and 124 had moderate-risk or low-risk NMIBC. In that study, the most intense proliferation area was selected in the evaluation of PPH3 staining and the evaluation was made by counting the mitosis cells in this area. MAI was selected by selecting the area where proliferation was the most intense at low magnification under the microscope of the specimens painted with H&E and the mitotic structures were counted at 400 magnification in a total area of 1.59 mm^2. Whether those three proliferation markers could be used to predict progression were investigated. The patients were divided into two groups as patients with and without progression, and their average results were compared. The mean value of PPH3 was found as 42 in the group with progression, 17 in the non-progressive group (p=0.31), and the mean value of Ki-67 as 40% in the group with progression and 16% in the non-progressive group (p=0.006). The mean value of the MAI was shown to be statistically

significantly superior in predicting progression compared to the mean values of the other two proliferation markers ($p<0.001$). As a result of the study, it was stated that PPH3 and Ki-67 alone could be used as prognostic markers related to progression, but it was concluded that they did not add additional prognostic value to MAI in the multivariate model.

Apart from the mentioned studies, studies on whether PPH3 can be used as a molecular marker in bladder cancer are very limited. In our study, when the mean values of the number of mitosis cells stained with PPH3 were compared, no significant difference was found between the two groups. In our study, unlike the study conducted by Mangrud et al. (14), only patients diagnosed as having high-risk NMIBC were included and the results of the patients were evaluated by a single uropathologist. While Mangrud et al. (14) showed that PPH3 alone did not contribute to progression as a prognostic marker, in addition to this, it was determined that PPH3 could not be used as a marker to predict recurrence in our study.

It is known that the most frequently mutated gene in patients with cancer is the P53 tumor suppressor gene. *P53* gene mutation in different tumor types has been demonstrated by immunohistochemical staining. Studies have shown that *P53* gene mutation correlates with progression, but studies indicating the opposite are also in the literature (15,16). In the literature, Abdelzaher and Kotb (17) investigated whether runt-related transcription factor-2 (RUNX2) and P53 were independent markers to predict recurrence of bladder cancers in 2014. A total of 87 patients with a diagnosis of MIBC together with primary NMIBC were included in that study. As a control group, sampling was made from the bladder mucosa of 17 patients without neoplasia. The patients were followed prospectively for an average of 28.8 months and their results were evaluated. The probability of predicting recurrence was found to be 40.9% for P53. When P53 value was considered together with RUNX2 in predicting recurrence, it was shown that both of them could accurately predict excessive expression and recurrence rate of 73.6%. However, it would not be correct to conclude that P53 could only be used as a predictive marker to show recurrence in patients diagnosed as having high-risk NMIBC due to the inclusion of patients with a diagnosis of MIBC with a high probability of recurrence and progression in that study. In our study, the mean P53 intensity value in group 1 was calculated as 2 (1-3), the mean prevalence value as 1.7 (1-5), and the total score mean value as 4.1 (1-15). In group 2, the mean P53 intensity value was 1.6 (0-3), the average prevalence value was 2.6 (0-59), and the total score mean value was 6.1 (0-15). In the statistical analysis, P53 prevalence, intensity and total score mean values were not found to be different between both groups ($p=0.377$, $p=0.102$, $p=0.380$).

Malats et al. (16) reviewed a total of 117 studies about whether P53 was a prognostic marker for bladder cancer in the meta-analysis in 2005. In only 9 (27%) of 34 studies on recurrence, P53 overexpression was found to have a prognostic value in showing recurrence. The reasons for this were that the pathological characteristics of the patients included in the studies were heterogeneous, the number of patients was below 100 in 82 (70%) studies and the absence of standard immunohistochemistry staining, scoring strategy, and positive staining definition. The result about P53 in our study shows parallelism with the result of this meta-analysis.

Ki-67 is proliferation-associated nuclear antigen and is expressed in the entire cell cycle except G0. Ki-67 protein is widely used as a proliferation marker reflecting the number of tumoral cell cycles (18). In some studies in the literature, the correlation of Ki-67 with progression was not observed, and it was shown that it was closely related with recurrence (19,20).

Ben Abdelkrim et al. (21) investigated the utility of topoisomerase 2 alpha, Ki-67 and P53 expression in predicting recurrence and progression in low-, moderate- and high-risk NMIBC in 2014. Seventy one patients were included in the study, and 69 patients were evaluated. Average follow-up period was calculated as 28 months. During the follow-up, 34 patients did not have recurrence, 20 patients had recurrence and 15 patients had progression. In that study, Ki-67 positive value was accepted as >10%. The number of Ki-67 positive patients was 27 (38%), and it was concluded that it was associated with recurrence. However, the relationship of Ki-67 with progression could not be demonstrated. In the study, only 19 of 69 patients were diagnosed as having high-grade NMIBC, and only 8 (42.1%) of these 19 patients were found to have a positive Ki-67 value (>10%). In our study, the Ki-67 positive value of patients with high-grade NMIBC was not determined in the evaluation of recurrence, and the mean values of both groups (group 1: 13% and group 2: 13%) were compared. The >10% method, which Ben Abdelkrim et al. (21) determined as the positive value of Ki-67, was shown to be positive in 14 (60%) patients in the group without relapses and in 9 (40%) patients in the group with relapses when applied in our study. Ki-67's status related to recurrence in the study of Ben Abdelkrim et al. (21) is in contradiction with the result of our study. The reason for this can be explained by the short mean patient follow-up period (28 months) and the presence of patients with NMIBC with heterogeneous pathological features (neoplasm with low malignancy potential, low-grade malignancy and high-grade malignancy).

Study Limitations

Our study had some limitations. The first was that it was retrospective. Second, the number of patients was limited. For all these reasons, prospective studies that would be conducted in the future might eliminate these deficiencies. Nevertheless, considering the limited number of studies in the literature on this subject, it can be thought that our study will contribute to the literature.

Conclusion

In this study, it was determined that PPH3, Ki-67, P53 could not be used as predictive molecular markers in determining recurrence in patients with high-risk NMIBC. Standard evaluation methods can only be developed in the presence of standard immunohistochemical staining methods. Other molecular markers are needed that can be used to predict the recurrence and progression of bladder tumors. There is a need for prospective and high quality studies on this subject.

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Ethics

Ethics Committee Approval: The study protocol was approved by the Cerrahpaşa Medical Faculty Ethics Committee (83045809/604.01/02-218946).

Informed Consent: The consent form was filled in by all participants and their families.

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Authorship Contributions

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

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Original Article

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Intravesical Mitomycin-C with Bladder Wall Hyperthermia in Intermediate and High-risk Non-muscle Invasive Bladder Cancers: Prospective Clinical Trial with a Single-treatment Arm

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Abstract

Objective: Bacillus Calmette-Guérin (BCG) limited availability, cost, and allergic response in some patients limit its use, leading to the search for alternative agents. We aimed to present the outcomes of intermediate- and high-risk non-muscle invasive bladder cancers treated with bladder wall thermochemotherapy (BWT) system via a single-arm prospective study.

Materials and Methods: Overall, 44 patients were enrolled and subjected to a treatment with mitomycin-C and BWT for 6 weeks, followed by a monthly maintenance for up to 1 year. The recurrence rate, progression rate, recurrence-free survival, progression-free survival, and side effects were evaluated.

Results: In the intermediate- and high-risk groups, the median follow-up duration was 14 and 17 months; recurrence rates were 28.6% and 23.3%; progression rates were 7.1% and 23.3%; the recurrence free survival at the 24th month were 78.6% and 80.0% and the progression free survival at the 24th month were 92.6% and 76.7%, respectively. All the patients suffered from dysuria lasting for 2-3 days; five of the 442 BWT application developed allergic reactions requiring treatments with oral agents.

Conclusion: BWT showed comparable recurrence and progression rates, but seemed safer than BCG when our findings were compared to those of published studies. It could be an alternative for individuals who are not suitable for BCG or in a case of BCG unavailability.

Keywords: Bladder, cancer, intravesical, mitomycin, thermo

Introduction

Among all cancers, bladder cancer (BC) ranks 10th in incidence among both sexes. At the time of diagnosis, most BCs (70%-80%) are non-muscle invasive (NMI) (1,2). It is advisable to stratify them into low-, intermediate-, and high-risk groups based on their clinical features, pathological stages, and grades because NMI-BC patients show varying risks in terms of recurrence and progression. For the low-risk group, one dose of intravesical chemotherapy immediately after transurethral resection of the BC (TURBT) is sufficient in almost all patients. However, for the intermediate- and high-risk groups, it is quite challenging to tailor the appropriate treatment. Although intravesical chemotherapy prevents recurrences, it is not as effective in preventing their progression as intravesical Bacillus Calmette-Guérin (BCG) for the intermediate-risk group. Intravesical BCG with a one-year maintenance was demonstrated to be superior to intravesical chemotherapy in preventing BC progression in the intermediate-risk group. Intravesical BCG with 1-3 years of maintenance or radical cystectomy is another treatment option suggested for the high-risk group (3). However, the fact that BCG has serious side effects and is not always readily available from the market has escalated the search for new alternatives such as intravesical mitomycin-C (MMC) application with

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hyperthermia [thermochemotherapy (TCT)]. Several studies have compared TCT with intravesical chemotherapy alone or with BCG, which employed a microwave technology as the heating system (4,5,6). A limited number of studies have employed a conductive heating system (7,8).

This paper presents the recurrence and progression outcomes of intermediate- and high-risk NMIBC treated with the bladder wall TCT system.

Materials and Methods

Patient Selection

The study was designed as a prospective study with a single-treatment arm, including MMC with TCT. The study group included NMIBC patients who were newly diagnosed or followed-up as recurrent patients between January 2014 and February 2015. They were stratified into intermediate and high-risk groups according to the criteria defined in the European Association of Urology Guidelines on "non-muscle invasive urothelial carcinoma of bladder" (3). All of them had been histologically diagnosed with urothelial carcinoma. The exclusion criteria included low bladder capacity (<150 mL), increased post-voiding residual urine (>150 mL), untreatable or uncontrollable urinary tract infection, history of urethral stricture, presence of bladder diverticula >1 cm size, pathology other than urothelial carcinoma, World Health Organization performance status >2, and upper urinary tract urothelial carcinoma diagnosis. Before the application of TCT, complete TURBT was performed. Restaging TURBT (RE-TURBT) was conducted within four weeks for patients with initial T1 pathology. Postoperative single-dose intravesical chemotherapy was applied to all the patients. The first TCT instillation was applied at 1 month following the TURBT or the RE-TURBT.

Thermochemotherapy Application and Treatment Schedule

The bladder wall TCT (BWT) system (Elmedical, Hod-Hasharon, Israel) was used as a conductive heating modality. MMC (40 mg; MMC Kyowa Hakko Kogyo Co., Ltd., Tokyo, Japan) was mixed with 50 mL of 0.9% saline solution and applied using a disposable silicone 20 Fr 3-way TCT catheter (UniThermia catheter; Elmedical). In each session, the bladder was irrigated with MMC solution at 42 °C - 45 °C for 45 minute via the BWT system. The treatment schedule consisted of an initial 6-week instillation, followed by control cystoscopy and urine cytology in the 3rd month and monthly instillations for up to 1 year. Urine cytology and cystoscopy were performed every three months. The samples were collected from the suspected areas during cystoscopy. At the end of the first year, a control cystoscopy with random bladder biopsies was conducted. During the second year, routine controls were conducted every three months. Subsequently, follow-ups were performed every six months. In case of the development of any complication in a patient, TCT was discontinued. Before each instillation of TCT, clear urine cultures were obtained from all the patients. No prophylactic anticholinergic agent was administered prior to the intravesical TCT. If TURBT pathology was Ta or T1 during the follow-up, it was accepted as a recurrence. If it was carcinoma *in situ* or T2, it was accepted as a progression. All the adverse events observed during the study were recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (9).

All the study protocols were approved by the local ethical committee at our institution on July, 4th, 2014 (IRB Approval number: 2014/387). An informed consent was obtained from all the patients.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 22 for windows (IBM, NY, USA) software package. Normality test was done with Shapiro-Wilks test. Survival analysis was done with Kaplan-Meier tests and survival tables.

Results

In total, 44 patients (females =2, rest were males) were enrolled in this study, of which 14 showed intermediate-risk NMIBC and 30 showed high-risk NMIBC. The patients' characteristics are summarised in Table 1. Eight patients had a history of intravesical chemotherapy or BCG. The median follow-up period was 14 months in the intermediate-risk group and 17 months in the high-risk group. In both groups, the median number of BWT instillation was 9. The recurrence rate was 28.6% (4/14) in the intermediate-risk group and 23.3% (7/30) in the high-risk group. Progression was detected in only one (7.1%) patients from the intermediate-risk group and seven (23.3%) patients from the high-risk group. Four patients showed progression to the T2 stage, three of whom received radical cystectomy and the remaining one patient was at the metastatic stage clinically and preferred a bladder-preserving treatment modality (chemo-radiotherapy). The progression pathology was carcinoma *in situ* in the remaining four patients. The initial pathology before TCT was also carcinoma *in situ* in two of them. Radical cystectomy was suggested to patients with carcinoma *in situ* after TCT, but they preferred intravesical BCG. In the intermediate- and high-risk groups, the recurrence free survival rates at the 24th month were 78.6% and 80% and the progression free survival rates at the 24th month were 92.6% and 76.7%, respectively. The Kaplan-Meier curves of recurrence-free survival and progression-free survival are shown in Figures 1 and 2.

After TCT, no patient reported bladder spasms, bladder pain, and urgency or frequency. However, all the patients reported dysuria resulting from catheterisation that lasted for 2-3 days. No action was taken other than the conservative management for dysuria. Overall, 442 TCT applications were conducted. Allergic reactions (skin rash and hyperemia) were observed in five out of the 442 TCT treated patients (1.12%), who were treated with oral anti-histaminic agents. None of these allergic attacks broke out with the first TCT, but the study protocol was discontinued for these patients. Urethral stricture developed in one patient after the 9th TCT application, upon which TCT was discontinued for them. It was hard to confirm TCT application as the reason for urethral stricture because this patient had BC

Table 1. Characteristics of intermediate and high-risk patients			
	Intermediate n=14	**High n=30**	**Overall n=44**
Gender			
• Male	13 (92.9%)	29 (96.7%)	42 (95.5%)
• Female	1 (7.1%)	1(3.3%)	2 (4.5%)
Age in years	68.14±10.75	64.73±8.74	65.82±9.43
Previous intravesical treatment			
• No previous treatment	12 (85.7%)	24 (80%)	36 (81.8%)
• MMC	1 (7.1%)	1 (3.3%)	2 (4.5%)
• BCG	1 (7.1%)	3 (10%)	4 (9.1%)
• MMC + BCG	0	2 (6.7%)	2 (4.5%)
Grade			
• Low Grade	14	16 (53.3%)	30 (68.2%)
• High Grade	0	14 (46.7%)	14 (31.8%)
Stage			
• Ta	14	6 (20%)	20 (45.5%)
• T1	0	22 (73.3%)	22 (50%)
• CIS	0	2 (6.7%)	2 (4.5%)
Follow-up in months -median (min-max)	14 (3-41)	17 (2-47)	16.5 (2-47)
# of BWT session-median (min-max)	9 (2-16)	9 (4-16)	9 (2-16)
Recurrence	4 (28.6%)	7 (23.3%)	11 (25%)
Progression	1 (7.1%)	7 (23.3%)	8 (18.2%)
Adverse event			
• Allergic reaction	1 (7.1%)	4 (13.3%)	5 (11.4%)
• Urethral stricture	0	1 (3.3%)	1 (2.3%)
Treatment after progression			
• Radical cystectomy	1 (7.1%)	2 (6.7%)	3 (6.8%)
• Radiotherapy & chemotherapy	0	1 (3.3%)	1 (2.3%)
• BCG with maintenance	0	4 (13.3%)	4 (9.1%)
MMC: Mitomycin-C, BCG: Bacillus Calmette-Guerin, CIS: Carcinoma *in situ*, BWT: Bladder wall thermotherapy, min: Minimum, max: Maximum			

for >5 year and a history of intravesical MMC and BCG. All these adverse events were of ≤ grade 2 according to CTCAE v4.0.

Discussion

The search for new agents and administration routes for intravesical treatment to prevent recurrence and progression in NMIBC is actively ongoing. MMC, which is safer than BCG, does not have the same efficacy to prevent progression as it does for recurrence (10).

Accordingly, in an attempt to increase its efficacy, MMC application with hyperthermia has gained much attention for application and research since the past 20 years. Colombo et al. (5) reported recurrence rates of MMC alone and TCT + MMC in a median 90 months of follow-up as 80% and 14%, respectively, whereas the progression rates were 15% and 8.6%, respectively.

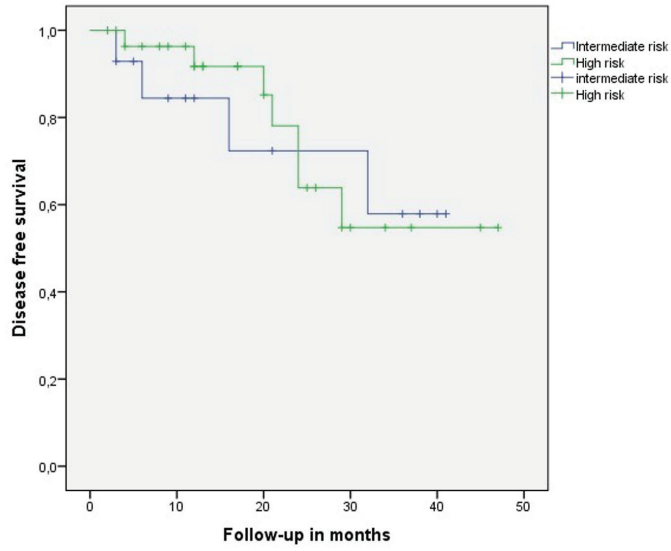


Figure 1. Kaplan-Meier curve of recurrence free survival in both groups

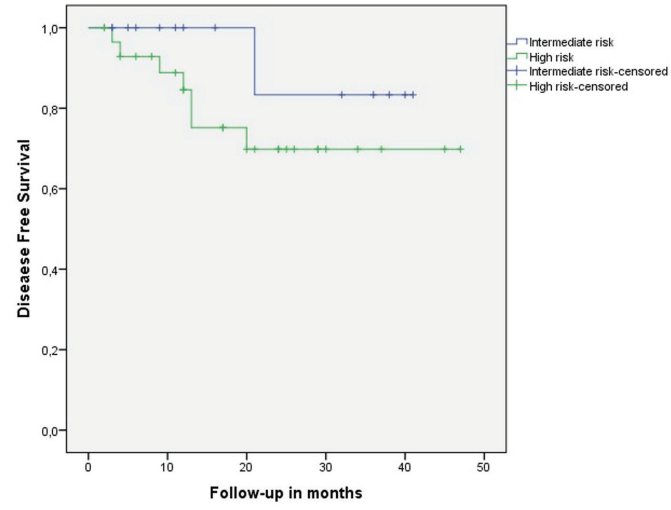


Figure 2. Kaplan-Meier curve of progression free survival in both groups

Another study (4) that used the same hyperthermia system reported a recurrence rate of 9% in the TCT group at the end of a medianof 289 days of follow-up. In the multicentric phases 1 and 2 study of the conductive heating modality, the recurrence and progression rates were stated as 35.3% and 23.5% with a median follow-up of 41 months (7). In another cohort using a conductive heating system with 40 high-risk NMIBC patients, the recurrence rate was 32.5% and the median recurrence-free survival period was 23 months (8). In a randomised prospective study, the recurrence-free survival at the 24th month was 81.8% for TCT + MMC and 64.8% for the BCG arm. Progression was observed in one patient with BCG (1.4%). In addition, in the case of CIS, no statistically significant difference was noted between the BCG and TCT + MMC groups (6). Unlike in the studies in the literature, this study evaluated the intermediate- and high-risk NMIBC groups separately. Initially, we planned to compare the TCT + MMC and BCG groups, but the unavailability of BCG did not allow it. The recurrence rates of 14 intermediate-

risk and 30 high-risk patients in this study were 28.6% and 23.3%, respectively. The progression rates were 7.1%, 23.3%, respectively. As compared with the published series, the recurrence rate was better, although the progression rate was higher in the study group.

Considering the adverse events, MMC showed a better profile than BCG. In a meta-analysis comparing intravesical treatments, 27%-84% granulomatous cystitis or lower urinary tract symptoms (dysuria, urgency and frequency), 21%-72% macroscopic haematuria, and 27%-44% fever were reported as BCG side effects (10). In another study that compared MMC + TCT with BCG application, bladder spasm (14.4%) and bladder pain (14.1%) were noted as the main side effects in the MMC arm, whereas dysuria (11.7%), nocturia (10.3%), and frequency (9.9%) were the side effects noted in the BCG arm. In this study, the sole adverse event was mild allergic reactions treated with oral agents and dysuria lasting for 2-3 days. This symptomatic process was treated conservatively. All the side effects recorded were of a grade ≤2.

Study Limitations

The limitations of this study were the small sample size and the single-arm approach. To attain more powerful oncologic results, there is no doubt the need for randomized double arm studies with more patients comparing MMC + BWT and BCG.

Conclusion

Comparing our results with that of the literature, MMC with BWT had comparable recurrence and progression rates as BCG, with the number of side effects being significantly lower than those with BCG. Thus, MMC + BWT can be considered as an alternative treatment option for selected cases in whom BCG cannot be applied or is not available. Furthermore, MMC + BWT costs less and produces lesser side effects compared with other hyperthermia systems, making it an attractive option.

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Ethics

Ethics Committee Approval: The study protocol was approved by the Erciyes University Clinical Research Ethics Committee (decision number: 2014/387, date: 04.07.2014).

Informed Consent: An informed consent was obtained from all the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.S., A.D., Design: G.S., Ak.D., A.D., Data Collection and Processing: Ş.T.T., T.D., Ak.D., Analysis and Interpretation: A.D., A.T., T.D., Literature Search: Ş.T.T., Writing: A.D.

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Original Article

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Influence of Primary or Secondary Muscle Invasive Bladder Cancer on Oncologic Outcomes After Radical Cystectomy

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Abstract

Objective: In this study, we aimed to investigate the oncologic outcomes of patients who were diagnosed with primary (muscle invasive cancer at the time of diagnosis) and secondary (cancer that showed progression from non-muscle invasive bladder cancer) muscle invasive bladder carcinoma (MIBC) before radical cystectomy (RC).

Materials and Methods: Patients who underwent RC at our clinic for MIBC between July 2008 and June 2017 were included in the study. They were divided into two groups based on their diagnosis as primary and secondary MIBC. Their clinical, pathological, and oncologic data (upstaging, adjuvant chemotherapy, overall mortality, overall survival, cancer-specific mortality, and cancer-specific survival) were evaluated retrospectively.

Results: A total of 80 patients underwent RC due to bladder cancer with a mean age of 64.4±7.8 years (range: 42-83 years) and a mean follow-up time of 32.9±32.1 months (range: 1-113 months). The overall and cancer-specific survivals of the patients were 64.7±6.6 and 74±6.8 months, respectively. Sixty-five and 15 patients were evaluated in the primary and secondary MIBC groups, respectively. Lymph node metastasis was higher in primary MIBC group (p=0.031). Although, there were no statistical differences between the groups, in secondary MIBC group, the overall survival (67.3±7.2 months vs 42.5±8.4 months; p=0.835) and cancer-specific survival (77.6±7.4 months vs 46.6±8.6 months; p=0.546) were lower, while the overall mortality (44.6% vs 53.3%; p=0.372) and cancer-specific mortality (32.3% vs 46.7%; p=0.293) were higher compared to primary MIBC group.

Conclusion: The pre- and postoperative pathological T stages were similar between the groups, whereas postoperative lymph node positivity was lower for secondary MIBC patients. The mortality was higher and overall and cancer-specific survivals were lower in secondary MIBC patients; however, these findings were not statistically significant.

Keywords: Bladder cancer, muscle invasive bladder cancer, oncologic outcomes, radical cystectomy, secondary muscle invasive bladder cancer

Introduction

According to the latest statistics, bladder cancer is the fourth most common cancer in men and the eighth in mortality (1). Approximately 75% of patients are non-muscle invasive bladder cancer (NMIBC), while 25% are muscle invasive bladder cancer (MIBC) at the time of diagnosis (2,3). The best treatment method for MIBC is extended lymph node dissection and radical cystectomy (RC) with urinary diversion. In the NMIBC group, especially in high risk patients, in addition to conservative treatment, RC can also be recommended due to the 30-50% risk of progression to MIBC (4-6). When we look at the MIBC patients we come across two groups of patients. These are patients who have been previously diagnosed as having high-risk NMIBC and have progressed to MIBC with muscle tissue invasion in their follow-up (secondary MIBC), and those who have been diagnosed as having primary MIBC at the time of initial diagnosis, and the best treatment modality is RC for both two groups (6,7). The requirement for chemotherapy (CT) before RC (neoadjuvant) or after RC (adjuvant) varies according to patient characteristics and physician's selection (8). When we look at the RC series, it is seen that 57% of the patients treated

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with RC due to primary MIBC and the rest are secondary MIBC (9). However, the oncological results of these two groups of patients are still discussed in the literature with conflicting results (7). For this reason, in this article, we investigated the post-RC oncological results of patients with primary and secondary MIBC who were diagnosed as having MIBC before RC.

Materials and Methods

Patients who underwent RC in our clinic due to MIBC between July 2008 and June 2017 were retrospectively analyzed. The study was retrospective and ethics committee approval was not applied for. Patients who had complete data and were followed up in our clinic and diagnosed as having MIBC (urothelial carcinoma) after transurethral resection (TUR-BT) were included in the study. Patients with non-urothelial bladder cancer, upper urinary tract tumor, NMIBC (Tis, Ta and T1), clinical T4 tumors, and missing follow-up data were not included in the study. The general characteristics, preoperative, peroperative and postoperative data of the patients were reviewed. General clinical characteristics of the patients (age, gender, American Society of Anesthesiologists score, Eastern Cooperative Oncology Group performance score, Charlson comorbidity index, presence of hydronephrosis), peroperative data (operation time, urinary diversion preference), pathological data (preoperative T stage and, grade, presence of carcinoma *in situ* (CIS), presence of squamous differentiation, postoperative T stage and grade, surgical margin positivity, lymph node positivity, number of dissected lymph nodes number and percentage of positive nodes, nodes, prostate, urethra and ureter invasions, lymphovascular invasion and perineural invasion) and oncological outcomes (upstaging, adjuvant CT, overall mortality and survival time, cancer-specific mortality and survival time) were evaluated. The patients were divided into two groups as primary and secondary MIBC. Patients with muscle invasion at the time of diagnosis [patients having muscle invasion according to the pathology report of the first TUR-BT (± re-TUR)] were included in the primary MIBC group. In the secondary MIBC group, patients who were followed up due to NMIBC and whose muscle invasion was detected in the last TUR-BT pathology were included.

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences, version 20.0 (SPSS, Chicago, Ill) program. The primary and secondary MIBC groups were compared using the Mann-Whitney U and chi-square tests. Additionally, Kaplan-Maier survival analysis and log-rank test were used for overall survival and cancer-specific survival data. The data in the tables were given as mean ± standard deviation, and the statistical results were analyzed over the median data. Statistical significance was accepted as p-value <0.05.

Results

In our clinic, among 167 patients who underwent RC for urothelial carcinoma of bladder 80 patients, all of whom were followed up in our clinic and who had complete data, were evaluated. Eight (10%) of the patients were female. The mean age was 64.4±7.8 (42-83) years and the mean follow-up period was 32.9±32.1 (1-113) months. The mean overall and cancer-specific survivals of the patients were 64.7±6.6 and 74±6.8 months. Sixty five and 15 patients were evaluated in primary and secondary MIBC groups, respectively. Patient characteristics and preoperative data and comparison results of patients with primary and secondary MIBC are given in Table 1. In the comparison between groups, patient characteristics and preoperative data were found to be similar. Preoperative, peroperative and postoperative pathological findings and comparison results of the groups are given in Table 2. Among the pathological data, lymph node metastasis was found to be higher in the primary MIBC group (p=0.031). While the number of dissected lymph nodes was similar between the groups (p=0.726), the number and percentage of positive lymph nodes were higher in the primary MIBC group (p=0.033 and p=0.041). Other pathological findings, urinary diversion preference and adjuvant CT status, and oncological results were similar between the groups (Tables 2 and 3). In primary MIBC group, Overall survival (67.3±7.2 months for primary

Table 1. Patient characteristics, preoperative findings and comparison results in primary and secondary muscle invasive bladder carcinoma groups

		Primary MIBC (n=65)	Secondary MIBC (n=15)	p
Age (years), mean ± SD (min-max)		63.8±8.3 (42-83)	67.2±4 (60-74)	0.081
Gender, n (%)	Female	5 (7.7)	3 (20)	0.166
	Male	60 (92.3)	12 (80)	
TUR number, mean ± SD (min-max)		1 (re-TUR in 5 patients)	2.9±1.1 (2-6)	-
Follow-up time, mean ± SD (min-max)		33.2±33.8 (0.3-119.6)	31.6±24.8 (2.1-77.8)	0.618
ASA score, n (%)	1	5	0	0.145
	2	43	9	
	3	16	5	
	4	1	1	
ECOG performance score, n (%)	0	17	3	0.199
	1	35	5	
	2	11	5	
	3	2	2	
	4	0	0	
Charlson comorbidity index, n (%)	0	1	0	0.147
	1	3	0	
	2	14	0	
	3+	47	15	
Preoperative hydronephrosis, n (%)		27 (41.5)	4 (26.7)	0.210
Hydronephrosis, n (%)	Unilateral	22 (92.3)	3 (20)	0.598
	Bilateral	5 (7.7)	1 (6.7)	

Mann-Whitney U test, chi-square test and Fisher's Exact test. SD: Standard deviation, MIBC: Muscle invasive bladder carcinoma, ASA: American Society of Anesthesiologists, ECOG: Eastern Cooperative Oncology Group, min: Minimum, max: Maximum

Table 2. Preoperative, peroperative and postoperative findings and comparison results in primary and secondary muscle invasive bladder carcinoma groups

		Primary MIBC (n=65)	Secondary MIBC (n=15)	p
Preoperative tumor grade, n (%)	Grade 2	3 (4.6)	1 (6.7)	0.572
	Grade 3	62 (95.4)	14 (93.3)	
CIS positivity, n (%)		21 (32.3)	4 (26.7)	0.464
Squamous differentiation, n (%)		10 (15.4)	3 (20)	0.458
Operation time (hour)		5.8±1.2 (3-8)	5.6±2.3 (3-9)	0.502
Postoperative T stage, n (%)	T0	3 (4.6)	2 (13.3)	0.197
	Tis-Ta-T1	5 (7.7)	4 (26.7)	
	T2	36 (55.6)	6 (40)	
	T3-T4	21 (32.3)	3 (20)	
Postoperative tumor grade, n (%)	1	1 (1.5)	2 (13.3)	0.101
	2	2 (1.5)	0 (0)	
	3	57 (87.7)	10 (66.7)	
Surgical margin positivity, n (%)		11 (16.9)	1 (6.7)	0.323
Number of dissected lymph nodes		12.5±3.9	12.1±4.8	0.726
Number of positive lymph nodes		0.65±1.3	0	0.033
Lymph node metastasis, n (%)		18 (27.7)	0 (0)	0.031
Percentage of positive lymph nodes		5.8±12.6	0	0.041
Prostate invasion, n (%)		7 (10.8)	0 (0)	0.253
Urethra invasion, n (%)		5 (7.7)	1 (6.7)	0.707
Ureteral invasion, n (%)		18 (27.8)	2 (13.3)	0.208
Lymphovascular invasion, n (%)		16 (24.6)	1 (6.7)	0.061
Perineural invasion, n (%)		9 (13.8)	1 (6.7)	0.349
Diversion type, n (%)	Ureterocutaneostomy	20 (30.8)	8 (53.3)	0.177
	Diversion	45 (69.2)	7 (46.7)	

Mann-Whitney U test and chi-square test. MIBC: Muscle invasive bladder carcinoma, CIS: Carcinoma *in situ*

MIBC and 42.5±8.4 months for secondary MIBC, p=0.835) and cancer specific survival (77.6±7.4 months for primary MIBC and 46.6±8.6 months for secondary MIBC, p=0.546) were higher and mortality rates (overall mortality 44.6% vs 53.3%, p=0.372; cancer specific mortality 32.3% vs 46.7%, p=0.293) were lower than secondary MIBC group, but there was no statistically significant difference between the two groups. The overall and cancer specific survival curves of the patients are given in Figure 1 and Figure 2.

Discussion

In comparisons between the primary and secondary MIBC groups; pathological T stage, tumor grade, surgical margin positivity and the number of dissected lymph nodes were similar between the groups, while number of lymph node positivity and percentage of lymph node positivity were higher in the primary MIBC group. When we looked at the oncological results, although there was no statistically significant difference, the numerical differences between the groups were remarkable. Accordingly, although the rates of T2-4 N + patients and adjuvant CT were higher in the primary MIBC group; the overall survival (67.3±7.2 months vs 42.5±8.4 months; p=0.835) and cancer-specific

Table 3. Postoperative findings, oncological results and comparison results of primary and secondary muscle invasive bladder carcinoma groups

		Primary MIBC (n=65)	Secondary MIBC (n=15)	p
Up-staging, n (%)		22 (33.8)	4 (26.7)	0.418
Stage change, n (%)	Up-staging	22 (33.8)	4 (26.7)	0.138
	Down-staging	8 (12.3)	5 (33.3)	
	No change	35 (53.8)	6 (40)	
Adjuvant chemotherapy, n (%)		16 (24.6)	1 (6.7)	0.114
Overall mortality, n (%)		29 (44.6)	8 (53.3)	0.372
Overall survival		67.3±7.2	42.5±8.4	0.835
Cancer specific mortality, n (%)		21 (32.3)	7 (46.7)	0.293
Cancer specific survival		77.6±7.4	46.6±8.6	0.546
Length of stay		11.7±5.6	11.8±6.7	0.482

Mann-Whitney U, chi-square test and Kaplan-Maier Survival analyses.
MIBC: Muscle invasive bladder carcinoma

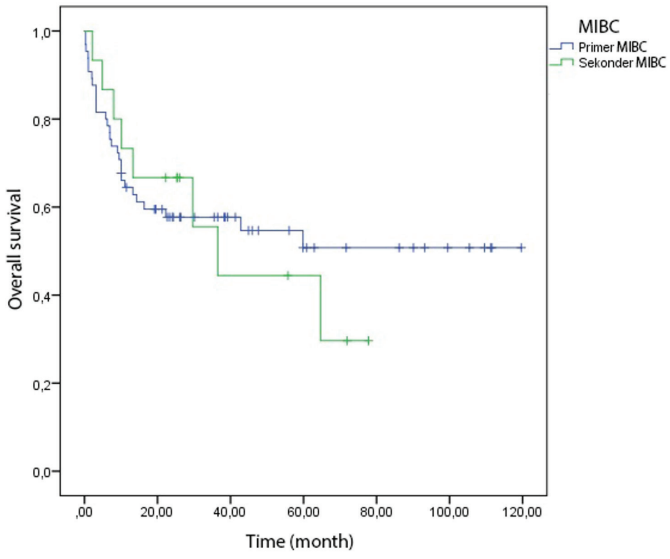


Figure 1. Overall survival curves of primary and secondary muscle invasive bladder carcinoma groups

MIBC: Muscle invasive bladder carcinoma

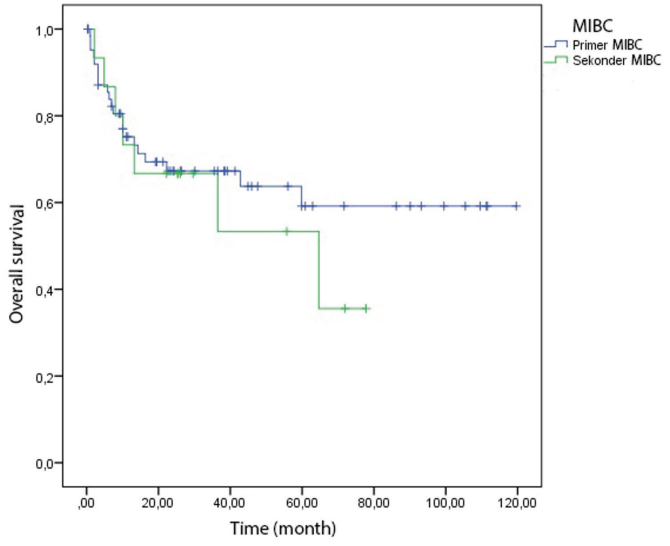


Figure 2. Cancer specific survival curves of primary and secondary muscle invasive bladder carcinoma groups

MIBC: Muscle invasive bladder carcinoma

survival (77.6±7.4 months vs 46.6±8.6 months; p=0.546) were lower, overall mortality (44.6% vs 53.3%; p=0.372) and cancer specific mortality (32.3% vs 46.7%; p=0.293) were higher in the secondary MIBC group without reaching a statistical significance.

In a study conducted by Moschini et al. (10) with 768 patients with primary and secondary (progressive) MIBC, 10-year recurrence-free survival (43% vs 36%; p=0.01), cancer specific survival (43% vs 37%; p=0.01) and overall mortality (35% vs 28%; p=0.03) results were shown to be worse in the secondary MIBC group. On the other hand, in a study by Aziz et al. (11), cancer-specific survival was similar in primary and secondary MIBC, while subgroup analysis of secondary MIBC showed that high European Organization for Research and Treatment of Cancer (EORTC) score was associated with short cancer-specific survival. In that study, it was emphasized that the EORTC risk score was not only associated with the progression to MIBC but also with the results after RC and the importance of early RC in these patients was highlighted (11). In a recently published meta-analysis evaluating 13 important studies, it was reported that oncologic results were worse in patients with secondary MIBC compared to patients with primary MIBC (7). Although early RC was emphasized in patients with secondary MIBC, it was also emphasized that it could not be routinely recommended in all patients with NMIBC (7). Considering the heterogeneity and progression-related factors (high grade, pT1 stage, multifocality, tumor diameter (>3 cm), CIS, complete non-responsiveness and P53 expression) in addition to the organ-sparing approach was important in disease management (7,12,13). Therefore, it can be concluded that oncological results may be poor after diagnosis of MIBC especially in patients with high risk of progression and that early RC is an important option in these patients.

Many studies have examined the time until RC after MIBC diagnosis and it has been shown that oncological results worsen as the time gets longer (14,15,16). It is also one of the questions to be asked that whether the time until RC in patients with secondary MIBC may be similarly prolonged. When the time until RC was examined in a study, it was observed that 12.5% of patients with primary MIBC had a period of >3 months, whereas this rate was 28.7% in patients with secondary MIBC (17). When we looked at the factors that may have caused this delay, neoadjuvant CT appeared as a reason. As a matter of fact, in a recent study by Pietzak et al. (18), it was shown that secondary MIBC was more resistant to neoadjuvant CT. In addition, another reason that may have prolonged this period, according to us, was that the patients became accustomed to the disease and wanted to avoid an operation with high morbidity such as RC. Therefore, it should be emphasized that the patient management should be discussed in detail with this patient group and that especially the oncological results may deteriorate. When we returned to the study conducted by Pietzak et al. (18), we saw that there were genomic differences between primary and secondary MIBC. In that study, 288 patients (245 patients with primary MIBC and 43 with secondary MIBC) who received neoadjuvant CT out of 2105 patients who underwent RC have been evaluated. Mortality developed in 103 of the patients with a median follow-up of 4 years. When the pathological responses were examined, it has been observed that the neoadjuvant chemo-response was lower in the secondary MIBC group compared to the primary MIBC group (45% vs 26%). At the same time, recurrence-free survival, cancer-specific survival and overall survival were also reported to be low in this group. In the study, *ERCC2, ATM, FANCC* and *RB1* gene mutations that may be related to neoadjuvant CT hve been also examined. Especially, the ERCC2 gene has been found to be lower in the secondary MIBC group (11% vs 1.8%, p=0.044). Also, while KMT2D change was more frequent in primary MIBC (23% vs 10%, p=0.013), STAG2 (7.8% vs 17%, p=0.014) and TSC1 (5.5% vs 14%, p=0.007) changes were more frequent in secondary MIBC (18). In the light of all this information, we see that secondary MIBC behaves differently from primary

MIBC both molecularly and oncologically. Therefore, besides the standard approach, disease-specific approaches should be developed for this patient group. When we examine the points that need to be emphasized, neoadjuvant CT and early RC in secondary MIBC should be investigated in large series, new agents as neoadjuvant options should be investigated and RC option should be discussed in the high risk NMIBC group.

Study Limitations

Considering the limitations of our study, the low number of all patients in the study and low number of patients in the secondary MIBC group were observed as important limitations. Our secondary MIBC rate (18.7%) was found to be lower than retrospective large series (31.7-43%) (7,9,10,18,19). However, our rate was observed to be similar to prospective series (14.9-23.4%) (11,17,18). Although the number of patients was small, the fact that patients with complete data were examined in our study, partially reduced the possibility of bias. Therefore, although no significant difference was observed in terms of the oncological results, the existence of significant survival differences between the groups showed that our results could be taken into account.

Conclusion

Pathological T stage after RC was similar in primary and secondary MIBC was similar, lymph node positivity was lower, mortality was higher, overall survival and cancer specific survival were lower in secondary MIBC statistically. This situation shows us that we should be careful in patient management both before and after the development of muscle invasion in patients with secondary MIBC and that early RC is an important option. Nevertheless, the findings of our study should be examined in larger series and with molecular mechanisms.

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Authorship Contributions

Concept: A.E., B.G., T.D., Design: S.Ç., Data Collection and Processing: İ.H.B., Analysis and Interpretation: E.Ş., S.Ç., Literature Search: İ.B., Writing: S.Ç., A.E.

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Original Article

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The Relationship Between Vitamin D Gene Polymorphisms and the Diagnosis of Prostate Cancer in Patients with High Prostate-Specific Antigen Value

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Abstract

Objective: To investigate the effects of vitamin D levels and vitamin D receptor (VDR) *BsmI, FokI, TaqI,* and *ApaI* gene polymorphisms on prostate cancer (PCa) diagnosis in Turkish men with high prostate-specific antigen (PSA) levels during screening.

Materials and Methods: Patients who were admitted to the outpatient clinic with elevated PSA levels and were scheduled for transrectal prostate biopsy were included. Patients diagnosed with PCa were divided into two groups of either localized disease (low/intermediate/high risk) or metastatic disease for subgroup analysis. The control group comprised patients whose biopsies revealed benign pathologies. Blood samples were collected from each patient after 12 hours of fasting before the prostate biopsy. Vitamin D levels and *VDR* gene polymorphisms were determined by ECLIA method and restriction fragment length polymorphism analysis, respectively.

Results: A total of 77 patients (PCa, 39; benign, 38) were included in the study. The frequencies of BsmI, FokI, TaqI, and ApaI genotypes for PCa and benign groups were evaluated. Vitamin D deficiency was detected in 88.6% and 94.9% of the benign and PCa groups, respectively (p=0.176). The FokI Ff and BsmI bb genotypes, and FokI FF and BsmI Bb genotypes were found to be more common in the PCa and benign groups, respectively. ApaI Aa and TaqI Tt were found to be more frequent in both groups. In patients with metastatic PCa; BsmI Bb genotype, ApaI Aa genotype, and TaqI Tt genotypes were found to be more common.

Conclusion: Although BsmI Bb genotype, ApaI Aa genotype, and TaqI Tt genotypes were more commonly found in patients with metastatic PCa, further studies with increased sample sizes are needed to support this relationship in the Turkish PCa population.

Keywords: Prostate cancer, vitamin D, gene polymorphism

Introduction

Globally, prostate cancer (PCa) is the 2nd most common cancer (13%) and 5th most common lethal malignancy (6.7%) in men per the GLOBOCAN data (1). Its etiology is multifactorial and includes factors like age, ethnicity, family history, environment, and genetic predisposition. Epidemiological evidence has suggested that low exposure to sunlight and vitamin D (vitD) deficiency may be one of the risk factors for PCa mortality (2). The active form of vitD inhibits the proliferation of human PCa cell lines in experimental studies (3). The anti-proliferative effect of vitD is regulated through a pathway involving vitamin D receptor (VDR), a member of the nuclear steroid hormone receptor family (4). The *VDR* gene is located on chromosome 12q12-q14. Some of the single-nucleotide polymorphisms (SNPs) of *VDR* gene are believed to be related with PCa. The most frequently studied SNPs are rs1544410 (BsmI), rs2228570 (FokI), rs731236 (TaqI), and rs7975232 (ApaI) polymorphisms (5).

Our aim was to investigate the effects of vitD levels and *VDR* gene polymorphisms (BsmI, FokI, TaqI, and ApaI) on PCa diagnosis in Turkish men with high prostate-specific antigen (PSA) levels during screening.

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Materials and Methods

Blood samples of 77 patients who reported to our outpatient clinic with high PSA levels were examined. Only those patients who did not have a previous history of cancer were included. Additionally, the study was conducted during the winter months to avoid the fluctuations in vitD levels. PCa diagnosis was made by ultrasound guided multifocal prostate biopsy that is considered as the gold standard. Patients diagnosed with PCa were further grouped into those with localized disease (low/intermediate/high risk) or metastatic disease for subgroup analysis (6); while those without PCa comprised the benign group.

The collected blood samples were centrifuged at 1,300 x g for 10 minutes and kept at -20 °C to be analyzed for 25(OH) D levels that were determined using an HPLC method (Thermo Finnigan, Germany) and commercially produced 25(OH)D extraction kit, calibrator, and control sera (Zivak Technologies, Turkey). Average intra- and inter-assay coefficients of variation for the indicated reference ranges of $25(OH)D_2$ (24.6-80.7 ng/mL) and $25(OH)D_3$ (21.5-75.5 ng/mL) were below 5%, and both $25(OH)D_2$ and $25(OH)D_3$ demonstrated linear correlation up to 200 ng/mL.

Polymorphisms were analyzed by collecting 6 mL whole blood samples into EDTA containing tubes (Becton Dickinson, USA) and stored at -20 °C until the DNA isolation procedure was performed.

DNA isolation was performed using a salt (ammonium acetate) precipitation method (7), while for the determination of *SNPs* gene, polymerase chain reaction (PCR)-restriction fragment length polymorphism method was used.

The PCR was performed using a thermal cycler (Eppendorf Mastercycler, USA) (Table 1) (8,9). PCR products were digested with ApaI, FokI, BsmI (Thermo- Scientific, USA), and TaqI (Fermantes, Lithuania) restriction enzymes. The digested products were analyzed on polyacrylamide gel (Vertical electrophoresis systems, Bio-Rad, USA) followed by silver staining (Carlo Erba, Italy).

The study has been approved by the Marmara University Clinical Research Ethics Committee (the protocol number: 09.2013.0157) and conducted in conformity with the Declaration of Helsinki in 1995. Written informed consent were obtained from all patients included in the study. In addition the study was supported by Marmara Universtity Scientific Research Projects Committee with the project number: SAG-B-041213-0442.

Statistical Analysis

Data was analysed using SPSS 17.0 and MedCalc 12.3.0 programs. Visual graphs (histograms etc) and appropriate statistical tests (Kolmogorov-Smirnov and Shapiro-Wilk) were used for the evaluation of the normality of data. Student's t-test or Mann-Whitney U test was used for the comparison of mean values of 2 independent groups.

Results

A total of 77 patients with high PSA levels (benign, 38; PCa, 39) were included in the study. Among the PCa subgroups, there were 10 (13%) and 29 patients with metastatic and localized disease, respectively. In the latter; 9 (11.7%), 13 (16.9%), and 7 (9.1%) patients had low, intermediate, and high risk, respectively. Treatment modalities for non-metastatic PCa included radical prostatectomy (RP) in 12 (41.4%), active surveillance (AS) in 8 (27.6%), and radiotherapy (RT) in 8 (27.6%) patients. Biochemical PSA recurrence after definitive treatment (RP and RT) was observed in 5 (20%) patients.

The demographic data for the PCa and benign groups, including age, smoking status, and body mass index (BMI) are shown in Table 2. VitD and PSA values are shown in Table 3.

There was no statistically significant difference between the two groups in terms of age, smoking status, and BMI. The vitD levels were higher in the benign than in the PCa group (p=0.176).

Patients with VitD levels below 20 ng/mL were diagnosed with vitD deficiency that was detected in 88.6% and 94.9% of the patients in benign and PCa groups, respectively. Conversely, PSA values of benign and PCa groups were significantly different due to the contribution of the high PSA values of the metastatic PCa patients (p=0.002).

Table 1. Polymerase chain reaction conditions and primer sequences of *VDR* gene

SNPs	Primers (F: forward; R: reverse)	PCR conditions
rs7975232 (ApaI)	F: 5'-CAG AGC ATG GAC AGG GAG CAA-3' R: 5'-GCA ACT CCT CAT GGC TGA GGT CTC-3'	94 °C/5 minutes (94 °C/1 minute 65 °C/1 minute - 72 °C/1 minute for 30 cycles) 72 °C/7 minutes
rs1544410 (BsmI)	F: 5'-GGG AGA CGT AGC AAA AGG-3' R: 5'-AGA GGT CAA GGG TCA CTG-3'	94 °C/3 minutes (94 °C /1 minute 54 °C/1 minute - 72 °C/1 minute for 30 cycles) 72 °C/7 minutes
rs2228570 (FokI)	F: 5'-GAT GCC AGC TGG CCC TGG CAC TG-3' R: 5'-ATG GAA ACA CCT TGC TTC TTC TCC CTC-3'	94 °C/3 minutes (94 °C/1 minute 60 °C/1 minute - 72 °C/1 minute for 30 cycles) 72 °C/7 minutes
rs731236 (TaqI)	F: 5'-CAG AGC ATG GAC AGG GAG CAA-3' R: 5'-GCA ACT CCT CAT GGC TGA GGT CTC-3'	94 °C/5 minutes (94 °C/1 minute 65 °C/1 minute - 72 °C/1 minute for 30 cycles) 72 °C/7 minutes

PCR: Polymerase chain reaction, VDR: Vitamin D receptor, SNPs: Single-nucleotide polymorphisms

The frequencies of BsmI, FokI, TaqI, and ApaI genotypes in benign and PCa groups are presented in Table 4. The FokI Ff and BsmI bb genotypes, and the FokI FF and BsmI Bb genotypes were more common in PCa and benign groups, respectively. ApaI Aa and TaqI Tt were found with similar frequencies in both groups. However, the results were not statistically significant.

On subgroup analysis of patients diagnosed with PCa there were no significant differences (p=0.436). In patients with metastatic disease; BsmI Bb genotype, ApaI Aa genotype, and TaqI Tt genotypes were found to be more common. Conversely, BsmI bb genotype, Fok Ff genotype, ApaI aa genotype, and TaqI TT genotypes were found to be more common in patients with low risk PCa group who were candidates for AS.

Table 2. The demographic data for the benign and prostate cancer groups

	Benign (n=38)	PCa (n=39)	p-value
Age (year)	69.6±2.64	69.2±5.9	p=0.96*
Smoking status (%)	52.6	64.1	p=0.307**
Body mass index (kg/m²)	26.9±2.85	27.07±3.39	p=0.82*

*Student t-test, **chi-square test, PCa: Prostate cancer

Table 3. Vitamin D and PSA values of the groups

	Benign (n=38)	PCa (n=39)	p-value
vitD (ng/mL)	12.04±4.15	10.3±5.91	p=0.176*
PSA (ng/dL)	6.76±4.35	33.01±48.6	p=0.002*

*Student t-test, PSA: Prostate-specific antigen, PCa: Prostate cancer, vitD: Vitamin D

Table 4. The frequencies of BsmI, FokI, TaqI, and ApaI genotype for benign and prostat cancer groups

		Benign (%)	PCa (%)	p-value
ApaI	**aa**	21.2	28.9	0.747
	Aa	45.5	39.5	
	AA	33.3	31.6	
FokI	**ff**	7.9	12.8	0.43
	Ff	42.1	51.3	
	FF	50	35.9	
TaqI	**tt**	15.2	7.9	0.567
	Tt	48.5	47.4	
	TT	36.4	44.7	
BsmI	**bb**	35.1	53.8	0.17
	Bb	45.9	38.5	
	BB	18.9	7.7	

PCa: Prostate cancer

Discussion

VitD could be defined as a hormone rather than a vitamin because of the complexity and diversity of its production. It is not categorized as an essential vitamin and can be synthesized by the help of ultraviolet-B rays. VDR protein is an intracellular receptor of vitD that is coded by the *VDR* gene. VitD affects the expression of targeted *VDR* genes through these special receptors (10). It is believed to have a role in cancer pathogenesis, especially in decreasing the proliferation, invasion, angiogenesis, metastatic spread, and cellular differentiation. However its deficiency is a major public health problem across all age groups, worldwide. In our study, both PCa and benign groups were deficient in vitD, with lower levels observed in PCa than in the benign group. PCa risk has been shown to be inversely associated with vitD concentration (11). However, large-sized prospective randomized studies are required to clarify the relationship between vitD and PCa (12).

Previous studies demonstrated that *VDR* gene polymorphisms that include; FokI, BsmI, ApaI, TaqI, and Cdx2; are associated with many organ cancers including that of the urinary system (13,14,15). Onen et al. (16) evaluated vitD polymorphism for PCa only at *ApaI, TaqI*, and *BsmI* genes in the Turkish population. Similar to our findings they found that ApaI Aa, TaqI Tt, and BsmI Bb alles were the dominant genotypes in benign groups. Additionally, ApaI Aa alles were the dominant genotype in PCa patients. The ratio of other alleles and their distribution in benign and PCa groups were also similar. FokI polymorphism is also considered as a potential biomarker for PCa risk identification in Caucasians (17). In our study, the FokI Ff and FokI FF genotypes were found to be more frequent in PCa and benign groups, respectively.

Although, there are many studies regarding the relationship between PCa and *VDR* gene polymorphisms, few have compared this according to the metastatic status or risk classification of PCa. Since PCa treatment modalities vary among patients, additional guidelines are needed; especially in the low-risk groups. For patients with low-risk PCa, AS without curative treatment is a possible treatment option (6). Therefore, it is particularly important to distinguish between low-risk groups and highly aggressive metastatic groups. In our study, we evaluated our results based on the distinction between the different risk groups and metastatic disease groups.

VDR gene polymorphisms differ among ethnic populations as the alleles of metabolic genes are not equally distributed (18). PCa is also affected by genetic differences; its incidence and mortality rates are highest in Australia, Europe, and North America and lowest in Asia, especially South-Central Asian ethnic populations (1). The observed association between the VDR polymorphism and PCa risk may be substantially different among populations. However, most of the meta-analyses indicated that there is no significant association between different populations and VDR genotypes and PCa risk. This may be because of the ethnic variations in genotypes, genotyping techniques, or the limited sample size that may not have enough statistical power (19,20,21).

Although, it has been demonstrated that vitD inhibits the growth of cells obtained from benign prostatic hyperplasia (BPH) tissue, few studies have reported that VDR polymorphisms are related to the risk of BPH (22). It is impossible to exclude BPH patients from the control group with their high PSA values. Although, few studies have claimed that they excluded patients with BPH,

this may not be entirely true. While, most of the studies included BPH patients in their control group, we did not consider the presence or absence of BPH in our control group. Therefore, our comparisons were limited, and this may have led to a potential bias.

Study Limitations

In our study, blood samples were drawn from 158 patients who reported to our outpatient clinic with high PSA levels; however the polymorphism results of only 77 patients could be obtained due to cold chain failure. Therefore, we were able to analyze only half of our sample. Furthermore, we analyzed patients from the Marmara local region in Turkey to ensure genetic homogeneity. However, this region comprises the highest number of immigrants, and this could have interfered with our intended objective. Lastly, we evaluated the vitD levels during the winter season to avoid seasonal fluctuations. However, the sun exposure was the lowest at this time and that may have affected the vitD levels adversely. We were also not aware of the duration of the vitD deficiency in our patients.

Conclusion

Although, the BsmI Bb, ApaI Aa, and TaqI Tt genotypes were more commonly found in patients with metastatic PCa; the FokI Ff and BsmI bb genotypes were more commonly found across all PCa risk groups. Large-sized, well-designed epidemiologic studies that evaluate the different risk groups and metastatic PCa groups may help to highlight the complex interactions between vitD, *VDR* gene polymorphisms, and PCa.

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Ethics

Ethics Committee Approval: The study has been approved by the Marmara University Clinical Research Ethics Committee (the protocol number: 09.2013.0157) and conducted in conformity with the Declaration of Helsinki in 1995.

Informed Consent: Written informed consent were obtained from all patients included in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.A., N.Ü., Ö.B., Design: M.A., Data Collection or Processing: M.A., N.Ü., A.Y., Analysis or Interpretation: E.E., G.H., İ.T., Literature Search: İ.T., Writing: M.A., İ.T.

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Original Article

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How Does Antibiotherapy Affect the Clinical Outcomes of the Patients with High Prostate Specific Antigen? An Observational Study

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Abstract

Objective: The purpose of this observational study is to investigate the effect of urologists daily practice antibiotic usage on prostate biopsy rates and clinically insignificant cancer diagnosis rates in patients with gray-zone prostate specific antigen (PSA).
Materials and Methods: Two hundred thirty two patients who have PSA values between 2.5 and 10 ng/mL were studied prospectively. Patients convinced that he can benefit from the antibiotherapy were treated with levofloxacin 500 mg orally for 14 days by different urologist. At the end of treatment, serum PSA levels were measured again. PSA values of untreated patients were repeated after 14 days. Patients were reevaluated by same urologists with second PSA values for biopsy indication. Groups compared for biopsy rate, biopsy-to-prostate cancer detection rate, prostate cancer rate of population (Table 1, Prostate Cancer Rate 2), and Gleason 6 Prostate Cancer rate.
Results: One hundred thirty six patients were treated with levofloxacin 500 mg for 2 weeks. Ninety six patients was untreated. PSA did not change or increased in 47 (35%) of patients which treated with antibiotics. Eight-nine (65%) patients had a decrease in PSA. Fewer biopsy indications were given in the group treated with antibiotics ($p<0.001$). When the all (biopsied and non-biopsied) patient groups were taken into consideration, fewer patients were diagnosed with prostate cancer in the treatment group ($p=0.024$). In the treatment group Gleason 6 cancer was 29%. Same rate was 45% in control group.
Conclusion: Although antibiotherapy leads urologists to make less biopsy, the rate of cancer diagnosed by biopsy does not increase.
Keywords: PSA, prostate cancer, antibiotherapy

Introduction

It is more accurate to examine the relationship between two tests performed at different time points, rather than the point-by-point evaluation of laboratory tests when making clinical decisions. Manipulation of prostate specific antigen (PSA) values, especially in the gray zone (2.5-10 ng/mL), with antibiotherapy is often the preferred clinical approach by urologists (1).

Some studies have shown that PSA may decrease with the use of antibiotics and that the biopsy requirement may be absent. The pilot study was published by Bulbul et al. (2). However, the clinical benefit of PSA reduction after antibiotherapy has not yet been clearly demonstrated. Although randomized clinical trials conducted in 2016 demonstrated a limited PSA reduction advantage with antibiotherapy, no difference was detected between positive prostate biopsy results (1).

Despite the controversial findings, antibiotherapy in the presence of high PSA continues to be frequently practiced clinically. Most clinical studies have shown that the PSA change obtained by antibiotics indicates the PSA's ability to separate prostate cancer cases from benign cases. However, there are insufficient observational studies that show which patients are specifically selected for antibiotics, or the effect of antibiotic therapy on biopsy rates and clinically insignificant cancers (Gleason 6, ISUP 1).

The purpose of this observational study was to investigate the effect of daily antibiotic use on prostate biopsy rates and clinically insignificant cancer diagnosis rates in patients with gray-zone PSA.

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Materials and Methods

In 2017, the clinical processes of men older than 40 years of age who applied to the urology outpatient clinics of Cerrahpaşa Faculty of Medicine were followed-up.

Ethical approval was obtained from Cerrahpaşa Faculty of Medicine Ethics Committee with the approval number: 83045809-604.01.02.

Of the 7.200 men, 3.096 (43%) who underwent PSA screening were prospectively monitored. PSA levels of 386 patients were in the gray-zone (2.5-10 ng/mL). Fifty-four patients had a known diagnosis of prostate cancer or a recent negative pathological results detected by the transrectal ultrasound prostate biopsy-Bx or transurethral resection of the prostate. In the follow up, 136 patients received antibiotherapy before the second PSA measurement, and the remaining 96 patients had repeated serum PSA measurements without treatment.

The patients were evaluated by different urologists. Patients convinced that they can benefit from the antibiotherapy were treated with levofloxacin 500 mg orally for 14 days. At the end of treatment, serum PSA levels were measured again. PSA values of untreated patients were repeated after 14 days. All PSA measurements were made in the same laboratory.

Patients and their second PSA values were re-evaluated by same urologists. Twelve-quadrant systemic biopsy was performed if indicated. In addition, cognitive fusion was applied for areas where the nodule was detected by rectal examination.

Statistical Analysis

Chi-square test was used to compare the biopsy rate, biopsy-to-prostate cancer detection rate, prostate cancer rate of population (Table 1, Prostate Cancer Rate$_2$), and Gleason 6 prostate cancer rate in patients treated and untreated. A p-value of <0.05 was considered statistically significant.

Results

The study included 136 patients who were treated with levofloxacin 500 mg for 2 weeks. Ninety-six patients who were untreated were tested again 14 days after initial evaluation. The mean ages of the patients were 65±7.9 in the treatment group, and 62±6.4 in the control group. There was a statistically significant difference in mean age between the two groups (p=0.007).

The groups were statistically similar in terms of comorbidity distribution (p=0.36). The most common comorbidities were diabetes mellitus (24%, 32/136), hypertension (31%, 42/136), and chronic obstructive pulmonary disease (8%, 11/136) in the treatment group. The same diseases were 12% (12/96), 9% (9/96), and 6% (6/96), respectively, in the control group.

The use of drugs that were clinically investigated for effects on PSA, such as statins, thiazide, and aspirin, did not differ between the groups (p=0.11). The groups were similar in terms of the use of other medical treatments (p=0.09).

The two groups were similar in terms of lower urinary tract symptoms but not prostate volumes (p=0.86 and p=0.014, respectively). There was no statistically significant difference between groups in terms of PSA parameters (tPSA, PSA-D, and >4 ng/mL PSA value; p=0.064, p=0.6, and p=0.68, respectively).

PSA did not change or increased in 47 (35%) of patients who were treated with antibiotics. Eighty-nine (65%) patients had a decrease in PSA. The mean PSA decrease was 1.23 ng/mL. The mean PSA decline rate was 21%. The mean PSA-D decrease was 0.023 ng/mL. PSA decreased below the 2.5 ng/mL cut-off value in 21% of patients after treatment (Table 2).

Differences in pathologic parameters were investigated between the two groups, which were similar in terms of distribution of other factors likely to affect PSA. Accordingly, there were fewer biopsy indications in the group treated with antibiotics (p<0.001). Although the rates of biopsies decreased, there was no statistically significant difference in prostate cancer detection rates among biopsied patients (p=0.74). However, when both the biopsied and non-biopsied patient groups were taken into

Table 1. Demographic data, prostate specific antigen parameters and biopsy results

Variables	Treatment Group	Control Group	p-value
Patient number	136	96	-
Age (year, mean)	65±7.9	62±6.4	0.007*
BMI	27.55±2.5	28.14±1.9	0.052*
Drug usage	46/136 (34%)	43/96 (45%)	0.09
NSAI	29/136 (21%)	14/96 (15%)	-
Statin	14/136 (10%)	15/96 (16%)	0.11
Tiaside	30/136 (22%)	12/96 (13%)	-
LUTS	88/136 (65%)	61/96 (64%)	0.86
Prostate volume (mL)	58.61±22.08	50.70±12.0	0.014*
PSA Parameters			
PSA (ng/mL, mean)	5.38±1.56	5.22±1.62	0.064*
PSA-D (ng/mL/mL, mean)	0.099±0.034	0.104±0.025	0.60*
>4 ng/mL	112/136 (82%)	77/96 (80%)	0.68
Biopsy rate	47% (64/136)	73% (70/96)	<0.001
Prostate cancer rate1	38% (24/64)	41% (29/70)	0.74
Prostate cancer rate2	18% (24/136)	30% (29/96)	0.024
Gleason 6 PCa rate	29% (7/24)	45% (13/29)	0.24

*Student t-test, other p values from chi-square, statistically significance value is p<0.05, BMI: Body mass index, NSAI: Non-steroidal anti-inflammatory, LUTS: Lower urinary tract symptoms, PSA: Prostate specific antigen, PCa: Prostate cancer

Table 2. After antibiotherapy variables

Variables		%
PSA Trend		
Increase	47/136	35%
Decrease	89/136	65%
PSA decrease (mean)	1.23 ng/mL	-
PSA decrease rate (mean)	21%	-
PSA-D decrease (mean)	0.023 ng/mL/mL	-
<2.5 ng/mL	19/89	21%

PSA: Prostate specific antigen

consideration, fewer patients in the treatment group were diagnosed with prostate cancer (p=0.024). Gleason 6 cancer rates were 29% in the treatment group and 45% in control group. Although there was less clinically insignificant cancer in the treatment group, the difference was not statistically significant (p=0.24) (Table 1).

Discussion

Although the contribution of PSA screening is not fully established, a clinically significant PSA reduction with antibiotherapy has been shown in many studies. In a study involving 61 patients, PSA reduction was reported in 80% of cases (3). The relatively high proportion reported in this study was attributed to the patients being diagnosed with chronic prostatitis. Patients with evidence of inflammation in prostate secretions were included in the study. This rate was 52% for the pilot study in which the effect of antibiotherapy on PSA was first investigated (2). A recently published prospective controlled trial showed that 46.5% of the patients had a PSA decrease after 3 weeks of ciprofloxacin treatment. This rate was 18% in the control group (4). In our study, 65% of the patients had PSA reduction with treatment. As shown in our study, clinically significantly PSA reduction by antibiotherapy can be obtained in approximately half of patients with a serum PSA level above 2.5 ng/mL.

In our study, PSA reduction after antibiotherapy was seen to suspend clinician from biopsy indication. Prostate biopsy was performed in 47% of patients in the treatment group and 73% of patients in the control group (p<0.001). There was a statistically significant difference in the final prostate cancer rates between the groups when all patients (biopsied and non-biopsied) were included (p=0.024). When the groups were examined from the point of pathological results, it was seen that the rate of Gleason 6 cancer in the antibiotherapy group was less. In summary, fewer biopsies were done with antibiotics, fewer prostate cancers were diagnosed, and higher Gleason score cases were detected.

Contrary to our results, there are studies that show antibiotherapy does not have a statistically significant effect on the decision of prostate biopsy. In a study involving 108 patients older than 50 years of age with serum PSA level greater than 2.5 ng/mL, prostate biopsy was performed following 3 weeks of antibiotic therapy (5). There was no significant difference between PSA parameters before and after treatment. A similar result was demonstrated in a prospective controlled study published from our country in 2013 (6). Atalay et al. (4) emphasized that even though a satisfactory decrease in PSA is obtained with antibiotherapy, it will not be enough to give up prostate biopsy. But none of these studies had an observational design. All patients underwent biopsy after antibiotherapy, regardless of the trend of PSA.

In a randomized controlled clinical trial conducted by Greiman et al. (1) 72% of the patients in the control group were biopsied and this rate was 62% in the treatment group. Similarly, in our study, antibiotherapy reduced the rate of indication for biopsy. Among the patients who underwent biopsy in the same study, 63% in the treatment group and 52% in the control group were diagnosed with prostate cancer. However, in our surveillance, there was no significant difference between the two groups (38% in the treatment group and 41% in the control group) with lower rates of cancer detection. That is, fewer patients were biopsied in the treatment group and prostate cancer was detected at similar rates to the control group.

A similar method was applied to work in a retrospective design published in 2009 (7). A 60% decrease in PSA was observed in the antibiotherapy group and a biopsy of 51% was performed. The rate of detection of cancer in biopsied patients is 18%. A 70% biopsy was performed in the control group and 24% of the biopsied patients had cancer. As in our study, fewer patient biopsies were performed and similar cancer rates were obtained. However, there is no data on the Gleason 6 cancer rates in this study or in the study of Greiman et al. (1).

Study Limitations

Our study has some limitations. Firstly, there was a statistically significant difference between the mean age and mean prostate volumes of the patients in the two groups. The mean age and prostate volumes of the patients in the treatment group were higher. This difference may have affected the PSA results.

Conclusion

Although antibiotherapy leads urologists to make fewer biopsies, the rate of cancer diagnosed by biopsy does not increase. Two groups with similar cancer diagnosis rates may suggest that more patients in the treatment group are away from the indication for prostate biopsy and miss cancer diagnosis. Although our study showed that Gleason 6 cancer was less common in the treatment group, it is difficult to explain this with antibiotherapy.

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

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Ethics

Ethics Committee Approval: For this study, approval was obtained from Cerrahpaşa University Faculty of Medicine Ethics Committee with the approval number: 83045809-604.01.02, date: 04.07.2017.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Z.T., O.Ö., Design: Z.T., O.Ö., Data Collection or Processing: O.Ö., Analysis or Interpretation: O.Ö., Literature Search: Z.T., O.Ö., Writing: O.Ö.

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Original Article

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Comparative Usefulness of High-frequency Doppler Ultrasonography, Serum PSA Density, and Free to Total Serum PSA Ratio in the Prediction of Prostate Cancer

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Abstract

Objective: In this study, we tried to assess whether power Doppler ultrasonography (PDU) evaluation along with transrectal ultrasound (TRUS) has an additional benefit in the diagnosis of prostate cancer in patients with prostate-specific antigen (PSA) levels of 4-10 ng/mL, when combined with the other methods proposed for this range of PSA.

Materials and Methods: Fifty-six patients with PSA values of 4-10 ng/mL were included in the study. Digital rectal examinations, evaluation of total and free PSA, and PDU assessments were done simultaneously with TRUS and eight-core systematic prostate biopsies. Along with the latter, additional biopsies were taken from the suspicious areas detected on PDU. The free/total PSA ratios, PSA density values, TRUS, PDU findings, and biopsy results of 56 patients were recorded and evaluated.

Results: Specificity and positive predictive values in detecting prostate cancer in patients with PSA range of 4-10 ng/mL, calculated using the criteria of free/total PSA values <15%, PSA density values >15%, and PDU findings, were 94.87% and 75%, respectively. These values were significantly higher than those of 89.75% and 69.73%, respectively, defined for the criteria of free/total PSA values <15% and PSA density values >15%.

Conclusion: The results of this study highlighted that PDU may be useful to detect prostate cancer, and decrease the number of unnecessary biopsy recommendations in patients with PSA values of 4-10 ng/mL, when used in combination with free/total PSA ratio and PSA density.

Keywords: Power Doppler ultrasonography, prostate cancer, prostate specisific antigen, PSA density

Introduction

Worldwide, prostate cancer is the second most common malignancy seen in men, and the fifth most common cause for their mortality; responsible for 3.8% of all cancer related deaths (1,2).

It develops more gradually than the other cancer types. In localized cancers with Gleason grade 2-4, the risk of cancer-related mortality within 15 years is around 4%-7% percent and biochemical recurrence free survival for Gleason scores < =6 is 96.6% for six years (3,4).

However, in non-localized, advanced-staged prostate cancers, mortality rates rise up to 70%-80%, and overall survival rates range from 26% to 30% at 5 years (5). These findings show that early diagnosis is important in prostate cancer.

The definitive diagnosis of prostate cancer is made by histopathological examination (6). Biopsy is indicated based on the results of prostate-specific antigen (PSA) test, digital rectal examination (DRE), and transrectal ultrasound (TRUS) (7). Among these, the most frequently used and useful method is PSA measurement (8,9,10,11,12). Since the chance of a malignancy is 25% when DRE reveals an abnormality, even with PSA levels <4 ng/mL, it is absolutely necessary to perform a prostate biopsy (13,14).

PSA measurements and DRE are recommended for the risk adopted prostate cancer screening along with counseling the patients on the potential risks and benefits (15).

The main problem in prostate cancer screening is experienced in patients whose PSA levels are between 4 and 10 ng/mL (16). In

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this range; defined as the gray zone, the specificity of PSA value alone is very low and the financial and psychosocial costs of a prostate biopsy are very high (12). Although, many methods have been developed to avoid unnecessary biopsies [free PSA measurement, free/total PSA ratio (f/t PSA)]; PSA density (PSAD), PSA velocity, etc; a satisfactory method that increases the diagnostic specificity, prevents unnecessary biopsies, and ensures the detection of greater number of cases with clinical cancer, is not available yet (17,18).

Although, increased blood flow in cancerous tissue is also observed in prostate examinations performed with color Doppler ultrasound, this method has not been found to be specific because increased blood flow can also be seen in prostatitis and benign prostatic hyperplasia (BPH). In recent years, high-frequency color Doppler ultrasound [power Doppler ultrasound - (PDU)] has been used with to increase the diagnostic specificity. PDU has shown to be more sensitive than the color Doppler US and less dependent on the probe in showing blood flow, number of vessels, and their distribution (16).

In this study, we tried to determine whether the TRUS-guided PDU examination performed in patients with PSA levels between 4 and 10 ng/mL will provide additional benefits when compared with other auxiliary methods used to increase the specificity of the PSA test.

Materials and Methods

Fifty-six patients who reported to our clinic with total PSA values between 4 and 10 ng/mL, as detected during the prostate cancer screening tests, also underwent free PSA evaluation (fPSA), DRE, TRUS-guided biopsy, and PDU examinations. Patients were informed about the study and a written informed consent were signed by the patients. PSA and fPSA values were determined using the Hybritech Tandem-R® test kit. TRUS and PDU findings were evaluated by the same radiologist in our radiology department by considering the presence (+) or absence (-) of malignancy that was based on the increased neo-vascularity of the tumor tissue seen in the color map generated by the amplitude or power of Doppler signal, specific to this Doppler ultrasonography (USG) method.

Eight quadrant TRUS-guided biopsies were performed in all patients by the radiologist and an additional biopsy specimen was obtained from a suspicious lesion seen in the PDU. Prostate sizes of the patients and number of biopsy quadrants were convenient with the least number of core biopsies recommended by The European Association of Urology (EAU) guidelines for these prostate sizes (15,19).

During this process, Toshiba power 7000® ultrasound device and 6.5 mHz endocavitary probe was used. All biopsies were evaluated by the same pathologist at our hospital. The f/t PSA ratios and PSA densities of the patients were calculated and recorded.

Statistical Analyses

SPSS (Statistical Package for Social Sciences) for Windows 10.0 program was used for statistical analysis of the study data. While evaluating the study data, Mc Nemar test was used to compare the qualitative data in addition to the descriptive statistical methods (mean, standard deviation, frequency). Results were evaluated within 95% confidence interval and the level of statistical significance was set at $p<0.05$.

Results

In 16 of 56 patients with a mean age of 68±15 (range: 51-88), biopsy results revealed the presence of prostate adenocarcinoma.

Prostate cancer (+) patients had Gleason scores of 6 (3+3, n=6), 7 (3+4, n=7), 9 (4+5, n=1), and 7 (4+3, n=2). When patients were evaluated according to TRUS findings, 10 of 15 patients with suspicious findings in TRUS contracted cancer. Of the remaining 41 patients with negative TRUS findings, 6 had cancer. According to these values, the positive predictive value of this test in detecting prostate cancer was 66%, while its sensitivity and specificity were calculated as 62% and 87%, respectively (Figure 1: Sensitivity, specificity, and positive predictive values of TRUS).

In PSAD evaluation, calculated according to the ratio of patients' PSA values to prostate volumes detected in TRUS, 13 of 31 patients with PSA densities (PSADs) >0.15 ng/mL and 3 of 25 patients with PSA densities <0.15 ng/mL contracted cancer, respectively. Per these values, the positive predictive value of this test in detecting prostate cancer was 41%; while its sensitivity and specificity were 81% and 55%, respectively (Figure 2: PSAD's sensitivity, specificity, and positive predictive value).

A cut-off value of 15% was used for f/t PSA ratio. While, cancer was detected in 11 of 18 patients below this value, only 6 of 38 patients with a ratio above this value had cancer. The positive predictive value, sensitivity, and specificity of f/t PSA ratio were 61%, 62%, and 82%, respectively (Figure 3: Sensitivity, specificity, and positive predictive value of f/t PSA ratio).

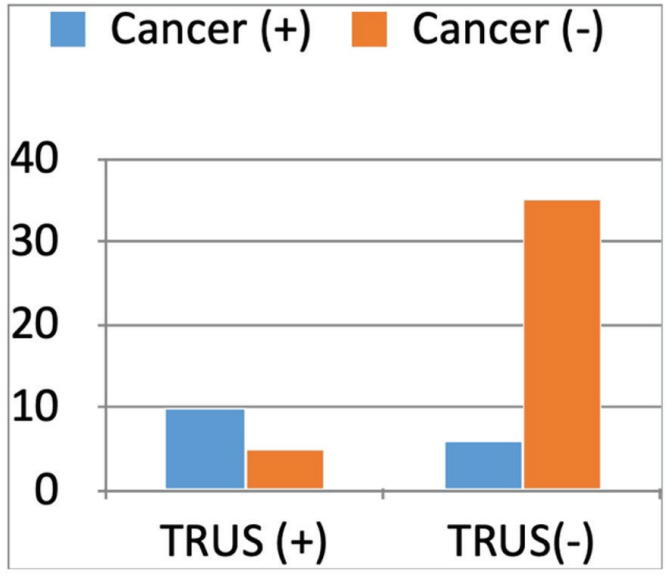


Figure 1. Sensitivity, specificity, and positive predictive values of TRUS
TRUS: Transrectal ultrasonography

While, cancer was detected in 8 of 17 patients with positive findings on PDU, 8 of 39 patients with negative findings were diagnosed on histopathology after their biopsy. Positive predictive value, sensitivity, and specificity of PDU were 47%, 50% and 79%, respectively (Figure 4: Sensitivity, specificity and positive predictive value of PDU).

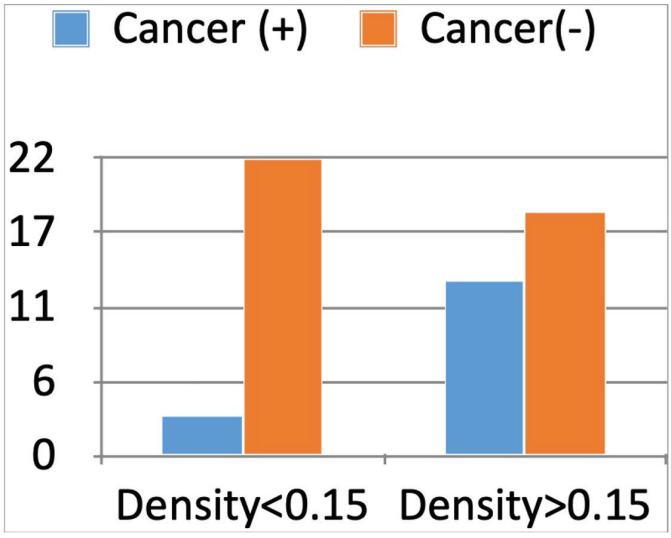


Figure 2. PSAD's sensitivity, specificity, and positive predictive value
PSAD: Prostate-specific antigen density

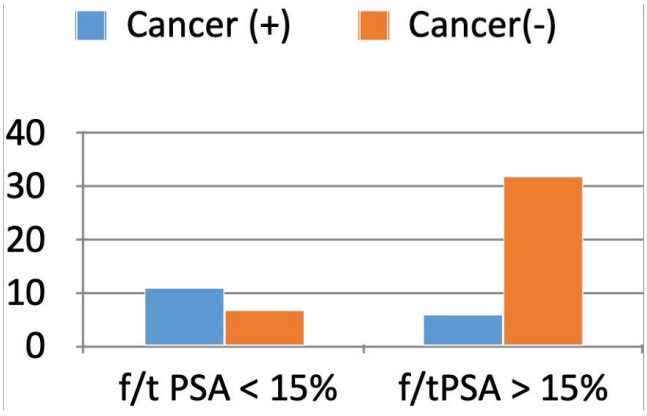


Figure 3. Sensitivity, specificity, and positive predictive value of f/t PSA ratio
f/t PSA: Free/total PSA ratio, PSA: Prostate-specific antigen

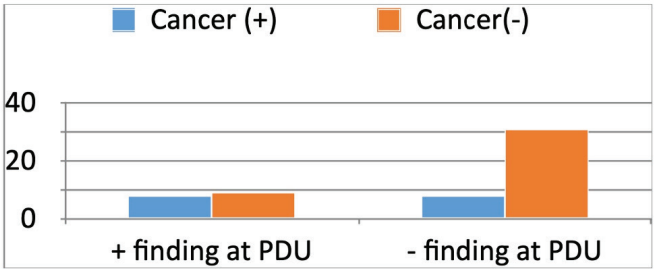


Figure 4. Sensitivity, specificity and positive predictive value of PDU
PDU: Power Doppler ultrasonography

PDU findings were positive for prostate cancer in only 3 of 18 patients without prostate cancer in those with PSADs >0.15 ng/mL, while the remaining 15 patients had negative PDU findings (Figure 5: PDU and PSAD).

When the cut-off value for f/t PSA ratio was taken as 15%, 7 patients with a f/t PSA ratio <15% did not have prostate cancer, and among them 3 patients had positive PDU findings (Figure 6). PDU findings of 2 out of 5 patients with the diagnosis of prostate cancer and f/t PSA ratios >15% had PDU findings favoring prostate cancer (Figure 6: PDU and f/t PSA ratios).

In patients with total PSA values between 4 and 10 ng/mL, combined use of f/t PSA ratios <15% with PSAD at the cut-off value of 0.15 ng/mL demonstrated 56.25% sensitivity, 89.75% specificity, and a predictive value of 69.23. When PDU, f/t PSA, and PSAD were used in combination, the sensitivity, specificity, and positive predictive values were 37.50%, 94.87%, and 75%, respectively. (Table 1: Sensitivity, specificity, and positive predictive values of combined PSADs and f/t PSA ratios; Table 2: Sensitivity, specificity, and positive predictive values of PDU, f/t PSA, and PSAD combination).

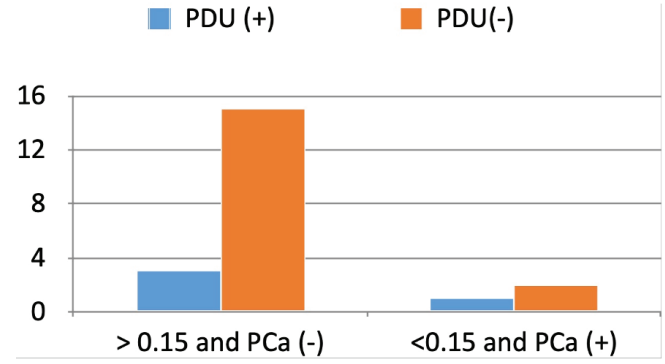


Figure 5. PDU and PSAD
PDU: Power Doppler ultrasonography, PSAD: Prostate-specific antigen density, PCa: Prostate cancer

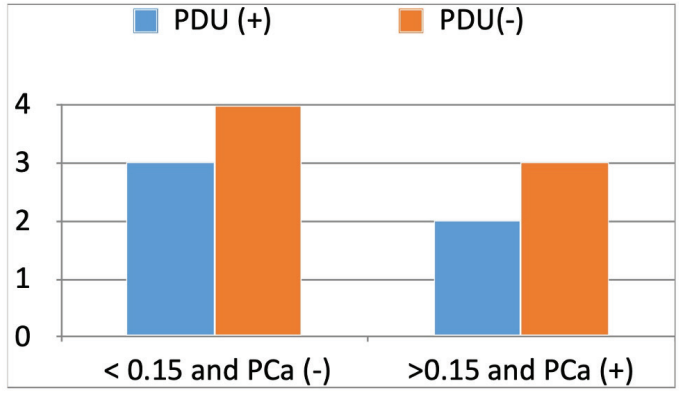


Figure 6. PDU and f/t PSA ratios
PDU: Power Doppler ultrasonography, f/t PSA: Free/total PSA ratio, PSA: Prostate-specific antigen, PCa: Prostate cancer

Table 1. Sensitivity, specificity, and positive predictive values of combined PSADs and f/t PSA ratios

Method	Sensitivity	Specificity	Positive predictive value
TRUS	62%	87%	66%
PSAD >0.15 ng/mL	81%	55%	41%
f/t PSA <15%	62%	82%	67%
PDU	50%	79%	47%

PSA: Prostate-specific antigen, PSAD: Prostate-specific antigen density, TRUS: Transrectal ultrasonography, PDU: Power Doppler ultrasonography, f/t PSA: Free/total PSA ratio

Table 2. Sensitivity, specificity, and positive predictive values of PDU, f/t PSA, and PSAD combination

Combined method	Sensitivity	Specificity	Positive predictive value
PSA density (>0.15 ng/mL + f/t PSA <15%)	56.25%	89.75%	69.23%
PSA density (>0.15 ng/mL + f/t PSA <15%) Power Doppler USG	37.50%	94.87%	75%

PSA: Prostate-specific antigen, PSAD: Prostate-specific antigen density, PDU: Power Doppler ultrasonography, USG: Ultrasonography, f/t PSA: Free/total PSA ratio

Discussion

Since, PSA is not perfect in predicting prostate cancer by itself; other methods are needed to increase the cancer detection rate and to prevent unnecessary biopsies (20,21). These methods include evaluation of PSAD, f/t PSA ratio, PSA velocity, and age-specific PSA. Among them, the most accepted and commonly employed tests are PSA density and f/t PSA ratio, in that order. However, none of these additional methods have been successful in predicting cancer, and more specific methods are needed. In our study, in addition to f/t PSA ratios and PSA densities, TRUS-guided biopsies were obtained from the suspicious areas seen during the simultaneously performed PDU. The ratio obtained by dividing serum PSA value by prostate volume was defined as PSAD (22). With this measurement that was developed based on the observation of greater amount of PSA secretion from hyperplastic tissue, unnecessary biopsies were reduced by 16%-55% when PSAD >0.15 ng/mL; however, nearly 11% of cancer cases were also overlooked (22,23). These findings show that the probability of detecting higher number of cancer cases by biopsy may increase by using PSAD (22,24,25). However, other researchers have not been able to demonstrate a superiority of PSAD over the use of PSA alone. Presti et al.(26) demonstrated that when sampling errors were corrected and used in patients whose PSA levels ranged between 4 and 20 ng/mL, PSAD was superior to PSA as demonstrated by functional characteristic analyses. However, this significance was lost in patients whose PSA levels were within the gray zone i.e. 4-10 ng/mL. Most of the PSA in serum is bound to alpha1- anti-chymotrypsin (ACT). Free or non-complexed PSA is found in relatively lower concentrations in serum. It has been thought that ACT is also found in the normal or malignant prostate epithelium, but not in BPH. It has been shown that the ratio of free PSA to complex PSA may be significant in detecting malignancy in the prostate. Chen et al. (27) did not observe any differences in the mean total PSA values of two separate groups of patients with benign and malignant prostate disease with PSA values between 4 and 10 ng/mL; while they observed significant differences between the average f/t PSA values of both groups. They also investigated the diagnostic value of fPSA in patients with total PSA levels between 4 and 10 ng/mL, and demonstrated that the f/t PSA ratio had higher specificity at almost every level of sensitivity (27). When these ratios are examined in patients with f/t PSA values between 4 and 10 ng/mL and normal DRE findings, it is also found that 95% of cancers can be detected and the number of negative biopsies can decrease by 20% in patients with f/t PSA ratios <23%. The f/t PSA ratio has been suggested to be used for deciding on the need for a repeat biopsy in patients with persistent PSA elevation but without any evidence of prostate cancer in the previous biopsy (28). This finding has also proved useful in distinguishing between BPH and prostate cancer (29).

A standard imaging method that can be used reliably in the diagnosis or staging of prostate adenocarcinoma has not been reported yet (30). However, the presence of neo-vascularity in malignancies is an established fact. The use of color Doppler USG that demonstrates this increased blood flow to identify tumors has also begun to draw attention as an interesting imaging modality since the 1990's (31).

Although, increased blood flow is observed in prostate cancer using color Doppler USG, this method has not been found to be specific since hypervascularity can be seen in prostatitis and BPH (32). Recently, high-frequency PDU has been used in an attempt to increase its diagnostic specificity.

PDU has been shown to be more sensitive than color Doppler and less probe dependent in demonstrating blood flow, distribution, and number of vessels (33). In our study, sensitivity, specificity, and positive predictive values of gray scale ultrasound were higher than those of PDU. We attributed these to the fact that the radiologist who participated in our study did not have sufficient experience in performing PDU as yet. It has also been reported that PDU is less sensitive than dynamic contrast-enhanced magnetic resonance imaging (MRI) in demonstrating hypervascularity in prostate cancer (34). In addition, Frauscher et al. (35) have reported that the anomalous regions visualized by PDU contain cancerous tissue 4.7 times more frequently relative to the normal appearing area adjacent to those regions. In many studies, apart from those conducted by Kuligowska et al. (36), investigating the use of this method for prostate cancer screening, the positive predictive value of color Doppler ultrasound was found to be higher than that of the gray scale ultrasound.

However, it has been suggested that patients with higher PSA levels already have a higher chance of harboring lesions detectable with gray scale ultrasound, and this may only be valid in patients with slightly elevated PSA levels (35,36).

Despite all these promising developments, studies have reported that the biopsy specimens obtained from the regions with positive PDU findings missed a significant number of cancers

compared with the cancers detected by laterally directed modified 6 quadrant biopsy (37). Some researchers have even indicated that the increased blood flow may actually depend on the patient's position (37,38). In our study, systematic biopsies were performed in all patients; however, when an anomaly was detected on PDU, an additional biopsy material was obtained from that region. A recent study demonstrated that in the first and second biopsies performed in patients with PSA levels between 2.5-10 ng/mL, PDU could exclude most of the non-cancerous patients and had a better sensitivity, specificity, and positive predictive value compared to the gray scale ultrasound (39).

In our study, when PDU was used as an independent screening method, it was found that its sensitivity, specificity, and positive predictive value in the detection of prostate cancer were 50%, 79%, and 47%, respectively. These values were lower than the corresponding values of 82.8%, 78.8%, and 87.9% cited in the literature (39). The sensitivity, specificity, and positive predictive values calculated in patients with PSADs >0.15 ng/mL were close to those determined by Akdas et al. (40) in Turkish patients with PSA levels <10 ng/mL (85%, 55%, and 41%, respectively). Again, the sensitivity, specificity, and positive predictive values calculated for the f/t PSA ratio were 62%, 82%, and 61%, which were close to respective 76%, 77% and 52% values cited in the literature (41).

We also evaluated the success of identifying those patients with cancer who could not undergo a biopsy, since their other tests yielded prostate cancer-negative results, and subsequently were not included in the screening. PDU positivity was detected in only 2 prostate cancer patients (40%) with f/t PSA ratios >15%. PDU-positivity was detected in only one of three patients (33%) with PSADs <0.15 ng/mL (33%). However, the number of patients in our study was not sufficient to render these values statistically significant.

While, PDU was found as the test with the lowest sensitivity in comparison with f/t PSA and PSAD in detecting cancer cases, the specificity of only f/t PSA ratio of <15% was greater than that of this method. The positive predictive value of PDU in detecting prostate cancer was found to be higher than that of the other tests only when the cut-off value of PSAD was accepted as 0.15 ng/mL.

However, in patients with PSADs >0.15 ng/mL and f/t PSA ratios <15% in the presence of suspicious findings revealed by PDU; specificity and positive predictive value in detecting prostate cancer (94.87% and 75%, respectively) were significantly higher in patients with PSAD values >0.15 ng/mL and f/t PSA ratios <15% (89.75%, and 69.23%, respectively) ($p<0.05$). These findings showed that this method may be useful in detection of prostate cancer when used in combination with other methods.

Prostate cancer detection rates of PDU in patients with only PSADs >0.15 ng/mL and f/t PSA ratios <15% were not statistically significant ($p>0.05$). However, cancer detection rates were found to be statistically significant in patients with positive PDU findings in those with PSADs >0.15 ng/mL and f/t PSA ratios <15% ($p<0.05$).

Study Limitations

An important limitation of our study was the lack of comparison of our findings with the current methodology of prostate biopsy; the MRI guided fusion biopsy. However, it is important to remember that systematic biopsy is an acceptable approach in case mpMRI is unavailable as is stated in EAU guidelines (15). Utilization of multi parametric MRI fusion biopsy could be challenging due to the high cost of the procedure, access to this type of biopsy systems by all clinicians, and technical requirements that are encountered not only by radiologists but also urologists. Hence, the result of this study may be a useful guide for the patients and centers without an access to MRI evaluation. Future studies including direct comparison of different methodologies would be helpful to find out a better method for the diagnosis of prostate cancer.

Conclusion

PDU has become popular recently and is one of the more promising imaging methods whose usefulness in prostate cancer has not yet been fully demonstrated. In this study, we found that when PDU was used in combination with PSAD (>15 ng/mL) and f/t PSA ratio (<15%) in screening patients with total PSA levels ranging between 4 and 10 ng/mL, who we most frequently encountered, it can be useful in detecting higher number of prostate cancer patients.

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Ethics

Ethics Committee Approval: As medical tests, evaluations and interventions were performed within the limits of routine medical practice, approval of local ethic committee, which was not present at the time period of the study, was not required.

Informed Consent: Patients were informed about the study and a written informed consent were signed by the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Critical Review: N.D.G., Concept: M.T.E., Design: M.T.E., Data Collection or Processing: M.T.E., Analysis or Interpretation: M.T.E., Literature Search: M.T.E., Writing: M.T.E.

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Original Article

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The Role of Multiparametric Magnetic Resonance Imaging to Detect the Extracapsular Extension in Robot-Assisted Radical Prostatectomy

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Abstract

Objective: This study aimed to evaluate the effectiveness of multiparametric prostate magnetic resonance imaging (mpMRI) in detecting extracapsular extension (ECE) and its impact on our preoperative surgical plan.
Materials and Methods: Overall, 150 patients who had undergone preoperative mpMRI and robot-assisted laparoscopic radical prostatectomy (RALRP) between June 2016 and March 2018 were enrolled. The preoperative International index of Erectile Function (IIEF) score of the patients was 22 or higher. On initial assessment, the patients' prostate specific antigen levels and digital rectal examination and pathology results of prostate biopsy specimens were evaluated to determine whether neurovascular bundle (NVB)-sparing surgery is feasible and appropriate. On the second evaluation, mpMRI results were considered in addition to the parameters included during the first evaluation to decide whether NVB-sparing surgery should be performed.
Results: The mean age of the patients was 65.2 years. The sensitivity, specificity, positive predictive value and negative predictive value of mpMRI were 89.6%, 90.2%, 81.1% and 94.8%, respectively. According to mpMRI findings, the surgical plan at the initial evaluation changed in 35 (23.3%) of the cases.
Conclusion: The high rate of detection of ECE with mpMRI prior to RALRP may guide the surgeon to decide for NVB-sparing surgery.
Keywords: Prostate cancer, multiparametric magnetic resonance imaging, robotic surgery, radical prostatectomy

Introduction

Pathological extracapsular extension (ECE) after radical prostatectomy increases the stage of the disease and cancer-related mortality (1,2). ECE may be detected by palpation during open surgery; however, it is difficult to detect ECE during the course of robotic surgery due to the absence of tactile sensation. The combination of transrectal ultrasonography and digital rectal examination (DRE) is not sufficient for the accurate detection of ECE (3). Nomograms such as Partin and Memorial Sloan Kettering Cancer Center provide information on ECE; however, they do not reveal detailed anatomical information (4,5). Accurately localising the tumour is beneficial in performing neurovascular bundle (NVB)-sparing surgery by preventing excessive extraprostatic tissue resection, determining the margins of the tissue which needed to be removed in order to achieve negative surgical margins which may provide better functional and oncological results (6,7). In recent years, multiparametric prostate magnetic resonance imaging (mpMRI) has been the most promising technique in detecting and staging of prostate cancer, which can present cite-specific results in ECE (8,9). In this study, we aimed to evaluate the effectiveness of mpMRI in detecting ECE and whether it affected our preoperative surgical plan.

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Materials and Methods

The data of 150 patients who underwent mpMRI before robot-assisted laparoscopic radical prostatectomy (RALRP) between June 2016 and March 2018 and whose IIEF score was >21 were retrospectively reviewed. mpMRI was performed using a 3-Tesla Siemens system without an endorectal coil. Diffusion-weighted MRI, T2-weighted MRI and dynamic contrast-enhanced MRI techniques were used for the localisation of the tumour site and possible ECE. mpMRI was performed according to the 2012 European Society of Urogenital Radiology prostate MRI guidelines (10) by a single radiologist (KE) with a 10-year experience; the radiologist was not blinded of the clinical diagnoses, DRE findings, prostate specific antigen (PSA) levels and biopsy results of the patients.

Moreover, RALRP was performed by two experienced surgeons (AFA, AEC). In the preoperative evaluation, the surgery planning was performed in two steps. First, DRE findings, PSA level and biopsy results were considered to determine whether NVB should be preserved or not. The final decision for propriety of NVB-sparing was made according to the mpMRI findings.

Patients who had previously received hormone therapy or radiotherapy and those whose mpMRI was reported in another centre were excluded from the study.

All prostatectomy specimens were examined by one dedicated uropathologist. The macroscopically dyed, formalin-fixed specimens were serially sectioned within a 3-mm-thick cutting surface, from apex to base and perpendicular to the posterior surface. Slices were further cut into 3-5 µm microscopic pieces and then stained with hematoxylin and eosin stain. ECE was defined as the tumour extending beyond the prostate capsule, through the extraprostatic tissues. TNM classification was used to determine the pathological T (pT) stage. Our study was approved by the Ankara Yıldırım Beyazıt University Ethics Committee (approval no: 16, date: 22.04.2020). Clinical data were retrospectively reviewed and analysed.

Statistical Analysis

Data analysis was performed using the IBM SPSS Statistics version 20.0 software (IBM Corporation, Armonk, NY, USA). Whether the continuous variables were distributed normally was determined by Kolmogorov-Smirnov test. Mann-Whitney U test was used for not normally distributed continuous variables, and the results were presented as median (minimum - maximum). The number of cases (n) and percentages (%) were used for categorical data. Categorical variables were analysed by continuity corrected chi-square test or Fisher's Exact test. Additionally, the diagnostic indicators (i.e., sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) and accuracy) for MRI were calculated. The statistical significance of the diagnostic value of mpMRI according to the gold standard pathology in terms of determining ECE was evaluated. P-value <0.05 was considered statistically significant.

Results

Overall, 177 patients who underwent RALRP were analysed. We excluded 1 patient who was receiving hormonotherapy, 4 patients whose mpMRI tests were taken in another health centre, and 22 patients who has IIEF score <22. Finally, 150 patients were included. The median age of the patients was 65 years (49-75). The demographic characteristics and clinical and pathological

Table 1. Descriptive statistics for the demographic features, clinical characteristics and pathological findings of the patients

Variables	**n=150**
Age (years) Median (min-max)	65 (49 - 75)
Preoperative PSA value (ng/mL) Median (min-max)	7 (1.2 - 96)
Prostate weight (g) Median (min-max)	40 (15 - 286)
Time from mpMRI to surgery (days) Median (min-max)	46 (2 - 359)
Time from biopsy to surgery (days) Median (min-max)	101 (53 - 475)
Time from mpMRI to biopsy (days) Median (min-max)	55 (40 - 426)
Largest lesion size in mpMRI (mm) Median (min-max)	20 (5 - 45)
ECE positivity in mpMRI n (%)	53 (35.3%)
PIRADS score n (%)	
3	9 (17.0%)
4	22 (41.5%)
5	22 (41.5%)
Clinical stage n (%)	
T1c	86 (57.3%)
T2a	41 (27.3%)
T2b	11 (7.3%)
T2c	9 (6.0%)
T3	3 (2%)
Positive core number in biopsy Median (min-max)	3 (1 - 10)
Biopsy Gleason score n (%)	
Grade Group 1	78 (52.0%)
Grade Group 2	40 (26.7%)
Grade Group 3	11 (7.3%)
Grade Group 4	14 (9.3%)
Grade Group 5	7 (4.7%)
Gleason score in specimen n (%)	
Grade Group 1	62 (41.3%)
Grade Group 2	47 (31.3%)
Grade Group 3	23 (15.3%)
Grade Group 4	10 (6.7%)
Grade Group 5	8 (5.3%)
Cancer percentage in specimen Median (min-max)	10 (1 - 90)
Tumor multifocality in specimen n (%)	50 (33.3%)
PSM n (%)	16 (10.7%)
ECE in pathology n (%)	48 (32.0%)
LN dissection n (%)	
Not performed	78 (52.0%)
Benign	66 (44.0%)
Malign	6 (4.0%)
Pathologic T stage n (%)	
T2a	31 (20.7%)

table 1 continuation	
T2b	4 (2.7%)
T2c	64 (42.6%)
T3a	44 (29.3%)
T3b	7 (4.7%)
NVB sparing n (%)	
Not performed	23 (15.3%)
Unilaterally performed	26 (17.4%)
Bilaterally performed	101 (67.3%)

PSM: Positive surgical margin, LN: Lymph node, NVB: Neurovascular bundle, ECE: Extracapsular extension, PSA: Prostate specific antigen, NVB: Neurovascular bundle, LN: Lymph node, mpMRI: Multiparametric magnetic resonance imaging, ECE: Extracapsular extension, PIRADS: Prostate imaging reporting and data system

results of the patients are smmarized in Table 1. mpMRI result was reported as ECE in 53 patients. ECE was detected in 48 patients in the final pathology after radical prostatectomy. NVB-sparing surgery was performed in 127 (84.7%) patients.

The initial surgical plan changed in 35 (23.3%) of the cases according to mpMRI findings reported during the preoperative evaluation. In 21 (60%) of these 35 patients, the surgical plan was changed from non-NVB-sparing surgery to NVB-sparing surgery. In the remaining 14 (40%) patients, the surgical plan was changed from NVB-sparing surgery to non-NVB-sparing, considering the mpMRI results.

When the patients were divided into two groups according to final pathology results as ECE detected (n=48) or not detected (n=102), there was no statistically significant difference between the two groups in terms of age (p=0.951). The median cancer percentage, median prostate imaging reporting and data system score and the largest lesion size in mpMRI were significantly higher in the group with ECE than in the group without ECE (p<0.001) (Table 2).

The sensitivity, specificity, PPV and NPV of mpMRI for detection of ECE were 89.6%, 90.2%, 81.1% and 94.8%, respectively. The diagnostic accuracy rate of mpMRI for ECE was 90%.

Table 2. Demographic features and clinical characteristics of the two groups which defined accordinto extracapsular extension positivity (n=48) or negativity (n=102) in pathology results

Variables	ECE positive (n=48)	ECE negative (n=102)	p-value
Age (years) Median (min-max)	64.5 (51-75)	65 (49-75)	0.966†
Cancer percentage in specimen Median (min-max)	7 (1 - 53)	23.5 (4 - 90)	<0.001†*
Largest lesion size in mpMRI (mm) Median (min-max)	17 (5 - 40)	27.5 (10 - 45)	<0.001†*
ECE positivity in mpMRI n (%)	10 (9.8%)	43 (89.6%)	<0.001‡*
PIRADS score n (%)			<0.001‡*
3	5 (50.0%)	4 (9.3%)	
4	5 (50.0%)	17 (39.5%)	
5	0 (0.0%)	22 (51.2%)	

*p-value <0.05 is considered as statistically significant.
† Mann-Whitney U test, ‡ Continuity corrected chi-square test.
mpMRI: Multiparametric magnetic resonance imaging, ECE: Extracapsular extension, PIRADS: Prostate imaging reporting and data system

Discussion

In this current study, mpMRI was shown as a convenient method with high sensitivity (89.6%) and specificity (90.2%) in preoperative evaluation for ECE. Our surgical plan which we determined through the routine examination before the surgery was changed in the preoperative period in a quarter of the patients through the mpMRI results.

In a study conducted by Feng et al. (11), which included 112 patients, the sensitivity, specificity, PPV and NPV of mpMRI for ECE were 84.6%, 87.2%, 66.7% and 94.9%, respectively. However, this study did not mention whether the radiologist knew about the clinical characteristics and biopsy pathology results of the patients. Moreover, in a study by Gaunay et al. (12) with 74 patients, the sensitivity, specificity, PPV, NPV and overall accuracy rate of mpMRI in detecting ECE were 58.3%, 97.8%, 93.3%, 81.5% and 84.1%, respectively. However, they did not state the experience of the radiologist and whether the radiologist had information about the patients' data. Park et al. (13) reported that the sensitivity, specificity, PPV, NPV and overall accuracy rate of mpMRI in predicting T3 prostate cancer were 55.9%, 82.2%, 59.1%, 80.2% and 73.9%, respectively. In this study, even though the sensitivity of the mpMRI was low, it was significantly and relatively high in stage T3 disease. However, the radiologists who interpreted the mpMRI findings did not know the PSA values, biopsy pathology results and DRE of the patients. The difference in sensitivity of mpMRI in diagnosis of ECE through the different studies may depend on the patient selection, the technique differences in mpMRI imaging such as field strengths, sequence and coil types and may be affected by the experience and/or the knowledge of the radiologist (14). In the current study, factors such as the knowledge of the radiologist about the clinical findings, PSA levels and biopsy results of the patients may have contributed to the increased sensitivity and specificity findings of mpMRI in detecting ECE.

In radical prostatectomy, the main goal is to provide negative surgical margins and to perform NVB-sparing surgery. Partin and MSKS nomograms consider clinical stage, biopsy Gleason score and PSA values in preoperative detection of ECE (4,5). Even though they are widely used, their accuracy rate in determining ECE varies in different studies (15,16). mpMRI provides surgeons detailed anatomical information useful for the establishment of a surgical plan. In this respect, mpMRI is an advantageous technique which provides information in both the detection and cite-specific localisation of the ECE. The absence of tactile sensation in robotic surgery makes it more valuable to use a sensitive and specific method such as mpMRI in addition to the routine examinations used. The surgeon pays more attention during the exploration of the area indicated as ECE in mpMRI to provide surgical margin negativity. Erectile dysfunction is one of the most common complications of RP. This crucial complication is observed less frequently in patients who underwent NVB-sparing surgery than in those who had non-NVB-sparing surgery (17). Selective NVB-sparing surgery can be performed even in

T3 disease to preserve erectile function (6). The absence of ECE in mpMRI and more desirable functional results may help the surgeon decide to perform NVB-sparing surgery.

It has been shown in previous studies that mpMRI contributed to the changes in preoperative plans in radical prostatectomy cases (13,18,19,20,21). Park et al. (13) reported that mpMRI affected the surgical plan for 26% of the patients. In a study performed by McClure et al. (18), the surgical plan changed for 28 of 104 patients (27%). Radtke et al. (21) reported a 31.1% change in their initial surgical plan after the mpMRI results. In the current study, we consistently observed a 23.3% change in initial surgical plan due to mpMRI results. On the other hand, the high sensitivity and specificity of mpMRI in the current study may explain the higher rate of NVB-sparing and less surgical margin positivity compared to those in the literature (20,22).

Study Limitations

The single-centre design, retrospective nature and evaluation of the mpMRI by a single experienced radiologist may be considered as the limitations of this study. All of the RALRP operations were performed by the same experienced surgeons, which may also be accepted as another limitation of this study.

Conclusion

mpMRI, which is performed during the preoperative period of the RALRP, appears to be a reliable technique in detecting the presence and localisation of the ECE, with high sensitivity and high specificity. Preoperative mpMRI may guide the surgeon in deciding to perform NVB preservation during RALRP.

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Ethics

Ethics Committee Approval: Our study was approved by the Ankara Yıldırım Beyazıt University Ethics Committee (approval no: 16, date: 22.04.2020).

Informed Consent: Clinical data were retrospectively reviewed and analysed.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.F.A., A.E.C., Concept: E.K., Design: E.K., Data Collection or Processing: E.K., B.G., K.E., B.G., Analysis or Interpretation: E.K., Literature Search: E.K., B.G., Writing: E.K.

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Original Article

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The Auxiliary Role of Hematological Parameters in Diagnosing Localized Germ Cell Testicular Tumor

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Abstract

Objective: There is a lack of information about the relationship between germ cell testicular tumors and hematological parameters commonly used in other tumors. In this study, it was aimed to determine the value of hematological parameters used in other malignancies in the diagnosis of localized germ cell testicular cancer.
Materials and Methods: Hematological parameters between patients who underwent radical orchiectomy with a pre-diagnosis of localized germ cell testicular tumor and those who underwent varicocelectomy in the same period as the control group between January 2015 and March 2019 in our clinic were compared to determine the diagnostic value of hematological parameters in testicular tumor.
Results: The mean age of 39 patients diagnosed as having localized testicular tumor was 33 years. While seminoma was detected in 17 patients, non-seminomatous germ cell tumors were detected in 22 patients. In the assessment of preoperative blood samples; neutrophil count (5.6 vs 4.1, p≤0.001), neutrophil percentage (65.8 vs 57.4, p≤0.001) and neutrophil/lymphocyte ratio (2.6 vs 1.8, p≤0.001) were significantly higher, while lymphocyte ratio was significantly lower (25.3 vs 31.4, p≤0.001) in patients with testicular tumor than in the control group (n=121). In the receiver operating characteristic analysis performed for the neutrophil/lymphocyte ratio, the cut-off point was found to be 2.25 (area under the curve =0.71, 95% confidence interval: 0.622-0.816, sensitivity: 66.7%, selectivity: 73.6%).
Conclusion: Neutrophil/lymphocyte ratio, which is one of the hematological parameters, can be used as an auxiliary tool for examination and imaging methods in the diagnosis of stage I germ cell testicular tumor, which is considered to be an early stage.
Keywords: Cancer, diagnosis, lymphocyte, neutrophil, testis

Introduction

Although testicular tumors are not very common, they are important because they are seen at a young age. Although tumor markers such as alpha fetoprotein (AFP), human chorionic gonadotropin (hCG), lactate dehydrogenase (LDH) are used in the clinical practice of testicular tumors in which prolonged survival can be achieved with early diagnosis; cheaper and useful diagnostic and follow-up methods are being investigated (1).

There is a close relationship between inflammatory response and tumorigenesis and tumor progression (2). Some of the systemic inflammatory response indicators that can be measured with hematological parameters are used in diagnosis and to predict the prognosis in different malignancies (3,4). Studies on the neutrophil/lymphocyte ratio (NLR) in urothelial tumors (mostly urothelial carcinomas) have been conducted, and it has been shown that NLR elevation is associated with poor prognosis in most studies (5,6,7). Also; it has been reported that parameters related to platelets involved in the inflammatory process of malignant tumors, such as platelet count, thrombocyte/lymphocyte ratio (PLR), mean platelet volume can also be used as biomarkers in various tumors (8).

There is a lack of information about the relationship between germ cell tumors (GCT), which constitute 95% of testicular tumors, with hematological parameters commonly used in other tumors. In this study, it was aimed to determine the value of hematological parameters used in other malignancies in the diagnosis of localized germ cell testicular tumor.

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Materials and Methods

After the study was approved by the local ethics committee, the data of patients who underwent radical orchiectomy and diagnosed as having localized GCT between January 2015 and March 2019 and those who underwent varicocelectomy within the same period were evaluated retrospectively. Patients with localized GCT up to pTx N0 M0 (stage I) and patients who underwent varicocelectomy within the same period and were assigned as the control group were included in the study. Computed tomography or magnetic resonance imaging and tumor markers were used in the staging of patients with germ cell testicular tumors. The patients were staged according to the 2009 tumor-node-metastases classification of the International Union Against Cancer. Patients with non-germ cell testicular tumor, active infection or chronic inflammatory disease, patients using anticoagulants, taking hormonal therapy in the last year, and patients with hematological disorders were excluded from the study.

Age, body mass index, tumor size and preoperative AFP, hCG, and LDH values of patients with germ cell testicular tumors were recorded. Among the hematological parameters; neutrophil, lymphocyte, platelet counts and mean platelet volume were measured from preoperatively collected peripheral blood samples. These values and ratios were compared between patients with localized GCT and patients in the control group to determine the diagnostic values of these parameters in germ cell testicular tumor.

Receiver operating characteristic (ROC) curve was created for NLR and PLR to evaluate them in the diagnosis of germ cell testicular tumor. The cut-off point value of NLR was calculated with the area under the curve (AUC). Sensitivity, selectivity, positive and negative predictive values of the NLR were determined.

Statistical Analysis

Whether the distribution of continuous variables was normal or not was determined by Kolmogorov-Smirnov test. Levene test was used to evaluate the homogeneity of variances. When appropriate, descriptive statistics for continuous variables were expressed as mean ± standard deviation or median (1st quarter to 3rd quarter). The number of patients and percentages were used for categorical data. Student t-test was applied to numerical data with normal distribution, and non-parametric Mann-Whitney U test was applied to numerical data without normal distribution. Categorical data were analyzed using the chi-square test with continuity correction. ROC curve analyzes for NLR and PLR, which could be used as determinants in the diagnosis of localized GCT, were performed to find the cut-off points. The Youden index method was used to find the best cut-off point of the NLR. Sensitivity, specificity, positive and negative predictive values and accuracy rates at the best cut-off point for NLR and neutrophil percentage/lymphocyte percentage ratio [NLR (%)] were calculated. Odds ratios and 95% confidence intervals (CI) were also calculated for each independent variable. Data analysis was performed in the "SPSS for Windows 17.0" package program (IBM Corporation, Armonk, NY, USA). Results for $p<0.05$ were considered statistically significant.

Results

Descriptive statistics of demographic and preoperative clinical data of patients with localized GCT in the study group are given in Table 1. In the evaluation performed in terms of preoperative hematological parameters among the groups diagnosed as having localized GCT and varicocelectomy, it was found that the median neutrophil count and neutrophil percentage of the localized GCT group were statistically significantly higher than the varicocelectomy group ($p<0.001$ and $p<0.001$). While there was no statistically significant difference between the groups in terms of lymphocyte counts ($p=0.244$), the percentage of lymphocytes in the localized GCT group was found to be statistically significantly lower than the varicocelectomy group ($p<0.001$). The median NLR of the localized GCT group was statistically significantly higher than the varicocelectomy group ($p<0.001$) (Figure 1). Additionally, the median NLR (%) ratio of the localized GCT group was found to be statistically significantly higher than the varicocelectomy group ($p<0.001$) (Table 2).

In the ROC analysis of NLR and PLR in both groups, the AUC of the NLR was found to be statistically significant in distinguishing the two groups (AUC: 0.719, 95% CI: 0.622-0.816 and $p<0.001$) (Figure 2). The best cut-off point of NLR in distinguishing the

Table 1. Demographic and preoperative clinical data of patients with localized germ cell testicular tumor in the study group

	n=39	Minimum-maximum
Age	33.2±10.6	17-60
Body mass index (kg/m²)	24.4±3.6	18.5-32.9
Tumor size (cm)	4.9	1.0-12.0
Pathology		
Seminoma	17 (43.5%)	-
Non-seminomatous germ cell tumor	22 (56.5%)	-
AFP (U/mL)	140.6±433.1	0.6-2514.5
hCG (mIU/mL)	166.8±425.2	0.5-1806.0
LDH (U/L)	234.9±96.4	140.0-615.0

AFP: Alpha fetoprotein, hCG: Human chorionic gonadotropin, LDH: Lactate dehydrogenase

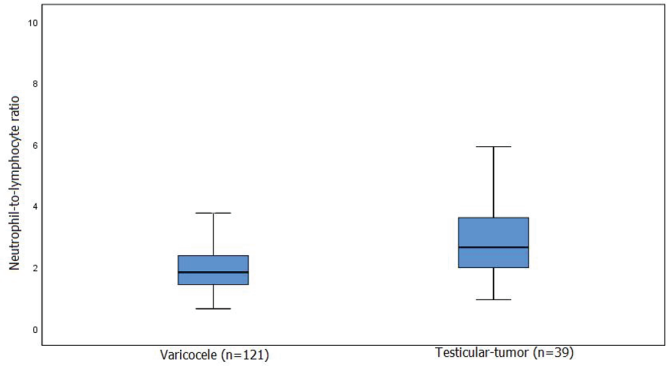


Figure 1. Box-plot graphs of the neutrophil/lymphocyte ratios of the localized germ cell testicular tumor group and the control group (patients who underwent varicocelectomy)

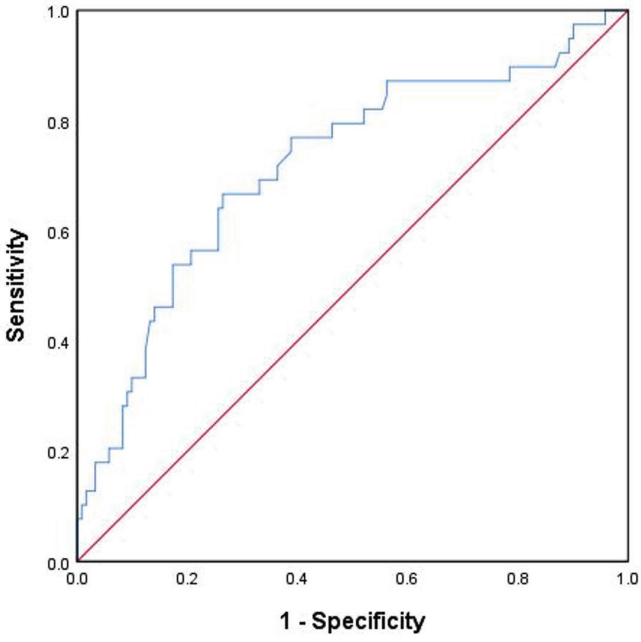


Figure 2. Receiver operating characteristics curve for neutrophil/lymphocyte ratio in patients with localized germ cell testicular tumor

Table 2. Preoperative hematological parameters of the localized germ cell testicular tumor group and the control group (patients who underwent varicocelectomy)

	Germ cell testicular tumor (n=39)	Varicocele (n=121)	p
Neutrophil count (10^3/uL)	5.6 (4.3-7.2)	4.1 (3.3-5.1)	**<0.001**[a]
Neutrophil percentage (%)	65.8 (58.5-72.7)	57.4 (52.1-62.9)	**<0.001**[a]
Lymphocyte count (10^3/uL)	2.1 (1.8-2.6)	2.2 (1.9-2.6)	0.244[a]
Lymphocyte percentage (%)	25.3±8.0	31.4±7.2	**<0.001**[b]
Platelet count (10^3/uL)	269.7±65.3	253.6±52.7	0.121[b]
Mean platelet volume (fL)	8.2±0.87	8.3±0.92	0.536[b]
Hemoglobin value (g/dL)	15.5±1.25	15.6±0.99	0.526[b]
Neutrophil/lymphocyte ratio	2.6 (2.0-3.6)	1.8 (1.4-2.4)	**<0.001**[a]
Neutrophil percentage/lymphocyte percentage ratio (%)	2.7 (1.9-3.7)	1.8 (1.4-2.4)	**<0.001**[a]
Platelet/lymphocyte ratio	124.5 (101.7-158.3)	112.2 (90.5-137.9)	0.051[b]

[a]: Mann-Whitney U test, [b]: Student's t-test, descriptive statistics are expressed as the median (1st quarter-3rd quarter). Data are shown as mean ± standard deviation

two groups was calculated as 2.2532. The sensitivity of NLR at this point was 66.7%, selectivity 73.6%, positive and negative predictive values were 44.8% and 87.3%, respectively and the diagnostic accuracy rate was 71.9%.

Likewise, the area under the ROC curve for NLR (%) was found to be statistically significant in distinguishing the groups (AUC: 0.715, 95% CI: 0.616-0.814 and p<0.001). The best cut-off point for NLR (%) was calculated as 2.5452 and at this point, sensitivity was 56.4%, selectivity was 82.6%, positive predictive value was 51.2%, negative predictive value was 85.5% and diagnostic accuracy was 76.3%.

The area under the ROC curve of PLR was not found to be statistically significant in distinguishing between localized GCT and varicocelectomy groups (AUC: 0.604, 95% CI: 0.499-0.709 and p=0.051) (Table 3).

Table 3. Receiver operating characteristics analysis results for neutrophil/lymphocyte ratio and platelet/lymphocyte ratio levels in differentiating localized germ cell testicular tumor group and varicocelectomy group

	NLR	NLR (%)	PLR
Area under the curve	0.719	0.715	0.604
95% confidence interval	0.622-0.816	0.616-0.814	0.499-0.709
p-value[a]	<0.001	<0.001	0.051
Best cut-off point	>2.2532	>2.5452	-
Sensitivity [TP/(TP+FN)]	26/39 (66.7%)	22/39 (56.4%)	-
Selectivity [TN/(TN+FP)]	89/121 (73.6%)	100/121 (82.6%)	-
PPV [TP/(TP+FP)]	26/58 (44.8%)	22/43 (51.2%)	-
NPV [TN/(FN+TN)]	89/102 (87.3%)	100/117 (85.5%)	-
Accuracy [(TP+TN)/(N)]	115/160 (71.9%)	122/160 (76.3%)	-
Odds ratio	5.563	6.162	-
95% confidence interval	2.553-12.119	2.801-13.560	-
p-value[b]	<0.001	<0.001	-

[a]: Receiver operating characteristics analysis, [b]: Chi-square test with continuity correction, TP: True positive, FN: False negative, TN: True negative, FP: False positive, PPV: Positive predictive value, NPV: Negative predictive value, N: Total number of patients, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio

Discussion

Systemic inflammation varies according to peptides secreted from tumor cells, the inflammatory response of the tumor cells, and the type and extent of the tumor (9). The relationship between tumor and immune system has a very important effect on the clinical course of patients. Immune system cells, on the one hand, fight the tumor, on the other hand, cause the activation of malignant cells with the growth factors they produce, and increase their invasive capacity and metastatic capacity (10). It has been determined that markers such as C-reactive protein, neutrophil and platelet count that measure systemic inflammatory response are independent prognostic factors in many types of cancer (11). NLR and PLR ratios are very suitable parameters for evaluating the inflammatory response with their easy measurement and low cost (12,13).

Studies on testicular tumors and inflammatory response generally evaluated the relationship between prognosis and metastasis

and response (14). The groups in the studies were generally heterogeneous, and there was no clear information about the use of NLR and about a standard cut-off value in the diagnosis of stage I testicular tumors. Our study included only patients with stage I GCT. Since other studies included patients with advanced stage testicular tumors, our study may have provided a clue for detecting patients in the localized stage of testicular tumors where early diagnosis was important. Since patients with stage I disease were included in the study group and the progression was low in this group, the relationship between inflammatory response and prognosis was not evaluated.

When the literature is reviewed, there are different opinions about the relationship between NLR and the stage and prognosis of the testicular tumor. Jankovich et al. (15) found that the NLR was significantly higher in the metastatic patient group with GCT in their study and reported that the NLR could give an idea about the stage of the disease when a diagnosis of testicular tumor was made. In contrast to this information, in a recently published study, it was reported that there was no relationship between preoperative NLR and stage, progression-free survival and cancer-specific survival (16). Interestingly, unlike these two studies, Imamoglu et al. (17) reported that the relationship between NLR and metastasis was limited only to seminomas. We looked at the relationship between inflammatory response and testicular tumor from a different perspective because of the inconsistency between studies, and the increased ease of access to information and awareness of patients in this age group. We evaluated the inflammatory response in terms of stage I which was the most frequently observed stage in testicular tumors at the time of diagnosis. Of course, we tried to homogenize our study with some exclusion criteria, taking into account the non-specific inflammatory response and its increase in many patients. However, it was clear that NLR could not be used as the primary diagnostic method in the diagnosis of testicular tumors. However, our results supported that in case of doubt, with its easy measurement and cost-effectiveness, NLR could be used as an auxiliary tool for diagnosis even in low tumor volumes, with its 2.25 cut-off point and relatively high sensitivity and selectivity.

There is no consensus in the literature regarding the relationship between PLR and the diagnosis, stage and prognosis of testicular tumor. Gokcen et al. (18) found a significant difference in terms of PLR between patients with testicular tumor at different stages and patients who underwent varicocelectomy. In another study, it was reported that PLR could only be an indicator for metastasis in non-seminomatous GCT (17). However, there are still doubts about the use of PLR in all malignancies, not just in testicular tumors (19). In our study, it was determined that the use of PLR for early diagnosis of testicular tumor had no value. However, studies evaluating the relationship of PLR with the prognosis of testicular tumor are needed.

Study Limitations

The most important limitations of our study were that it was a single center and retrospective study, and it included relatively a small number of patients. In addition, although surgical intervention was performed in patients without evidence of infection and routine preoperative evaluation was performed by urologists and anesthesiologists; the failure to evaluate preoperative acute phase reactants could be considered as a limiting factor.

Conclusion

Hematological parameters NLR; with its easy measurement and cost advantage, it can be used as an auxiliary tool to the clinician with a standard cut-off value even in the diagnosis of stage I patients with good prognosis in testicular tumors where early diagnosis is important even if not used primarily.

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Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Board. (decision no: 72/01, date: 23.09.2019)

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Case Report

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Primary Leiomyosarcoma of the Prostate Invading the Rectum and Bladder

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Abstract

Prostate sarcomas originate from the mesenchymal tissues including smooth muscle, fibromuscular stroma, paraganglia, nerves, and blood vessels. They account for less than 0.1% of all prostate tumors and often present with obstructive symptoms. Patients with leiomyosarcoma of the prostate commonly have poor prognosis and their life expectancy varies between 0% and 60% depending on the stage of the disease at the initial diagnosis. Histopathological examination is essential for definitive diagnosis, and can be performed at an early stage using guided transrectal prostate biopsy. Since prostate specific antigen levels are generally normal, digital rectal examinations are extremely important. We report on a 50-year-old man who was diagnosed with leiomyosarcoma based on the histopathology of his transurethral prostatectomy specimen.

Keywords: Digital rectal examination, invasion, leiomyosarcoma, prostate cancer

Introduction

Sarcomas of prostate originate from the prostatic stroma, and are extremely rare. They are responsible for less than 0.1% of all primary prostate malignancies (1,2). Among these, leiomyosarcoma is the most common, comprising 38%-52% of sarcomas, and is highly aggressive (3,4). Herein, we present a patient diagnosed with prostate leiomyosarcoma after transurethral prostatectomy (TUR-P).

Case Presentation

A 50-year-old man admitted to an external clinic with lower urinary tract symptoms (LUTS) was referred to us after he underwent a TUR-P and was diagnosed with leiomyosarcoma based on the histopathology of his specimen. On preoperative digital rectal examination (DRE), the right lobe of the prostate was abnormal and fixed. Prostate specific antigen (PSA) level was 0.63 ng/mL. All laboratory tests including urine analysis, serum creatinine, glucose, complete blood count etc were normal. His F18 fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) demonstrated a mass of 6 cm × 4.5 cm with an irregular size, covering the majority of the prostate gland. Maximal standardized uptake value of this lesion was 51.5 (Figure 1A). Magnetic resonance imaging (MRI) showed a mass lesion of 7 cm × 5 cm. Pressure effect was observed in the rectum and the bladder base. Bilateral parailiac lymph nodes with an index of about 10 mm were observed (Figure 1B) without any signs of distant metastasis.

Thereafter, radical cystoprostatectomy and Miles operation were performed. The patient was discharged 12 days postoperatively.

In the macroscopic examination of the radical cystoprostatectomy specimen involving the adjacent rectum, the prostate showed an ulcerated appearance invading the bladder. Diameter of this lesion was 6.7 cm × 4.5 cm. Microscopic examination revealed nuclear pleomorphism and spindle shaped hyperchromatic nuclei. Tumor cells invaded into the bladder (Figure 2A), seminal vesicles (Figure 2B), and deep muscular layer of the colon (Figure 3A). Numerous typical and atypical mitotic figures were observed among the tumor cells (Figure 3B). Immunohistochemical examination of the tumor revealed positive staining with

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smooth muscle markers such as smooth muscle actin, heartin, caldesmon, and desmin (Figure 4). C-kit and Dog-1 staining

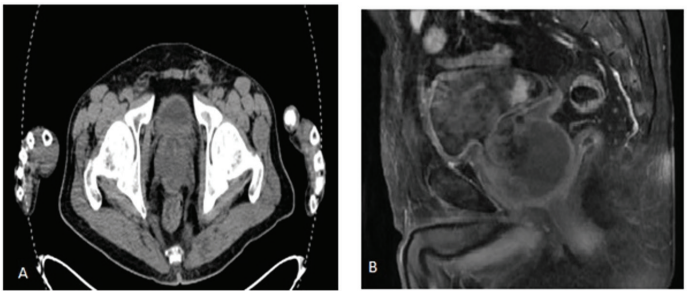


Figure 1. MR and PET/CT imaging findings of prostate leiomyosarcoma. A: PET/CT heterogenous hypodense mass showed hypermetabolic (SUVmax: 51.5) FDG uptake at this level of malignancy. B: Prostatic MRI depicts local invasion of the bladder and rectum in contrast-enhanced T1-weighted images in prostate

MRI: Magnetic resonance imaging, PET/CT: Positron emission tomography/computed tomography, FDG: Fludeoxyglucose, SUV: Standardized uptake value

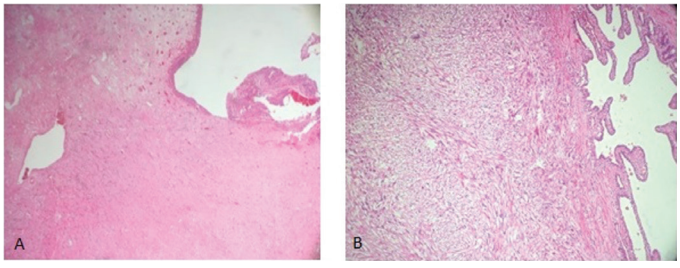


Figure 2. A: Histopathological presentation of prostate leiomyosarcoma, Invasion of the tumor into the bladder. B: Histopathological presentation of prostate leiomyosarcoma, (4x, H & E) Seminal vesicle invation

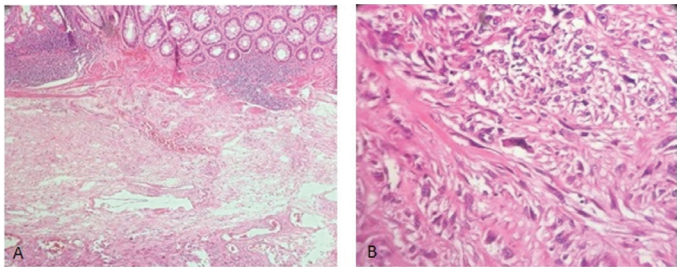


Figure 3. A: Histopathological presentation of the prostate leiomyosarcoma, the area where the tumor is infiltrated into the colon. B: Histopathological presentation of prostate leiomyosarcoma (40x, H & E) tumor cells showing mitosis and pleomorphism

were negative. Tumor cells were not observed in the pelvic lymph nodes.

Discussion

Primary sarcomas of the prostate are extremely rare. The most common among these is leiomyosarcoma originating from the smooth muscles of the prostate. It has an aggressive clinical course (4). Presenting complaints include perineal and pelvic pain, frequent urination, hematuria, constipation, and obstructive symptoms. Serum PSA levels are typically normal due to their non-epithelial origin, making it highly difficult to

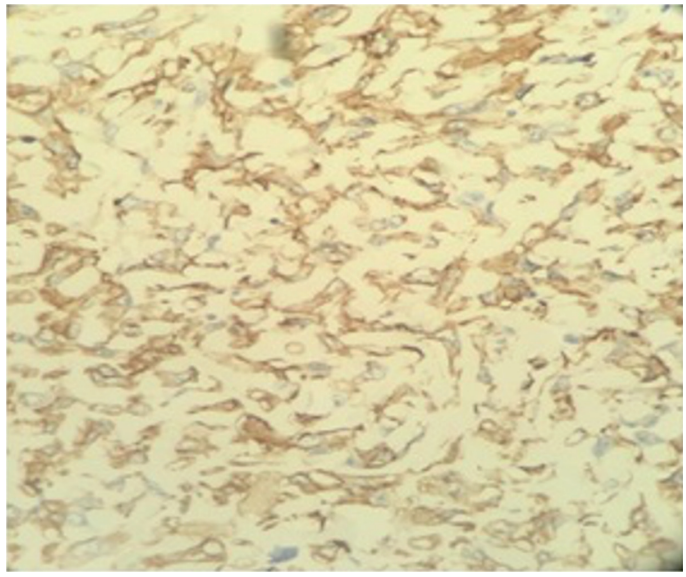


Figure 4. Histopathological presentation of prostate leiomyosarcoma, (40x) Desmin (immunohistochemistry) and tumor cells

differentiate these from benign prostatic diseases. The final diagnosis is usually accomplished via transrectal ultrasonography guided needle prostate biopsy, TUR-P, and less frequently by open surgery (4,5). In this case, the diagnosis was accomplished via TUR-P. The largest diameter of the tumor was 7 cm, it was macroscopically infiltrative, and its size was compatible with that in the literature (3-21 cm) (6).

Leiomyosarcoma of prostate was described by Gaudin et al. (7) in 1998. World Health Organization classifies this tumor as a distinct spindle cell neoplasm (8). Recently, "Stromal tumors of uncertain malignant potential (STUMP)" was used to define the clinical course and histological features of these tumors. Four different types of STUMP were described based on their histology. Stromal sarcoma may occur as a de novo primary or coexist with pre-existing or synchronous STUMP, indicating that the latter may potentially convert into stromal sarcoma.

Differential diagnoses of prostatic stromal sarcoma include prostate adenocarcinoma, benign prostatic hyperplasia, and prostate abscess; however, imaging features are variable.

Such tumors can invade adjacent structures such as the bladder and rectum, as in our patient. Therefore, a combination of radical cystoprostatectomy, abdomino-perineal resection, and Miles operation was performed. Routine pelvic lymphadenectomy is usually not recommended unless pathological lymph nodes are observed on radiological examination (9). We performed pelvic lymphadenectomy due to the suspected 1 cm large lymph nodes on MRI.

Although, there are no standardized imaging protocols to detect metastasis for prostatic leiomyosarcoma, F18 PET/CT or conventional CT and MRI have been widely used (3,4,9,10,11). Moreover, F18 PET/CT provides additional benefits in the diagnosis, staging, and follow-up of sarcomas (10,11). We performed both F18 PET/CT and MRI for our patient.

The most important tool for early diagnosis is DRE that can detect the size of the prostate, stiffness, and the involved mass.

However, patients may sometimes reject DRE. This report also highlighted the need for DRE to be a part of the routine physical examination, even in patients with normal PSA levels.

The prognosis of leiomyosarcoma of the prostate is poor, and it may show wide regional and distant metastasis to the lungs, liver, and bones via lymphatics and blood vessels. Approximately 25% of patients present with distant metastasis (12). About 50%-75% of patients with leiomyosarcoma die within 2-5 years (13). Therefore, these patients must be evaluated at centers with significant experience. The treatment should be guided by the stage of the disease. In the absence of metastasis, the most preferred treatment is radical surgery; however, total excision may not be possible in the majority of patients. Achieving negative surgical margins is rather difficult due to the invasion into the adjacent structures (4). In our patient, invasion into the right and left seminal vesicles, rectum, and bladder was observed. Additionally, the tumor had invaded the right and left posterior abdominal wall. Based on the histopathological findings, the uro-oncology council decided to prescribe chemotherapy and radiotherapy for the patient, and he is currently receiving his treatment.

Conclusion

Leiomyosarcoma of the prostate is a rare disease with a poor prognosis. Patients commonly present with LUTS, and a DRE usually reveals an abnormal prostate. Therefore, the significance of DRE should never be underestimated, even in patients with normal PSA levels.

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Video Article

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Robotic Seminal Vesicle Surgery: The Key Steps

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Abstract

Seminal vesicle (SV) cystic masses are rarely encountered entities in daily clinical practice. They are mostly asymptomatic and require no treatment; however, surgical removal of the cyst is highly effective treatment in symptomatic cases. Due to embryological mesonephric duct abnormality, surgical SV cysts most often present as a part of Zinner's syndrome (renal agenesis, ipsilateral SV cyst and ejaculatory duct obstruction). In this video article, we summarise our minimally invasive surgical approach to two consecutive cases of symptomatic SV cyst at our institution.

Keywords: Seminal vesicle, seminal vesicle mass, seminal vesicle cyst, robotic surgery, laparoscopy

Before the main procedure, cystoscopy was performed and a six Fr ureteral catheter was placed in the healthy solitary kidney. After placing the Foley catheter, the patient was repositioned.

The patient was placed in a low lithotomy, 30 degree Trendelenburg position. All pressure points were carefully padded to avoid secondary injuries. Capnoperitoneum was created using the Veress needle technique. After introducing an 8-mm robotic camera port, the remaining robotic trocars were introduced into the abdomen under direct vision. All robotic trocars were placed in a straight line. A 12-mm assistance trocar was placed most laterally to the left lateral robotic trocar, while a 5-mm assistance trocar was placed more cranially on the pararectal line. The robotic system was placed at the patient's feet and docked. The procedure was conducted under an average pressure of 13-15 mm Hg. Throughout the procedure, the assistant remained on the left side of the patient, and the assistant's monitor was placed on the right side of the operating table. Maryland bipolar, fenestrated prograsp and monopolar scissors instruments were utilised.

The parietal peritoneum was incised at the level of Denonvilliers fascia and dissection was performed in a sharp and blunt fashion anteriorly to Denonvilliers fascia and posteriorly to SV. Later on, the dissection plane was advanced anteriorly to the SV. Afterwards, lateral and medial dissections were performed. The left vas deferens was identified and transected as well.

Throughout the dissection, bleeding was controlled either by bipolar or monopolar cautery. Blood supply to the cystic tissue through irregular vessel structures were controlled using Hem-o-lock clips when necessary.

Specimens were retrieved from the abdominal cavity using an endo-catch bag. Afterwards, the incised peritoneum was repaired with Hem-o-lock clips. Trocars were removed and the drain was placed through the previously formed trocar defect on the abdominal wall under direct camera vision. The ureteral catheter was removed immediately after the procedure in the operating room, while the foley catheter and abdominal drain were removed within 12 and 24 hours after the surgery, respectively.

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