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

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

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

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

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

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

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Instructions to Authors

1. General Information

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

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

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

All submitted manuscripts are committed to rigorous peer review.

THE BULLETIN OF UROONCOLOGY DOES NOT CHARGE ANY ARTICLE SUBMISSION, PROCESSING OR PUBLICATION CHARGES, NOR DO AUTHORS RECEIVE ANY REMUNERATION OR COMPENSATION FOR THEIR MANUSCRIPTS.

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

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

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

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

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

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

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

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

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

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

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

3. Peer-Review Process

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

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

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

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

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

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

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

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

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

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

-Abbreviations:

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

-Units of Measurement:

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

-Statistical Evaluation:

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

-Language:

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

5. Article Types

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

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

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

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

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

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

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

3) References

4) Figure legends

5) Short Quiz for review articles.

Tables and figures should be uploaded separately.

Also, "Acknowledgements Form" should be uploaded separately.

A. Original Research Articles

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

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

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

-Introduction

- Materials and Methods

- Results

- Discussion

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

-Tables and figures should be uploaded separately.

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

Preparation of research articles, systematic reviews, and meta-analyses must comply with study design guidelines: CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consortstatement.org/); PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/); STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.)(http://www.stard-statement.org/); STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/); MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

A word count for the original articles (excluding title page, acknowledgements, references , figure and table legends) should be provided not exceed 3000 words. Number of references should not exceed 30. Number of figure/tables is restricted to five for original articles.

B. Case Reports

Case reports should include cases which are rarely seen and distinctive in diagnosis and treatment. These can include brief descriptions of a previously undocumented disease process, a unique unreported manifestation or treatment of a known disease process, or unique unreported complications of treatment regimens, and should contribute to our present knowledge.

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

- First page: Title - Abstract (limited to 150 words, unstructured - Keywords (List 3-5 key words using Medical Subjects Headings [MeSH])

-Introduction

-Case Presentation

-Discussion

-References

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

-Tables and figures should be uploaded separately.

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

A word count for the case reports (excluding title page, acknowledgements, references, figure and table legends) should be provided not exceeding 1500 words. Number of references should not exceed 15. Number of figure/tables is restricted to three for case reports.

C. Review Article

These are manuscripts which are prepared on current subjects by experts who have extensive experience and knowledge of a certain subject and who have achieved a high number of publications and citations. Reviews are usually submitted directly or by invitation of the editorial board. Submitted reviews within the scope of the journal will be taken into consideration by the editors. The content of the manuscript should include the latest achievements in an area and information and comments that would lead to future studies in that area. Number of authors should be limited to three.

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

- First page: Title -Abstract (maximum 250 words; without structural divisions - Keywords (List 3-5 key words using Medical Subjects Headings [MeSH]).

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

-Conclusions

-References

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

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

-Tables and figures should be uploaded separately.

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

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

D. Literature Review

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

E. Editorial Commentary

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

F. Letters to the Editor

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

G. Surgery Videos on Urooncology (Video-urooncology)

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

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

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

Video-urooncology submission should include:

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

2) Title Page

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

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

6) "Acknowledgements From" should be uploaded separately.

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

6. Manuscript Preparation

Manuscripts should be prepared following sequence according to article type:

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

B. Title Page

The title page should include the following:

-Full title

-Running title

-Authors' names and institutions

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

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

C. Main Text (without authors' credentials)

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

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

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

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

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

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

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

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

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

Examples for writing references:

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

Example:

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

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

Example:

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

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

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

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

D. Tables and Figures

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

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

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

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

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

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

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

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

Submissions must include according to the following sequence:

A-Original Article

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

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

4) Table(s)

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B. Case Reports

1) Copyright Transfer and Author Declaration Statement Form

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

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

4) Table(s)

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C-Review Article

1) Copyright Transfer and Author Declaration Statement Form

2) Title Page

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

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

4) Table(s)

5) Figure(s)

6) Acknowledgements Form

D. Literature Review

1) Copyright Transfer and Author Declaration Statement Form

2) Title Page

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

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

4) Table(s)

5) Figure(s)

6) Acknowledgements Form

E. Editorial Commentary

1) Copyright Transfer and Author Declaration Statement Form

2) Title Page

3) Main text (Text, References)

4) Acknowledgements Form

F. Letters to the Editor

1) Copyright Transfer and Author Declaration Statement Form

2) Title Page (The title is "Letter to Editor about.....")
3) Main text (Text, References)
4) Acknowledgements Form

G. Surgery Videos (Video-urooncology)

1) Copyright Transfer and Author Declaration Statement Form
2) Title Page
3) Summary (without authors' credentials)
4) Video
5) Acknowledgements Form

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The Importance of Early Diagnosis and Tumor Size in Testicular Cancers

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Keywords: Testicular tumor, tumor size, seminoma, early diagonosis, testicular cancer

To the Editor,

Accounting for just 1% of total malignancies in males, testicular cancers are the most prevalent organ malignancies in males aged 20-40 (1). Although still relatively uncommon, researchers have yet to identify why the rate of occurrence of these tumors has been rising over the last twenty years (2). An early indication of testicular cancer is most frequently a palpable mass that is not painful. The absence of pain may result in diagnostic delay, which is a clinically important problem. The complete cure rate for testicular cancer is now nearly 100%, mostly attributable to timely diagnosis and to the fact that these types of tumors are highly sensitive to both chemotherapy and radiotherapy (3). Therefore, tumor size has become a significant factor both in the clinical stage of testicular cancers and surgical treatment. With seminomas in particular, which are the most common type, tumor size is a staging criterion and a risk factor for occult metastatic disease. The eighth publication of the American Joint Committee on Cancer includes an important revision to Tumor-Node-Metastasis classification. Two subgroups were created for pathological tumor stage (pT1) seminomas based on tumor size, with a tumor <3 cm now categorized as pT1a and a tumor >3 cm considered as T1b (4). Moreover, meta-analyses showed that in stage 1 seminomas, patients with tumors >4 cm and/or presenting with rete testis involvement were at risk for developing occult metastatic disease (5,6). In a study we conducted last year in the Antalya region, the mean tumor size in radical orchiectomy materials from patients diagnosed as having seminoma was 4.75±2.04 cm, which is not encouraging (7). In further research on testicular tumors carried out in conjunction with our study nearly two decades earlier, the average seminoma specimen tumor was found to be 4.92±3.03 cm (8). This indicates that tumor size when initially diagnosed has not seen notable improvement in the last twenty years. In addition, the size of the testis remains relevant when determining the extent of surgical treatment. Radical orchiectomy is still considered the gold standard for testicular tumor treatment; however, partial orchiectomy (PO) is a viable option in certain cases. In order to maintain the production of testosterone and development of sperm cells, preserving testicular function with PO is critical. Subsequent studies have shown that PO has no significant local or distant recurrence risk that may affect progression (9). Therefore, the latest American Urology Association guideline suggests that PO can be considered for patients with normal serum tumor markers and solitary tumors sized ≤2 cm (10). In a recent study, 124 patients operated for testicular tumors between 2011 and 2019 had tumors that measured 4.01±2.29 cm on average, and unfortunately, tumors were ≥2 cm in 76.4% of these patients (7). If evaluated from this point of view, we see it is already too late for PO at the time of diagnosis. These findings underline the importance of ensuring the public is well informed about early diagnosis, particularly those individuals who fall into the high-risk category based on age. The simplest and least expensive method to detect tumors of the testes is through self-examination (11). For males who are 15-45 years old in particular, and within society at large, increasing knowledge of the importance of routine self-checks will facilitate the detection of tumors in the testes at smaller sizes.

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Review

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Management of Localized Prostate Cancer in Elderly Patients

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Abstract

There are uncertainties concerning treatment management in elderly patients diagnosed with localized prostate cancer. The patient's age and morbidity are the most important factors affecting the treatment to be applied. Many screening scales are used for this purpose. It is reported that standard definitive treatments are suitable for patients with a life expectancy of more than 10 years, who are considered fit according to these screening scales. However, treatment options should be discussed in detail with patients in this group, which are already old and getting older. Therefore, elderly patients can be considered as the group that should be given the most information about the side effects of treatments. It is very important to properly evaluate the current state of the patient prior to treatment and inform them well to ensure that they have more rational expectations.
Keywords: Elderly patients, management, prostate cancer

Introduction

According to the global cancer statistics data, in 2020, prostate cancer was the second most common type of cancer after lung cancer in men, with approximately 1.4 million new cases. It is also the fifth leading cause of death due to cancer (1). At the time of diagnosis, 60% of patients are over the age of 65 years, and 70% of prostate cancer-related deaths occur in those aged 75 years and over (2). It is predicted that these rates will gradually increase as the world population ages (3).

Patients Selection

Age is an important factor in both the etiology and treatment selection of prostate cancer. However, in elderly patients that are planned to be treated for prostate cancer, treatment selection should be planned according to the biological age and health status of the patient, not according to chronological age (4). When determining the health status of this patient group, it is recommended to perform a comprehensive geriatric evaluation, including data on their comorbidities, nutritional status, physical functions, and cognitive-mental status (5). Studies have shown that a comprehensive geriatric evaluation has positive effects on the survival and quality of life of these patients (6). However, this type of evaluation requires specialist geriatricians and is a very time-consuming process. In addition, not all elderly patients need a comprehensive geriatric evaluation. Therefore, a number of geriatric screening tools have been developed to determine which patients need this evaluation, with the most accepted being the Geriatric-8 (G8) screening scale (Table 1) (7,8).

Patients who have a score above 14 on the G-8 screening scale, which also has Turkish validation, do not require a comprehensive geriatric evaluation. However, a score of ≤14 has been reported to be associated with three-year mortality, and therefore a comprehensive geriatric evaluation is recommended for these patients (7,9,10).

The International Society of Geriatric Oncology (SIOG) recommends evaluating the capacity of elderly cancer patients to properly evaluate the information provided for them and make informed decisions about their treatment processes. There are many screening scales developed for this purpose. SIOG recommends the use of the Mini-Cog™ test (Table 2) for the evaluation of cognitive functions in elderly patients with prostate cancer (11). This is a short test consisting of a combination of three word registration, clock drawing and three word recall tasks to distinguish patients with dementia from those without dementia. The evaluation is made over a total of 5 points. Patients with a score of ≤3 should be further evaluated for dementia (12).

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Table 1. G8 screening tool (7)	
Item	**Score**
Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0= Severe decrease in food intake 1= Moderate decrease in food intake 2= No decrease in food intake
Weight loss during the last 3 months	0= Weight loss greater than 3 kg 1= Does not know 2= Weight loss between 1 and 3 kg 3= No weight loss
Mobility	0= Bed or chair bound 1= Able to get out of bed/chair but does not go out 2= Goes out
Neuropsychological problems	0= Severe dementia or depression 1= Mild dementia 2= No psychological problems
BMI = Weight in kg/(height in m)^2	0= BMI less than 19 1= BMI 19 to less than 21 2= BMI 21 to less than 23 3= BMI 23 or greater
Takes more than 3 prescription drugs per day	0= Yes 1= No
In comparison with other people of the same age, how does the patient consider his/her health status?	0= Not as good 0.5= Does not know 1= As good 2= Better
Age	0= >85 years 1= 80-85 years 2= <80 years
BMI: Body mass index	

The European Association of Urology (EAU) and the SIOG Prostate Cancer Working Group recommend the use of a decision tree model (Figure 1) using the G8 screening scale and the Mini-Cog™ test for the treatment planning of prostate cancer cases aged over 70 years (13,14). According to the decision tree model, patients are divided into three groups: Group 1, fit; group 2, vulnerable (sensitive and susceptible); and group 3, frail (weak, fragile). All patients in group 1 and those with reversible disorders in group 2 should receive the same treatment as younger patients after their existing problems have been resolved. The treatment of patients in group 3 with irreversible disorders should be managed with treatment models tailored to each patient. For patients whose condition is even more severe, only palliative treatments are recommended (13).

Most patients with prostate cancer over the age of 65 years die due to co-morbidities (15). The most common co-morbidities in elderly patients with prostate cancer are lung and heart diseases, followed by vascular diseases, kidney diseases, and diabetes mellitus (16). These co-morbid conditions are known to be independent prognostic factors for survival in patients with cancer (17). Therefore, in order to decide how the current co-morbidities of elderly patients will affect the selection of treatment, first, these co-morbidities need to be evaluated systematically. Various methods have been developed for this purpose, with the most commonly used examples being the Charlson co-morbidity index (CCI) (Table 3) and the Cumulative Illness Rating Scale for Geriatric Individuals (Table 4) (18).

In CCI, the patient's co-morbid conditions are scored from 1 to 6, depending on the risk of death with which they are associated, and the total score obtained is used to predict mortality risk (19). There are studies showing that CCI can also be used to predict progression-free survival, postoperative complications, and length of hospital stay (20).

Localized prostate cancer treatment options should be reviewed by evaluating all these factors of patients. The most appropriate treatment method should be decided after informing the patient about the advantages and disadvantages of treatment options, such as active surveillance, watchful waiting, radical prostatectomy, and radiotherapy.

Treatment Options

Active Surveillance and Watchful Waiting

Treatment decisions concerning elderly patients with localized prostate cancer should be based on the risk evaluation. In this group of patients, the risk of death due to prostate cancer and the risk of death due to co-morbidities should be evaluated, and the potential risks and side effects of the treatment to be applied, as well as patient preferences should be considered (21).

Active surveillance aims to delay curative treatment as much as possible in patients with clinically localized prostate cancer. Here, the aim is to protect the patient from the potential side effects of curative therapy. Meanwhile, patients are followed up closely based on the prostate-specific antigen (PSA) value, digital rectal examination and multiparametric magnetic resonance imaging findings, and recurrent prostate biopsies. The aim of active surveillance is to identify and treat patients who will need active treatment during the follow-up protocol before missing

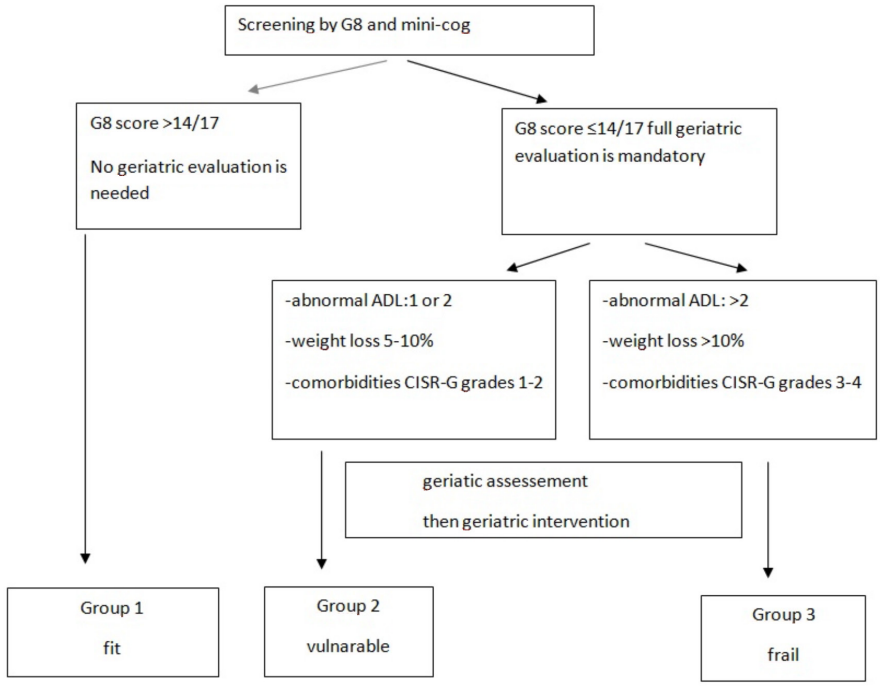

Figure 1. EAU geriatric assessment flow-chart (13). Decision tree for health status screening (men >70 years)

EAU: European Association of Urology

the chance for curative treatment (22). In a study including 993 patients under active surveillance, four factors associated with general mortality were defined: >70 years of age, high Gleason score, high prostate volume, and high PSA level. It was reported that among elderly patients, mortality mostly occurred for reasons other than prostate cancer, and when evaluated in terms of cancer-specific survival, patients aged >70 years did not differ from those aged <70 years (23).

It is also necessary to mention some of the disadvantages of the active surveillance option. An important handicap of the active surveillance option is the need for repeat biopsy procedures during the follow-up. Each biopsy poses a higher risk for sepsis and bleeding for the elderly group of patients compared to the younger patient group. Therefore, the patient should be well informed about the risks involved. In addition, the patient, who is already old and is getting older, may develop further co-morbidities during the process of transition to definitive treatment. Delaying definitive treatment constitutes a further problem due to the possibility of the risk group of the patient changing during this process. Therefore, active surveillance may have to switch to watchful waiting. Active surveillance can be considered as the treatment option that is most difficult to decide in the elderly patient group. In light of all these findings, active surveillance can be regarded as a rational treatment option in elderly patients with a low risk.

In watchful waiting, patients that are considered unsuitable for curative treatment due to their general health conditions and have a life expectancy of less than 10 years are followed up without treatment until the development of symptoms related to local or systemic progression. After this stage, palliative treatments are applied to these patients (24). Considering older age and scoring system parameters, watchful waiting may be the most accurate option for patients in the frail group.

According to the SIOG prostate cancer study group, elderly patients with prostate cancer that are in the low and intermediate risk groups according to the D'Amico classification can be followed up with either active surveillance or watchful waiting depending on their individually determined life expectancy (13).

Radical Prostatectomy

There are studies showing that patients aged ≥75 years who have undergone open radical prostatectomy have higher rates of mortality and morbidity, as well as more perioperative and postoperative complications compared to those aged <75 years (25,26). Due to these high morbidity and mortality rates, elderly patients are often not considered suitable for curative treatment options for prostate cancer and are followed up with conservative methods. However, prostate cancer detected in older men tend to pose a higher risk (27). It is known that patients with high-risk diseases face a greater risk of death when followed up with conservative treatments (28). Studies show that patients who are not given local curative treatment only due to their chronological age have increased mortality rates associated with prostate cancer, as well as significant morbidities, such as long-term urethral catheterization, development of hydronephrosis, nephrostomy opening, and colostomy opening due to the local progression of prostate cancer (28,29). Recently, there has been growing awareness that elderly patients with cancer are under-treated, especially in terms of local curative therapy (30). Developments in the surgical technique and the increasing adoption of minimally invasive methods have encouraged the

Table 2. Mini-Cog™ test (10)

Step 1. Three word registration

Look directly at person and say, "Please listen carefully. I am going to say three words that I want you to repeat back to me now and try to remember. The words are (select a list of words from the versions below). Please say them for me now." If the person is unable to repeat the words after three attempts, move on to Step 2 (clock drawing)

The following and other word lists have been used in one or more clinical studies.1-3 for repeated administrations, use of an alternative word list is recommended

Version 1	Version 2	Version 3	Version 4	Version 5	Version 6
Banana	Leader	Village	River	Captain	Daughter
Sunrise	Season	Kitchen	Nation	Garden	Heaven
Chair	Table	Baby	Finger	Picture	Mountain

Step 2. Clock drawing

Say: "Next, I want you to draw a clock for me. First, put in all of the numbers where they go." When that is completed, say: "Now, set the hands to 10 past 11."

Use preprinted circle (see next page) for this exercise. Repeat instructions as needed as this is not a memory test. Move to step 3 if the clock is not complete with in three minutes

Step 3. Three word recall

Ask the person to recall the three words you stated in step 1. Say: "What were the three words I asked you to remember?" Record the word list version number and the person's answers below

Word list version: _____ Person's answers: _____ _____ _____

Scoring

Word recall: _____ (0-3 points)	1 point for each word spontaneously recalled without cueing
Clock draw: _____ (0 or 2 points)	Normal clock = 2 points. A normal clock has all numbers placed in the correct sequence and approximately correct position (e.g., 12, 3, 6 and 9 are in anchor positions) with no missing or duplicate numbers. Hands are pointing to the 11 and 2 (11:10). Hand length is not scored. Inability or refusal to draw a clock (abnormal) = 0 points
Total score: _____ (0-5 points)	Total score = Word recall score + Clock draw score. A cut point of <3 on the Mini-Cog™ has been validated for dementia screening, but many individual swithc clinically meaningful cognitive impairment will score higher. When greater sensitivity is desired, a cut point of <4 is recommended as it may indicate a need for further evaluation of cognitive status

widespread use of radical prostatectomy in elderly patients (31). In a study evaluating 800 patients who underwent robot-assisted laparoscopic radical prostatectomy, the patients were divided into two groups as <70 years and ≥70 years. At the end of the study, no difference was found between the groups in terms of perioperative complications (32). In another study, Iguchi et al. (33) compared the results of 28 patients over 70 years of age and 47 patients under 70 years who underwent robotic radical prostatectomy for prostate cancer. All patients underwent a urodynamic examination preoperatively and at three months after the operation. The presence of persistent overactive bladder symptoms in the group with ongoing postoperative urinary incontinence was reported to be significantly higher in the elderly patient group. It was also determined that the presence of overactive bladder symptoms before the operation was associated with incontinence regardless of age. Therefore, the preoperative evaluation of continence status, overactive bladder symptoms, and evaluation of urethral closure pressure with urodynamic studies, if necessary, may be useful in terms of more rational expectations (33). A recent study published in Turkey evaluated the results of robot-assisted laparoscopic radical prostatectomy performed in patients aged <70 years (n=819) and ≥70 years (n=151). At the end of the study, the authors reported that they did not detect any difference in terms of oncological and operative results, although the functional results were statistically significantly worse in the elderly group (34). In another study conducted in our country; as emphasized by Tavukçu and Kaplan (35), in the elderly patient group with frail but treatable disease, standard treatment can be applied after existing comorbidities are corrected or improved. Considering all these findings, patients aged ≥75 years should be informed about the increased risk of perioperative morbidity and mortality compared to younger patients.

Age is an independent risk factor for urinary incontinence in patients undergoing radical prostatectomy (36). Studies have demonstrated an inverse relationship between advancing age and continence rates (37,38). The rate of erectile dysfunction development after radical prostatectomy is also negatively affected by age (39).

While the EAU guidelines suggest that patients who will undergo radical prostatectomy should have a life expectancy of at least 10 years, the National Comprehensive Cancer Network guidelines state that this period is 10-20 years depending on the

Table 3. Charlson co-morbidity index	
Score	**Comorbid condition**
1	Myocardial infarction Congestive heart failure Cerebro vascular disease Peripheral vascular disease Dementia Chronic obstructive pulmonary disease Connective tissue disease Peptic ulcer disease Mild liver disease Age[a]
2	Diabetes Hemiplegia Moderate/severe renal disease Diabetes with end-organ damage Any solid tumour Leukemia Lymphoma
3	Moderate/severe liver disease
6	Metastatic solid tumour Acquired immunodeficiency syndrome
[a]For each decade after 40 years, a point is added (1 point for age group 41-50, 2 points for age group 51-60, 3 points for 61-70, 4 points for 71 or older)	

risk groups (40). In a review of radical prostatectomy performed in patients over 75 years of age, Mandel et al. (41) reported that biological age should not constitute a definite contraindication to radical prostatectomy. The authors stated that the perioperative morbidity and mortality rates were higher and oncological and functional outcomes were worse in the elderly group but the results were still acceptable. Considering all these factors, the authors emphasized that radical prostatectomy was a viable treatment option in a well-selected patient group aged 75 and over (41). In a study including 2,000 patients who underwent radical prostatectomy, Porres et al. (42) evaluated the functional outcomes of 45 patients aged 75 years and older. In the third month, the continence rate was 18.0% in the elderly patient group and 37.5% in the younger group. However, at the 12th-month evaluation, the authors determined these rates to be 76.7% and 85.7%, respectively, indicating no statistically significant difference (p=0.084). As a result, although the authors found no difference between the continence rates of the groups in the first year, they emphasized that the elderly patients needed more time to achieve continence.

When evaluated in terms of impotence, it is not surprising that the functional results of elderly patients are worse. The most important factors in impotence are pre-operative potency status and whether a nerve-sparing approach is applied. A study evaluating patients who underwent bilateral nerve-sparing surgery by Mandel et al. (41) was reported the postoperative potency rates as 66.2% for the young patient group and 39.6% for the elderly patient group. Similarly, in a study conducted by Sokolov et al. (43) with 117 patients over 65 years of age who underwent radical prostatectomy, it was observed that age had no effect on oncological outcomes and the potency ratios of the cases, especially those in which the bilateral nerve-sparing approach was used improved earlier regardless of age.

Table 4. Cumulative Illness Rating Scale (17)	
Rating strategy of comorbidity	
0= No problem	Organ system not compromised
1= Mild	Illness/impairment with or without Requirement of therapy, excellent prognosis, patient with normal activity
2= Moderate	Illness/impairment requiring therapy, good prognosis, compromised activity
3= Severe	Illness/impairment with urgent requirement of therapy, prognosis unclear, marked restriction in activity
4= Extremely severe	Life threatening illness/impairment, emergency case of therapy, adverse prognosis
Assess illness/impairment in each of the following systems on a scale from 1 to 4:	
System	**Score**
Heart	
Blood pressure	
Vascular	
Respiratory	
Eye/ear/nose/throat/larynx	
Upper gastrointestinal	
Lower gastrointestinal	
Liver	
Renal	
Genitourinary	
Musculoskeletal	
Endocrine/metabolic	
Neurological	
Psychiatric	
Total	

Compared to younger patient groups; worse postoperative functional results are expected in elderly patients due to longer recovery times and worse preoperative erectile functions and urinary continence. In brief, radical prostatectomy is a strong option in well-selected elderly patients. However, it is important to inform the patient well that this option has worse functional outcomes.

Radiotherapy

In localized prostate cancer, radiotherapy is an important treatment modality with cancer control rates similar to radical prostatectomy (44). In the literature, modifications of radiotherapy applications due to age-related specific toxicities in elderly patients have been evaluated. In a recent study including 3,216 patients divided into two groups as <75 and ≥75 years, each group was further randomized into three groups as 74 Gy-37 fraction (conventional method), 60 Gy-20 fraction, and 57 Gy-19 fraction. As a result of the study, no difference was found between the <75 and ≥75 years groups in relation to the biochemical or clinical failure (BCF)-free rates after radiotherapy. In the ≥75 years group, the BCF-free rates were 84.7% for the

74 Gy subgroup, 91% for the 60 Gy subgroup, and 87.7% for the 57 Gy group. In the same study, the authors reported that there was no increased risk of radiation-induced acute bowel and bladder toxicity in the ≥75 years group (45).

In another study evaluating 902 patients who underwent external beam radiotherapy and 1,527 patients who underwent brachytherapy for clinically localized prostate cancer, the patients were divided into two groups as ≥80 years and <80 years. As a result of the study, no significant difference was found between the age groups in terms of the five-year biochemical failure-free survival rates (91.3% vs. 85.9%, p=0.6171) and cancer-specific survival rates (100% vs. 99.3%, p=0.6171). The long-term results of the study that the gastrointestinal toxicity rates were similar between the groups. The authors stated that among the patients that received brachytherapy, the rate of late genitourinary toxicity was significantly higher in the ≥80 years group than in the <80 years group, and the former required sensitive care in terms of late genitourinary toxicity (46).

Considering the similar efficacy and acceptable side-effect profile, radiotherapy is a strong treatment candidate in the curative treatment of localized disease in elderly patients. However, it should be kept in mind that a closer follow-up is required in terms of postoperative genitourinary and intestinal toxicity.

Conclusion

There are many factors that should be considered when deciding on treatment in elderly patients with prostate cancer. The basic principle in treatment management should be to take action according to co-morbidity risk scores, which may change depending on the co-morbidity status of the patient during the treatment process. The elderly constitute a patient group in which the advantages and disadvantages of each treatment option should be discussed with utmost sensitivity. Accurate and proper patient information is valuable in preventing irrational expectations. This process should be managed by evaluating all factors, and follow-up should be personalized according to the current co-morbidities of patients. This will help patients achieve the highest benefit from the treatment and keep their comfort at an optimal level.

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Short Quiz

1- Which of the following is the most accurate nodal staging method?

A) CT or MR imaging

B) PSMA/PET CT imaging

C) Extended lymph node dissection

D) Abdominal ultrasonography

E) Transrectal ultrasonography

Answer: C

2- Which of the following is incorrect about a 78-year-old patient diagnosed with localized prostate cancer?

A) It is not suitable for definitive treatment, watch full waiting treatment should be applied.

B) Comorbidity scores should be used in making the treatment decision.

C) Oncological outcomes after radical surgery are similar to younger patients.

D) It should be informed that the postoperative functional results are worse than the younger patient group.

E) Radiotherapy has high success rates.

Answer: A

3- Which of the following is incorrect for a diagnosis of advanced age localized prostate cancer?

A) Patients with a life expectancy of more than 10 years can be treated with standard treatment methods.

B) Longer follow-up is required in terms of intestinal toxicity in elderly patients who received radiotherapy.

C) Active surveillance is not accepted as a treatment option due to advanced age.

D) Watch full waiting can be applied to patients with a life expectancy of less than 10 years.

E) Hypofractionation can be used for radiotherapy.

Answer: C

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Review

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The Current Approach for Small Adrenal Masses

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Abstract

Adrenal tumors originate from the medulla or cortex of the adrenal gland and may be benign or malignant, functional or non-functional. Adrenal tumors discovered during imaging for non-adrenal indications are called incidentalomas and are more common than non-incidental masses. Most incidentalomas are hormonally inactive and benign. Adrenal masses are approximately 30-35 mm in diameter at the time of diagnosis. While masses less than 4 cm are generally considered to be small masses, they are at lower risk for malignancy than adrenal masses larger than 4 cm. An incidentally detected adrenal mass should be investigated for malignancy and functional activity. Hormonal activity or malignancy of the adrenal mass are indications for surgery. Laparoscopic surgery for adrenal adenomas is the gold standard. Evaluation is important to determine the treatment and follow-up process. Although the frequency of benign small adrenal masses increase with age, even if the mass size is <4 cm in young patients, because of their rarity at this age, a closer follow-up is required. The ideal follow-up schedule for these small masses <4 cm in diameter has not been precisely defined. However, clinical guidelines recommend clinical and hormonal follow-up for at least 4 years, and follow-up imaging [computed tomography (CT), magnetic resonance imaging] 6-12-24 months after the first CT. If the size increase in a followed mass is >0.8 cm/year, surgery is recommended, but the malignancy rate is low in these masses.

Keywords: Adrenal, adrenalectomy, incidentaloma

Introduction

Anatomy and Physiology of the Adrenal Gland

Adrenal glands are organs in the upper part of both kidneys, located at the level of the 11th and 12th ribs, and are approximately 4-5 gr and 0.5-1x4-5x2-3 cm in size. In front of the right adrenal gland is the liver and medially the vena cava. The left adrenal is adjacent to the aorta medially, splenic vein and artery, the body of the pancreas and stomach anteriorly (1,2,3).

The adrenal gland is rich in vascular structure, and during stress, it has 5-6 times the normal blood flow. Blood flow is provided by the superior, median and inferior adrenal arteries. The venous return is directly to the inferior vena cava with a short segment on the right, and to the left renal vein after merging with the inferior phrenic vein on the left (Figure 1). Lymphatic drainage is provided by the paraaortic lymph nodes on the left and the paracaval lymph nodes on the right. Autonomic innervation of the adrenal glands includes preganglionic sympathetic fibers going to the chromaffin cells of the adrenal medulla, while postganglionic fibers originating from the splanchnic ganglia provide innervation of the adrenal cortex (1,2,3,4,5,6). Figure 1 shows the anatomy of the adrenal gland in detail (7).

The adrenal gland consists of the medulla, which functions as a neurocrine organ, and the cortex, which functions as an endocrine organ. The adrenal cortex consists of 3 layers. The zona glomerulosa is the outermost part of the adrenal cortex and is responsible for the production of mineralocorticoids. The zona fasciculata, which is located in the middle layer and forms 75% of the cortex, synthesizes glucocorticoids. The innermost layer is the zona reticularis, which is responsible for androgen synthesis. The adrenal medulla, on the other hand, works as a part of the autonomic nervous system and is responsible for the synthesis and regulation of catelocamines (8).

Adrenal Masses

Adrenal tumors originate from the medulla or cortex of the adrenal gland and may be benign or malignant, functional or non-functional. Adrenal tumors discovered during imaging for non-adrenal indications are called incidentalomas and are more

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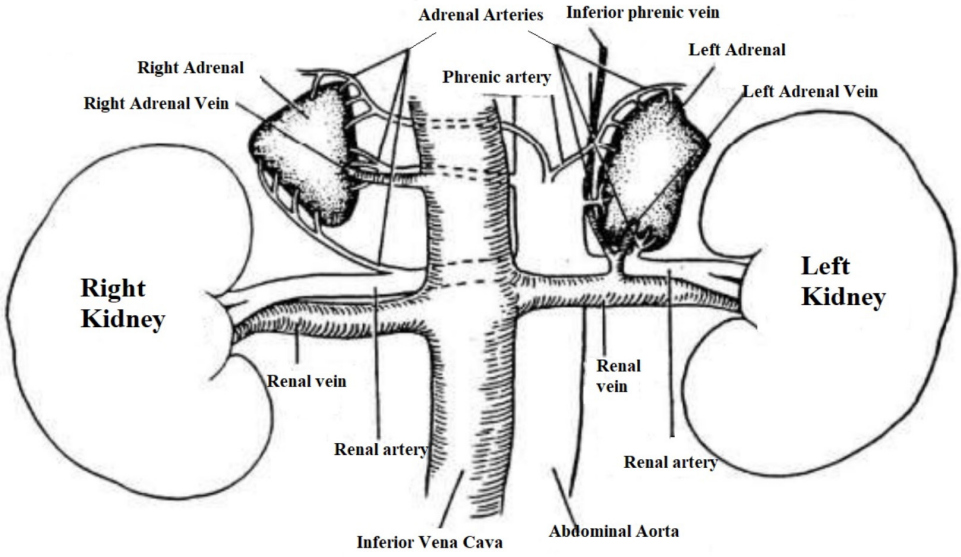

Figure 1. Adrenal gland anatomy (7)

common than non-incidental masses. Most incidentalomas are hormonally inactive and benign. However, in approximately 10% of cases, the adrenal mass may be functional. Cushing's syndrome (CS) is the most common cause of functional tumors originating from the adrenal cortex, while functional tumors originating from the adrenal medulla are most commonly caused by pheochromocytoma. The etiology of adrenal masses was also investigated in the study conducted by the adrenal tumors study group of the Italian Society of Endocrinology, which included 1,004 patients. The etiology and rates of adrenal masses according to this study are summarized in Table 1 (9).

Hormone Evolution

Clinical situations in which the adrenal function is accelerated should be analyzed well.

Cushing Syndrome

CS is the general name of the clinical status that occurs after an increase in glucocorticoids due to endogenous or exogenous causes. The most common cause is exogenous steroid intake. Endogenous causes are classified as adrenocorticotropic hormone (ACTH)-dependent (caused by pituitary or ectopic tumor) (80%) and ACTH-independent (caused by adrenal gland) (20%) (10,11).

Tests can be used to screen patients for hypercortisolemia. These tests are; Dexamethasone suppression test, salivary cortisol level at midnight (repeated two or three times), free cortisol level in 24-hour urine. If hypercortisolemia is detected by these tests, ACTH determination should be made. Adrenal masses that secrete cortisol are ACTH dependent. The first choice among these tests is the dexamethasone suppression test. Although there is no consensus in the literature on the amount of dexamethasone for this test (1 mg, 2 mg for 2 days, 3 mg or 8 mg), the mostly recommended approach is to determine the cortisol in the blood measured at 08:00 the next morning after an oral 1 mg dexamethasone tablet at 23:00. As a general opinion, for subclinical CS, the cortisol value measured after the test has been reported as 5 mcg/dL.

For cortisol values below 1.8 mcg/dL after dexamethasone, ACTH-independent autonomic glucocorticoid-secreting pathologies should be excluded. Patients with a cortisol level of 5 mcg/dL and above in the dexamethasone suppression test should be considered as subclinical CS (or CS if clinical findings are evident). Intermediate values should be considered on a patient basis and the above-mentioned tests should be used for further examination for the diagnosis of subclinical CS (12,13,14,15).

Primary Hyperaldosteronism (Conn Syndrome)

The increase in aldosterone levels due to the involvement of the glomerulosa layer of the adrenal cortex is responsible for the formation of a clinic such as hypertension, hypokalemia, hypernatremia, metabolic alkalosis and polyuria. Its prevalence in the hypertensive patient population has recently been reported to increase to 5-16%. The most common cause is bilateral adrenal hyperplasia. Other causes include aldosteronomas, adrenal carcinomas, and glucocorticoid-regulated hyperaldosteronism (16,17). Adrenal vein sampling is currently performed to confirm that the present mass is the pathology causing hyperaldosteronism.

In the differential diagnosis of an incidental adrenal mass, plasma potassium, renin and aldosterone levels should be checked for primary hyperaldosteronism. As a screening test, the ratio of serum aldosterone level (ng/dL)/plasma renin activity (ng/mL/hour) is used. If this ratio is above 20, it is necessary to proceed to confirmatory tests and subtyping tests. Since the renin-angiotensin-aldosterone system can also be affected by postural changes, some rules must be followed while performing the

test. The patient should be called for sampling in the morning hungry, at least half an hour must have passed after getting out of bed, and sampling should be done after the patient has been sitting for at least 15 minutes. Some drugs and renal dysfunction may affect the result of the test. For this reason, antihypertensive treatments used by the patient should also be reviewed and discontinued before the procedure (14,18).

Pheochromocytoma

Pheochromocytoma is a tumor of the adrenal medulla with catecholamine overproduction. About 1-2 in 100,000 people a year are diagnosed with pheochromocytoma. In most studies, it has been stated that pheochromocytomas constitute 4-7% of incidentalomas (19,20). Pheochromocytomas can be seen as a part of sporadic or hereditary syndrome [multiple endocrine neoplasia type 2 (MEN-2A or 2B), neurofibromatosis type 1 (NF-1), Von Hippel-Lindau syndrome, Sturge-Weber syndrome and Von Recklinghausen disease etc.] (21). Tumors are predominantly in the adrenal medulla. Also have a malignant potential of 10% and are seen bilaterally in 10% of cases (22).

Pheochromocytoma is a pathology that must be kept in mind when evaluating an adrenal mass. Pheochromocytoma should be screened whether the patient has hypertension or not. The most appropriate screening test is the evaluation of fractionated metanephrines in a 24-hour urine sample. For an ideal test, patients should restrict their fluid and food intake after midnight. In addition, drugs such as levodopa, labetolol, tricyclic antidepressants, sympathomimetics, severe infection, acute cardiovascular events may alter fractionated metanephrine excretion and cause misdiagnosis. In order to exclude the diagnosis of pheochromocytoma as a result of the test, urine fractionated metanephrines should be found to be normal. For the diagnosis of pheochromocytoma, the fractionated metanephrine levels were required to be 3-4 times higher than the upper limit of the reference range of the test. In addition, for the differential diagnosis of pheochromocytoma, plasma catecholamine level, plasma free metanephrine level, and plasma normetanephrine level should also be measured (23,24).

Other

Tumors that secrete sex hormone are symptomatic in the early period and are less likely to be seen incidentally, as they manifest themselves by virilization or feminization. The most common adrenal lesion with sex hormone secretion is adrenal carcinoma, and it is usually accompanied by excessive cortisol secretion. For this pathology, dehydroepiandrosterone sulfate (DHEA-S) level, testosterone and estradiol are measured. An increase in DHEA-S suggests the presence of adrenal androgens and shows a level proportional to the size of the adrenal mass. DHEA-S is important for the differentiation of benign and malignant. It reaches very high values in adrenal carcinoma. For differential diagnosis, serum 17-OH progesterone level and corticotropin stimulation test are performed. About 50% of the adrenal lesions that secrete sex hormone are benign. For this reason, routine screening testing is not recommended (25,26).

Radiological Imaging in Small Adrenal Masses

Many methods can be used for imaging adrenal masses. Table 2 summarizes the criteria that can be used to differentiate benign and malignant lesions in adrenal masses radiologically. Today, in the light of technological developments, there has been an increase in the diagnosis of adrenal masses that are small in size with radiological imaging methods (27).

Ultrasonography

Ultrasonography (USG) is frequently used in the evaluation of large sized masses and can detect up to 65% of small adrenal masses (<3 cm) (28). Right adrenal lesions are seen more frequently with ultrasonography in the diagnosis of incidentaloma. Ultrasonographic evaluation of adrenal masses is more difficult on the left side due to the anatomical position of the organs (29).

Computed Tomography

Computed tomography (CT) is the first choice for the detection and classification of especially small adrenal masses. However, computed tomography does not provide the opportunity to differentiate about the function of the adrenal mass.

On unenhanced CT, adrenal masses with ≤10 Hounsfield units are usually diagnosed as adrenal adenoma. In recent years, washout has been used routinely to differentiate lipid-poor adenomas from other adrenal masses (30).

Magnetic Resonance Imaging

It is important to distinguish adrenal masses as adenoma and non-adenoma. Adrenal adenomas usually give an equal or lower signal than the liver on T2-weighted images. Adrenocortical carcinomas are hyperintense compared to the liver in T2 on magnetic resonance imaging (MRI), they do not lose signal on MRI (31). Metastases do not lose signal on MRI and are more hyperintense on T2 compared to the liver (32). Pheochromocytomas appear hypointense on T1-weighted images and characteristically bright on T2-weighted images (33).

Table 1. Adrenal masses, etiology and percentages

Tumor type	Percent (%)
Hormonally inactive tumors	74
Hormonally active tumors	
Cortisol secreting (Cushing)	9.2
Pheochromocytoma	4.2
Aldosteronoma (Conn)	1.5
Adrenal carcinoma	4.0
Other adrenal tumors	
Myelolipoma	3
Cysts (cyst, pseudocyst)	1.9
Ganglioneuromas	1.5
Adrenal metastases	0.7
Other (teratoma, hematoma, hamartoma, neurofibroma, amyloid, granuloma)	

Positron Emission Tomography Pet (18F-Fluorodeoxyglucose)

While metabolic activity is increased in most malignant adrenal masses, no activity is observed in benign masses. It may be useful in small adrenal metastatic mass or adrenocortical carcinoma (34).

Biopsy in Small Adrenal Masses

Histologically, it is not reliable enough to distinguish adenomas from carcinomas. The place of adrenal biopsy is limited due to its complications and risks (bleeding, pneumothorax, hemothorax, adjacent organ injury, pancreatitis, etc.). With modern imaging and clinical characters, a nearly complete diagnosis can be achieved (35). In cases where the diagnosis of small adrenal masses cannot be made clearly or in the presence of suspected metastasis, USG or CT-guided biopsy is helpful (36).

Treatment in Small Adrenal Mass

Indication criteria for adrenal mass surgery are mainly the size of the mass, hormonal activity of the mass and radiological features.

Mass Size

According to the American National Health Organization, it is recommended that masses >6 cm in size be considered malignant and surgically removed until proven otherwise. Between 4-6 cm in size, the decision should be made according to the hormonal status of the patient, clinical findings and radiological appearance of the mass (37). In a study, no adrenocortical cancer cases were found in masses <4 cm. Therefore, it is stated that a threshold value of 4 cm for excision may be effective in reducing surgery for benign tumors since it has a high sensitivity of 93% despite low specificity in identifying primary malignant tumors (38). Despite this, it is stated that asymptomatic myelolipoma and simple cysts may not require surgery even if the diameter is larger than 4 cm (39).

Although the frequency of benign small adrenal masses increases with age, even if the mass size is <4 cm in young patients, because of their rarity at this age, a closer follow-up is required. If the size increase in a followed mass is >0.8 cm/year, surgery is recommended, but the malignancy rate is low in these masses (40).

In summary, surgical recommendations based on tumor size are derived from non-standardized studies on the duration of follow-up or estimating the risk of carcinoma. For this reason, a threshold value of 4 cm is used when surgical removal of the mass is required, but surgical treatment may be preferred for masses larger than 6 cm in clinical approaches. It is generally accepted that masses smaller than 4 cm should also be followed. The threshold value of 4 cm is more important in making the decision to follow the masses below this size. In patients with a tumor between 4 and 6 cm, the removal of the mass should not only be based on size, but also other criteria should be taken into consideration. The literature on adrenal incidentaloma has increased over the past few years. Unfortunately, the lack of controlled studies makes it difficult to formulate diagnosis and treatment strategies. More studies are needed on this subject (28,37,41).

Hormonal Activity

Surgical treatment is recommended regardless of the size of hormone-producing functional masses, including small adrenal masses. Surgical resection is recommended in patients with clinically asymptomatic aldosteronoma and pheochromocytoma because of the possibility of life-threatening complications (28,42,43). In the presence of a clinically symptomless condition described as preclinical CS, especially in young patients. Since it has been shown that metabolic conditions such as hypertension, obesity, diabetes and osteoporosis can improve after surgery, surgical treatment is also recommended in this clinical situation (44,45).

Radiological Appearance

Important criteria for radiologically benign-malignant distinction are given in Table 2. Among these criteria, chemical shift MRI has the highest specificity and sensitivity in the differentiation

Table 2. Criteria that can be used to differentiate benign and malignant lesions radiologically (24)

Criteria	Malign	Bening
Size	>4 cm	<4 cm
Homogeneity	Heterogeneous	Homogeneous
Growth rate	Fast	Slow
Contrast uptake	Different rates of uptake, slow clearing	Fast uptake, fast clearing
MRI signal on T2	High	Low
Signal loss out of phase on MRI	<30%	>30%
Shape-border	Thick/Irregular	Round/Regular
Adrenal/Splenic ratio	>70%	<70%
Density in CT	>10 HU	<10 HU (lipid-rich) >10 HU (lipid-poor)
Lipid ratio	Low	High (except lipid-poor ones)
Absolut washout	<60%	>60%
Relative washout	<40%	>40%

MRI: Magnetic resonance imaging, CT: Computed tomography, HU: Hounsfield units

of benign and malignant. In general, in radiological evaluations, surgical resection is recommended for rapidly growing masses, heterogeneous or irregularly circumscribed, containing necrotic or calcified areas, and invading adjacent structures (46).

Surgical indications can be summarized as follows (47,48):

- >4 cm masses
- Isolated adrenal metastases
- Masses that grow ≥1 cm in follow-up
- Functional adrenal masses (excessive cortisol secretion, pheochromocytoma, excessive aldosterone secretion)
- Giant or symptomatic myelolipoma
- Presence of radiological findings with suspicion of malignancy.

Pre-surgery Patient Preparation

Hormonally active adrenal masses can cause two main serious conditions such as acute adrenal insufficiency and hypertension crisis. In CS, in the preoperative period, the patient's hyperglycemia and electrolyte imbalance should be regulated and the operation should be performed under steroid support. In the postoperative period, the steroid dose should be decreased gradually and support should be continued for the recovery of the hypothalamo-pituitary-adrenal axis (49).

Preoperative preparation is important for pheochromocytoma. A complete cardiac examination, including electrocardiography and echocardiography, in the preoperative period is important to evaluate the end-organ damage that may be caused by hypertension. In order to provide hemodynamics and blood glucose regulation, preoperative sympatholytic therapy with α-adrenergic blockers should be started at least 2 weeks before the surgery and continued until the day of surgery. The most commonly used of this group is phenoxybenzamine, a long-acting alpha-blocker. Despite all the preparations, it was also determined that there were hypertension crises during the removal of the tumor (50).

Surgical Methods in Small Adrenal Masses

Large left adrenal tumor was totally removed by Knowsley-Thornton in 1889 in a 36-year-old female patient with hirsutism. In 1992, the first successful transperitoneal laparoscopic adrenalectomy was performed by Gagner (2,51).

When laparoscopic adrenalectomy is compared with open surgery; it offers less pain, shorter hospital stay, less blood loss and faster recovery. Currently, the laparoscopic approach is used in most adrenal masses (52). In patients with known or suspected adrenal carcinoma, the laparoscopic approach is generally preferred if the adrenal mass is <10 cm in diameter and no local invasion is apparent. Apart from this, open adrenalectomy is recommended for all large (>10 cm) adrenal masses (53,54). The reason why robotic adrenalectomy is especially preferred today is that the right adrenal vein is shorter and the limitation of movement due to the location of the adrenal tissue under the liver is eliminated.

Open Adrenalectomy

Open surgery can be performed with a retroperitoneal or transperitoneal approach. Frequently, the transperitoneal subcostal anterior approach provides better exploration of large tumors and better access to the retroperitoneum and great vessels. In obese patients, the lateral extraperitoneal approach is generally preferred. The posterior retroperitoneal approach may be preferred in patients who are prone to wound complications due to a history of cardiopulmonary disease or CS, have undergone previous abdominal surgery and are at high risk of abdominal adhesions. The positive aspects of the retroperitoneal approach are less ileus and short hospitalization, but it should be known that the retroperitoneal approach is difficult, especially in obese patients. It is not suitable for masses >6 cm because the working area is small (42).

Laparoscopic Adrenalectomy

The most widely used method in the world is laparoscopic transabdominal adrenalectomy. It is performed transperitoneally or retroperitoneally, and there is no difference between these methods in terms of operative parameters. For this reason, the choice of the surgeon and the condition of the patient are important when deciding between the two methods. Especially in the presence of large and irregular tumor, un-block removal of the tumor and surrounding adipose tissue is important, as there is a possibility of malignancy (55).

In general, if a patient is suitable for anesthesia for open surgery, laparoscopic surgery can also be performed for the same patient. Laparoscopic adrenalectomy can be considered the treatment of choice for all benign adrenal tumors from 12 cm to 14 cm in size. It remains unclear whether laparoscopic resection of masses ≥8-10 cm or potentially malignant tumors is appropriate due to technical difficulties and concern for local recurrence. However, large tumors suspected to be primary malignancies based on imaging features should be approached with an open technique. In addition, it is better to avoid the laparoscopic technique in obese patients or patients with Cushing's disease until the surgeon has sufficient experience in laparoscopic adrenalectomy. Irrespective of tumor size, morbidity, mortality, and hospital stay are similar to open surgery, but experience is required in both laparoscopic and adrenal surgery. Therefore, indications and contraindications for laparoscopic adrenalectomy are closely related to the skill and experience of the surgeon (56,57,58).

Transperitoneal Approach

Although it is often applied with the lateral approach, it can also be preferred with the anterior approach. The advantage of the lateral position is that it offers a larger working area due to the lowering of the intestines.

Retroperitoneal Approach

This method is applied in the full lateral position. It is preferred in unilateral and relatively small adrenal masses due to its smaller working area compared to the transperitoneal approach (<4-5 cm). It is not preferred for symptomatic pheochromocytoma (59).

Partial Adrenalectomy

Partial adrenalectomy can be considered as an alternative to complete adrenalectomy for small or possibly benign adrenal lesions and is generally preferred for bilateral small lesions (60). Although there is no specific consensus, it is considered

reasonable to perform partial adrenalectomy to preserve the adrenal gland in lesions <3 cm located anterior or lateral to the adrenal gland (61).

Robotic Adrenalectomy

This method, which is performed with the help of a robot, can be applied transperitoneally or retroperitoneally. Especially robotic surgery is more suitable in retroperitoneal adrenalectomy, since the mobility of the tools to be used in the retroperitoneal area is more limited in other methods (62).

Monitoring

Periodic follow-up is recommended in small, hormonally inactive adrenal masses <4 cm in diameter, if there is no radiological suspicion of malignancy. The ideal follow-up schedule for these small masses <4 cm in diameter has not been precisely defined. However, clinical guidelines recommend clinical and hormonal follow-up for at least 4 years, and follow-up imaging (CT, MRI) 6-12-24 months after the first CT. In order to make radiological comparison, the same method should be used in the follow-up. At the end of 4 years, there is no data on the necessity of continuing follow-up in cases where there is no progress in hormonal and clinical follow-up performed annually and there is no increase in lesion size radiologically (28,63).

Conclusion

Adrenal masses are approximately 30-35 mm in diameter at the time of diagnosis. While masses less than 4 cm are generally considered to be small masses, they are at lower risk for malignancy than adrenal masses larger than 4 cm. An incidentally detected adrenal mass should be investigated for malignancy and functional activity. These evaluations are important to determine the treatment and follow-up process.

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Original Article

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Clinical Preferences of Turkish Urologists in Screening and Diagnosis of Prostate Cancer and Adherence to European Association of Urology Guidelines

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Abstract

Objective: To compare the clinical preferences of urologists in prostate cancer screening and diagnosis with current guideline recommendations.
Materials and Methods: The study is based on an online survey that consists of 21 single response or multiple response questions. By e-mail, 2,305 certified urologists in active practice as well as urology residents in their last year of training were invited to participate in the study. Descriptive statistics were used to analyze practice patterns and demographics. The respondents were divided into groups based on their experience in urology, hospital type and academic title.
Results: Our results show that preferences of the majority of urologists conflicts with recommendations of European Association of Urology Prostate Cancer Guidelines regarding prostate biopsy method, management of a patient with high prostate-specific antigen value, use of additional test and performance scoring systems, role of multiparametric prostate magnetic resonance imaging.
Conclusion: Urologists act in the direction of their habits or clinical experience rather than current guidelines regardless of their experience. Both clinicians and professional organizations should work on what can be done about the reflection of rapidly changing scientific knowledge on the field and the improvement of the health service provided.
Keywords: Diagnosis, guidelines, prostate cancer, screening

Introduction

Prostate cancer is the most common cancer among men (1). Therefore, screening and diagnosis of prostate cancer is one of the most frequent tasks of urologists in daily practice. Clinical practice guidelines are commonly used by clinicians for the standardization of these applications. Clinical practice guidelines were first formally defined in 1990 by "Clinical Practice Guidelines: Directions for a New Program" published by the Institute of Medicine of the United States (2). Nowadays, the need for using these guidelines has increased due to medico-legal concerns, the need to reduce cost, the need to reduce overdiagnosis and overtreatment, and the need to have a universally accepted approach to the diseases (3). Many studies show that adherence to guidelines increases interventions that show benefit, while at the same time reducing ineffective or harmful treatment, potentially reducing mortality and morbidity (4,5,6). European Association of Urology (EAU) Guidelines on Prostate Cancer have been prepared to assist medical professionals in the evidence-based management of prostate cancer (7). With the development of information technologies, it has become easier to reach these guides. However, it is questionable to what extent these guidelines are known and applied by clinicians in real-world practice. In our study, we aimed to compare the clinical preferences of urologists in prostate cancer screening and diagnosis with current guideline recommendations.

Materials and Methods

The study is based on an online survey that consists of 21 single response or multiple response questions. The questionnaire was prepared using the checklist for reporting results of internet E-Surveys (8). Questions about the respondents' baseline

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characteristics make up the first section. In the second part, the urologists were asked whether they perform a biopsy and if they do, their preferences regarding the biopsy method. The third part includes urologists' preferences for managing a patient with a high prostate-specific antigen (PSA) value. In the fourth part, the participants were asked about their preferences to use additional tests to PSA, performance status tests, and multiparametric prostate magnetic resonance imaging (mpMRI). In the last section, re-biopsy preferences of the participants were evaluated. After testing for feasibility with 10 responders, e-mail invitations were sent to 2,305 certified urologists who are currently in practice as well as urology residents who are in their last year of training. Reminder e-mails were also sent out after four weeks. Since the study was not based on patient groups, informed permission was not required. The survey was accessible between June and October 2020 through the web program Google Forms (Alphabet Co., Mountain View, CA). The Zonguldak Bülent Ecevit University Non-Invasive Clinical Research Ethics Committee approved this study (decision no: 2020/10, date: 13.05.2020).

Statistical Analysis

Demographics and practice patterns were analyzed using descriptive statistics. Respondents who perform prostate biopsy were asked about their preferences of prostate biopsy methods. We demonstrated the numbers and percentages of answers and respondents separately for multiple response questions. Statistical analyses were performed by using IBM Statistical Package for Social Sciences, version 26.0, software (IBM SPSS Corp., Armonk, NY, USA). A post hoc power analysis was conducted using the software package, GPower (Faul and Erdfelder, 2009). A p-value less than 0.05 were considered statistically significant.

Results

A total of 351 out of 2,305 urologists participated. The response rate was 15.2%. Fourty four incomplete questionnaires were excluded from the study and 306 responses were evaluated. To check if our sample size represents all urologist in Turkey, we conducted post hoc power analyses which showed us an n of 270 would be enough with power (1-β) set at 0.80 and α=0.05.

The median age of the responders was 36 (27-66). The responders had a urology practice for a median of 10 (4-39) years. Demographics and other practice patterns are shown in Table 1.

In their hospital, 230 (75.2%) of 306 respondents perform prostate biopsy. As for the hospital type, percentages of performing biopsy in university hospitals, training and research hospitals, Private hospitals, and state hospitals were 100%, 85%, 84.4%, 49.6% respectively (p<0.001). When 76 (24.8%) urologists who do not perform biopsy were asked about the reason they are not performing, the main reason was lack of equipment (71.1%), followed by risk of complication (23.7%), other (19.7%), lack of auxiliary staff (18.4%), financial concerns (5.3%%) (percentages are based on respondents, total 138.2% as it is a multi-response question).

In their hospital or city, 175 (57.2%) of the urologists do not have a targeted magnetic resonance imaging-transrectal ultrasound (MRI-TRUS) fusion prostate biopsy to which they can refer patients if needed.

Prostate Biopsy Method

Table 2 shows the preferences of urologists about enema administration, rectal cleansing, oral restriction prior to biopsy, and number of cores they get in a standard prostate biopsy. In subgroup analyzes made according to academic title and experience in urology, no statistical significant difference was found in the pre-procedure enema administration (titles: residents 73.3%, specialists: 72.6%, academicians: 76.2% p=0.901; years of experience: 0-5: 71.9%, 5-10: 78.4%, 10-15: 69.2%, 15-20: 72%, >20: 71.4% p=0.836). There was no statistical significant difference in rectal cleansing prior to the biopsy in subgroup analyses based on academic title and years of experience in urology (titles: residents: 37.3%, specialists: 39.8%, academicians: 35.7% p=0.852; years of experience: 0-5: 38.6%, 5-10: 41.9%, 10-15: 38.4%, 15-20: 16%, >20: 45.7% p=0.178). There was no statistical significant difference in oral restriction prior to biopsy in subgroup analyses based on academic title and experience in urology (titles: residents: 20%, specialists: 22.1%, academicians: 23.8% p=0.861; years

Table 1. Demographic data of the respondents

Academic titles	**n**	**%**
Resident	76	24.8
Specialist	185	60.5
Academician	45	15.7
Total	306	100
Hospital type	**n**	**%**
University	78	25.5
Research hospital	60	19.6
Private hospital	51	16.7
State hospital	117	38.2
Total	306	100
Geographic location	**n**	**%**
Marmara	88	28.8
Aegean	44	14.4
Central Anatolia	54	17.6
Eastern Anatolia	18	5.9
Southeastern Anatolia	12	3.9
Black sea	54	17.6
Mediterranean	36	11.8
Total	306	100.0
Experience in urology (years)	**n**	**%**
0-5	63	20.6
5-10	110	35.9
10-15	48	15.7
15-20	32	10.5
20 and more	53	17.3
Total	306	100.0

Table 2. Urologists' preferences about enema administration, rectal cleansing, oral restriction prior to biopsy and number of cores they get in a standard prostate biopsy		
Do you administer an enema prior to the biopsy?		
	n	**%**
Yes	169	73.5
No	61	26.5
Total	230	100.0
Do you perform rectal cleansing with povidone-iodine or chlorhexidine prior to the biopsy?		
	n	**%**
Yes	88	38.3
No	142	61.7
Total	230	100.0
Do you restrict the patient's oral intake prior to the biopsy?		
	n	**%**
Yes	50	21.7
No	180	78.3
Total	230	100.0
How many cores do you get in a standard biopsy procedure?		
	n	**%**
6-9	4	1.3
10-11	19	6.2
12	260	85.0
More than 12	23	7.5
Total	306	100.0

of experience: 0-5: 21.1%, 5-10: 20.3%, 10-15: 15.4%, 15-20: 28%, >20: 28.6% p=0.501).

Regarding prophylactic antibiotics, urologists prefer 69.6% fluoroquinolones, 24.8% cephalosporins, 14.8% fosfomycin, 14.3% aminoglycoside, 3.9% other, 0.4% none (percentages are based on respondents, total 127.8% as it is a multi-response question). When the antibiotic preferences of the participants were compared according to their academic titles and experience in urology, no statistically significant diference was found (p=0.137, p=0.381 respectively).

As for the anesthetic methods, urologists prefer rectal anesthetic agents 69.6%, sedation 24.8%, periprostatic blockage 14.8% (percentages are based on respondents, total 132.2% as it is a multi-response question).

Preferences for Managing a Patient with a High PSA Value

Table 3 compares urologists' preferences for managing patients with PSA values of 3 ng/mL and 9 ng/mL. When we performed subgroup analyzes for patients with a PSA value of 3 ng/mL according to academic title statistical significant differences were found for the answers; antibiotics administration (titles: residents: 6.6%, specialists: 16.8%, academicians: 6.7% p=0.034), digital rectal examination (titles: residents: 93.4%, specialists: 77.3%, academicians: 88.9% p=0.004), mpMRI (titles: residents: 11.8%, specialists: 12.4%, academicians: 33.3% p=0.002) and, additional tests (titles: residents: 18.4%, specialists: 6.5%, academicians: 11.1% p=0.014). When we performed subgroup analyzes for patients with a PSA value of 3 ng/mL according to years of experience in urology, statistical significant differences were found for the answers; antibiotics administration (years of experience: 0-5: 4.8%, 5-10: %9.1, 10-15: 18.8%, 15-20: 28.1%, >20: 15.1% p=0.009) and, digital rectal examination (years of experience: 0-5: 92.1%, 5-10: 90%, 10-15: 75%, 15-20: 71.9%, >20: 71.7% p=0.002). When we performed subgroup analyzes for patients with a PSA value of 9 ng/mL according to academic title statistical significant differences were found for the answers; antibiotics administration (titles: residents: 19.7%, specialists: 33.5%, academicians: 15.6% p=0.012), digital rectal examination (titles: residents: 92.1%, specialists: 81.6%, academicians: 71.1% p=0.011), mpMRI (titles: residents: 31.6%, specialists: 28.6%, academicians: 48.9% p=0.033). When we performed subgroup analyzes for patients with a PSA value of 9 ng/mL according to years of experience in urology, only statistical significant difference were found for the answer; digital rectal examination (years of experience: 0-5: 88.9%, 5-10: 88.2%, 10-15: 85.4%, 15-20: 75%, >20: 66.7% p=0.003). It was determined that as experience increased, the tendency to perform digital rectal examination (DRE) decreased, for both PSA values. No statistically significant difference was found between the subgroups for any of the other responses.

Table 3. Urologists' preferences for managing patients with PSA values of 3 ng/mL and 9 ng/mL						
	PSA: 3 ng/mL			**PSA: 9 ng/mL**		
	n	**%**	**% of respondents**	**n**	**%**	**% of respondents**
Antibiotherapy	39	6.3%	12.7%	84	11.1%	27.5%
Repeat PSA after 6 weeks	192	31.0%	62.7%	139	18.3%	45.4%
DRE	254	41.0%	83.0%	253	33.3%	82.7%
MpMRI	47	7.6%	15.4%	99	13.0%	32.4%
Biopsy	12	1.9%	3.9%	147	19.4%	48.0%
Additional test	31	5.0%	10.1%	35	4.6%	11.4%
Annual follow-up	45	7.3%	14.7%	2	0.3%	0.7%
Total	620	100.0%	202.6%	759	100.0%	248.0%
PSA: Prostate-specific antigen, DRE: Digital rectal examination, MpMRI: Multiparametric prostate magnetic resonance imaging						

Use of Additional Tests and Performance Scoring Systems

Urologists were asked at what PSA levels they use additional tests to help in their biopsy decision in a patient with normal DRE. Answers were 2-10 ng/mL for 25.2%, 4-10 ng/mL for 66.7%, 10-20 ng/mL for 4.2%, other for 3.9%.

Additional tests that urologists use in this patient group are shown in Table 4. When we performed subgroup analyzes academic titles and experience in urology, residents, academicians and urologist with experience less than five years tended to use mpMRI more than other groups (titles: residents: 78.9%, specialists: 59.5%, academicians: 88.9% p<0.001; years of experience: 0-5: 81%, 5-10: 66.4%, 10-15: 56.3%, 15-20: 68.8%, >20: 69.8% p=0.006). No statistically significant difference was found between the subgroups for any of the other tests.

When respondents were asked which scoring system they use to evaluate geriatric patients' performance status when making a biopsy decision, answers were Eastern Cooperative Oncology Group (ECOG) for 24.8%, Karnofsky for 24.8%, G8 for 5.6%, mini-cog for 1.0%, other for 2.9%, none for 65.0% (percentages are based on respondents, total 112.7% as it is a multi-response question).

Role of mpMRI

When urologists were asked their opinions about area of usage of multiparametric MRI in biopsy planning, the most common answer was before re-biopsy (Table 5).

Re-biopsy Preferences

Most of the urologists (42.8%) prefer to wait 6 months before re-biopsy after a previous biopsy. Followed by 3 months (34.6%), 12 months (17%) and 1 month (5.6%).

Methods used by the urologist for re-biopsy were determined as saturation biopsy 44.4%, MRI-TRUS fusion biopsy 25.8%, standard biopsy 17.6%, and cognitive fusion biopsy 12.1%, respectively.

Discussion

The main finding of our study was low adherence to guidelines in prostate cancer screening and diagnosis among Turkish urologists. Although there were statistically significant differences in some preferences, it was observed that there was not enough compliance with the guidelines regardless of experience or academic title.

There are studies showing similarly low adherence to guidelines by urologists in North America, Canada, and Europe (9,10,11,12). Reasons for this are complex. Makarov et al. (13) investigated the reasons for guideline-discordant use of

Table 4. Urologists' preferences for using additional tests

Which of the following do you use in addition to PSA in the biopsy decision?			
	n	**%**	**% of respondents**
PSA density	80	13.0%	26.1%
PSA velocity/doubling time	79	12.8%	25.8%
F/T PSA ratio	225	36.6%	73.5%
PCA3 marker/SelectMDX/Mi prostate score /ExoDX	1	0.2%	0.3%
MpMRI	210	34.1%	68.6%
None	20	3.3%	6.5%
Total	615	100.0%	201.0%

PSA: Prostate-specific antigen, PCA3: *Prostate cancer antigen 3* gene, MpMRI: Multiparametric prostate magnetic resonance imaging

Table 5. Urologists' preferences for using multiparametric prostate magnetic resonance imaging

At which stage do you think multiparametric MRI should be used first in biopsy planning?				
	Screening n (%)	**Before the first biopsy n (%)**	**Before re-biopsy n (%)**	**During re-biopsy method (targeted MR-TRUS fusion biopsy) n (%)**
Academic title				
Resident	2 (2.6%)	12 (15.8%)	48 (63.2%)	14 (18.4%)
Specialist	0 (0%)	56 (30.3%)	67 (36.2%)	62 (33.5%)
Academician	0 (0%)	19 (42.2%)	16 (35.6%)	10 (22.2%)
p<0.001				
Experience in urology				
0-5 years	1 (1.6%)	12 (19.0%)	38 (60.3%)	12 (19%)
5-10 years	1 (0.9%)	30 (27.3%)	52 (47.3%)	27 (24.5%)
10-15 years	0 (0%)	13 (27.1%)	19 (39.6%)	16 (33.3%)
15-20 years	0 (0%)	14 (43.8%)	8 (25%)	10 (31.3%)
>20 years	0 (0%)	18 (34%)	14 (26.4%)	21 (39.6%)
p=0.025				
Total	2 (0.7%)	87 (28.4%)	131 (42.8%)	86 (28.1%)

MRI: Magnetic resonance imaging, TRUS: Transrectal ultrasound

imaging to stage incident prostate cancer. Most physicians self-reported that they know and trust imaging guidelines yet some were still likely to follow their own intuition, whether due to clinical suspicion or years of experience. Additionally, physicians reported that medico-legal concerns, fear of missing associated diagnoses, tendency to practice in line with more senior colleagues, influences rates of imaging despite guidelines (13).

Passive dissemination via publication of guidelines alone is rarely enough to effect widespread guideline adherence (14). Nowadays, it is anticipated that social media may play an important role in disseminating the guidelines (15).

Prostate Biopsy Method

A meta-analysis of eight RCTs demonstrated that use of a rectal povidone-iodine cleansing prior to biopsy, in addition to antimicrobial prophylaxis, led to a significant decrease of infectious complications (16,17,18). EAU guidelines on prostate cancer recommends the use of rectal cleansing with povidone-iodine before transrectal prostate biopsy strongly (7). However, only 38.6% of the respondents use rectal cleansing.

A meta-analysis evaluating the use of rectal enema preparation before transrectal biopsy, showed no significant benefit in terms of infectious complications (7). 73.5% of the urologists who perform biopsy administer enema prior to transrectal biopsy.

Fluoroquinolones are widely used as antibiotic prophylaxis before transrectal biopsy. However, fluoroquinolone resistance has increased as a result of overuse of the drugs. Furthermore, the European Commission has implemented strict regulations on the use of fluoroquinolones for perioperative antibiotic prophylaxis (7). EAU prostate cancer guidelines recommends using either target prophylaxis (based on a rectal swab or stool culture); augmented prophylaxis; or alternative antibiotics for antibiotic prophylaxis for transrectal biopsy (7). A recent study shows 67.6% fluoroquinolone resistance in patients with urinary tract infections in Turkey (19). Half of the urologists that perform prostate biopsy uses only fluoroquinolone as prophylaxis.

EAU prostate cancer guidelines recommends Ultrasound-guided peri-prostatic block for pain control (7). Intra-rectal instillation of local anesthesia was shown to be inferior to peri-prostatic infiltration (20). However, our study showed that majority of the urologists do not perform peri-prostatic block.

Preferences for Managing a Patient with a High PSA Value

In asymptomatic men with a PSA value between 2-10 ng/mL and a normal DRE, EAU guidelines recommends use of a risk calculator, imaging, or an additional serum, urine, or tissue-based test (7). Clinicians should not perform biopsy immediately with only a limited increase in PSA. After a few weeks PSA value should be confirmed under standardized conditions (21,22). Antibiotics should not be used in asymptomatic patients to reduce PSA levels (23). Two questions were asked to the respondents about what to do when a PSA value of 3.0 ng/mL and 9.0 ng/mL of a patient who meets the screening and treatment conditions for prostate cancer and does not have active complaints. According to recent EAU guidelines, there is no difference in recommendations for these PSA values (7). However, our study showed that there is a considerable difference in the clinical preferences of urologists. The percentage of the respondents who prefer DRE, and an additional test did not change significantly. For a patient with a PSA value of 3 ng/mL, respondents were more likely to repeat PSA after 6 weeks and follow patients annually. For a patient with a PSA value of 9 ng/mL, respondents were more likely to administer antibiotherapy, perform mpMRI, perform biopsy. It is understood that the 2-10 ng/mL psa treshold is not accepted among urologists yet.

In clinical decisions about prostate cancer, not only age, but also individual life expectancy, health status and comorbidities of the patient should be considered. Patients who are frail and above the age of 70 should have a full geriatric evaluation. EAU guidelines recommends the use of a performance scoring system for geriatric patients to determine patients' life expectancy, health status, and co-morbidities. Scoring systems that are mentioned in EAU guidelines are Geriatric 8 (G8) screening tool for a systematic evaluation of health status minicog for cognitive function, Karnofsky and ECOG for physical function (24,25,26). However, the majority of urologists do not use any performance scoring system when evaluating elderly patients.

Role of mpMRI

Recent guidelines do not recommend mpMRI as a screening tool. For biopsy naive patients, mpMRI is strongly recommended before the biopsy. And it is also recommended for patients with prior negative biopsy if no mpMRI has been performed before the initial biopsy (7). Majority of the respondents think that mpMRI should be used before re-biopsy. Although most of the academicians and urologist with experience of 15-20 years think that mpMRI should be used before first biopsy, the percentages do not exceed 44%.

Study Limitations

First, as with any survey study, there is a possible recall and response bias. Only individuals who are interested in or are not interested in prostate cancer and biopsy may have answered, we cannot exclude the possibility of a systematic bias as the reason for response vs. nonresponse. Another limitation is, due to demographic bias, the findings cannot be expanded. Like all survey data, the quality of our data is dependent on the truthfulness and/or potential biases of the respondent. As our study is descriptive in nature, it cannot determine the causes and clinical outcomes of low adherence to guidelines.

Conclusion

Studies show that it takes time for changes in guidelines to enter clinical practice. In some cases, it can be explained by the late spread of technology and the difficulty of accessing equipment, or the lack of training in use. However, in subjects such as patient management or antibiotic prophylaxis, it was seen that urologists act in the direction of their habits or clinical experience rather than current knowledge regardless of their experience. We think that urologists should be more active in following up-to-date information which is easy to access directly and online. Both clinicians and professional organizations should work on

what can be done about the reflection of rapidly changing scientific knowledge on the field and the improvement of the health service provided.

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Ethics

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Authorship Contributions

Concept: H.A.Y., E.D.D., S.M., M.D.D., Design: H.A.Y., E.D.D., S.M., M.D.D., Supervision: H.A.Y., E.D.D., S.M., M.D.D., Data Collection-Processing: H.A.Y., E.D.D., S.M., M.D.D., Analysis-Interpretation: H.A.Y., E.D.D., S.M., M.D.D., Literature Review: H.A.Y., E.D.D., S.M., M.D.D., Writing: H.A.Y., E.D.D., S.M., M.D.D., Critical Review: H.A.Y., E.D.D., S.M., M.D.D.

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Original Article

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Is Extraperitoneal Approach in Radical Cystectomy Really Effective on Bowel Recovery? A Comperative Analysis of Extraperitoneal Versus Transperitoneal Approach

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Abstract

Objective: Radical cystectomy with extended pelvic lymph node (LN) dissection is a gold standard surgical treatment for muscle-invasive bladder cancer which is a common urological malignancy in elderly people. Despite common surgical technique is a transperitoneal approach, we aimed to analyze the benefit of extraperitoneal approach radical cystectomy in the gastrointestinal system.

Materials and Methods: We retrospectively analyzed a total number of 110 (52 intraperitoneal and 58 extraperitoneal) radical cystectomy patients operated extraperitoneal or transperitoneal by 2 expert urologists between January 2016 to December 2019 in this study. All operated patients had indications for radical cystectomy and extended LN dissection and Wallace type ileal loop were performed adding to the operations. Patients have available data were included in this study and complications were assessed by Clavien- Dindo classification system.

Results: The median age of a total number of 110 patients was 66 (minimum: 43 - maximum: 82) years. There were no differences between groups in terms of surgical region infection, urinary leakage, ileus treated surgically, and emergency admission after discharge of patients. Twenty-four (46.1%) patients in the transperitoneal group needed for erythrocyte transfusion whereas, 16 (27.5%) patients in the extraperitoneal approach group (p=0.04). Additionally, 13 (19.2%) patients in the transperitoneal group had ileus treated conservatively, whereas, 8 (13.7%) patients in the extraperitoneal approach group (p=0.02).

Conclusion: Extraperitoneal approach and retroperitonealization of an ileal loop in radical cystectomy are safe and effective on oncological surgical principles. It may also provide better gastrointestinal motility after surgery.

Keywords: Radical cystectomy, extraperitoneal approach, ileus, bowel recovery

Introduction

Bladder cancer is a common urological malignancy in elderly people. Radical cystectomy with extended pelvic lymph node (LN) dissection is a gold standard surgical treatment for muscle-invasive bladder cancer (1). Despite progress in improvement even open or minimally invasive surgical techniques and postoperative medical care, there are still serious morbidity and mortality rates.

Enhanced recovery after surgery (ERAS) protocol is multimodal care before and after surgery was first used in colorectal surgery still under investigation by maintaining the preoperative organ functioning to reduce or prevent surgical complications. ERAS consisted of many evidence-based preadmission educations and counseling, all interventions and postoperative care for the aim of keeping patient earlier recovery to return to the normal activities (2). Although this kind of protocol leads to improvement in cardiopulmonary function, early return of bowel function and a reduction in complications and hospital stay, still major morbidity in radical cystectomy is due to gastrointestinal complications affects one out of three patients (3,4).

In addition to pre-and postoperative care, technical clinical improvements in surgery have been started to reduce complications. The intraperitoneal approach is frequently preferred as a major surgical technique in radical cystectomy. Kulkarni et al. (5) first described the extraperitoneal approach for radical cystectomy in 1999 and reported that the extraperitoneal

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approach had some advantages in decreasing gastrointestinal complications. Here, in this study, we aimed to investigate the operative and early postoperative results of the extraperitoneal versus the intraperitoneal approach of radical cystectomy.

Materials and Methods

This study was approved by Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee by providing the decision in protocol number 2018/264 (date: 06.08.2018). We retrospectively analyzed a total number of 110 (52 intraperitoneal and 58 extraperitoneal) radical cystectomy patients operated by 2 expert urologists between January 2016 to December 2019 in this study. All patients before the operation were examined by laboratory and screening tests explained in the European Association of Urology (EAU) guidelines (1). All operated patients had indications for radical cystectomy explained in the EUA guideline and patients have available data were included in this study.

The day before surgery, polyethylene glycol for laxative and the intravenous crystalloid solution was applied for all patients. The extraperitoneal and intraperitoneal approach of radical cystectomy was performed according to described by Kulkarni et al. (5) and Hautman et al. (6) respectively. Extended pelvic LN dissection was performed after cystectomy was completed. Before the ileal loop was extraperitonealized, Wallace-type ureteroileal anastomosis was performed on all patients (7). Postoperative feeding was initiated with the resumption of nature bowel sounds and gradually increased according to patient tolerance. Ileus was described as a patient suffering from nausea or vomiting associated with abdominal distention needed for insertion of nasogastric tube or cessation of enteral feeding (8). Conservative treatment of ileus was defined as any intervention without surgical operation. All operative and postoperative complications were assessed by Clavien-Dindo classification system.

Statistical Analysis

All statistical analyses were performed using the SPSS 22.0 (IBM Corp, Chicago, USA) software. Kolmogorov-Smirnov test was applied to describe the normality of variables. Quantitative data were presented as mean ± standard deviation and median [minimum (min) - maximum (max)]. Categorical variables were expressed as numbers and percentages to define the parameters. Comparison of categorical variables was accomplished using Pearson chi-square or Fisher's Exact tests. Mann-Whitney U test and t-test were performed to compare 2 groups of quantitative data. The confidence interval was 95% and the level of significance of the value of p was considered at <0.05.

Results

The median age of a total number of 110 patients was 66 (min: 43 - max: 82) years. One hundred and four (94.5%) and 76 (69.1%) of patients were male and had a smoking history, respectively.

The average body mass index (BMI) of all patients was 26.24±3.74 and the median Charlson comorbidity index without age was 1 (min: 0 - max: 7). Demographics and preoperative biochemical results of patients were described in Table 1.

There was no statistical difference in age, gender, BMI, smoking history, Charlson comorbidity index without age, follow-up time, and biochemical parameters among the groups. In the preoperative evaluation, 8 (15.3%) patients operated by intraperitoneal approach had clinical LN positivity whereas 2 (3.4%) patients operated by extraperitoneal approach (p=0.03). However, there was no difference in pathological LN positivity and the total number of excision of LN between groups (p=0.50 and p=0.12, respectively). In the perioperative results, the mean operative time was 270±45 minutes in extraperitoneal and 245±60 minutes in the intraperitoneal approach (p=0.35). Furthermore, there was no difference between groups even minor or major complications in Clavien-Dindo classification system (p=0.17). In the postoperative follow-up, there were no differences between groups in terms of surgical region infection, urinary leakage, ileus treated surgically, and emergency admission after discharge of patients (p>0.05). Twenty-four (46.1%) patients in the transperitoneal group needed for erythrocyte transfusion whereas, 16 (27.5%) patients in the extraperitoneal approach group (p=0.04). Additionally, 13 (19.2%) patients in the transperitoneal group had ileus treated conservatively, whereas, 8 (13.7%) patients in the extraperitoneal approach group (p=0.02). There was no difference among groups in the results of patients clinical T stage or surgical margin positivity in final pathology (p=0.93 and 0.49, respectively). Comparison of groups in terms of preoperative, operative, and postoperative outcomes are summarized in Table 2.

Table 1. Demographics and preoperative biochemical results

		Mean	SD	Median (minimum-maximum)	n (%)
Age, y		64.78	8.18	66 (43-82)	
Gender	**M**				104 (94.5)
Gender	**F**				6 (5.5)
Smoking history, yes					76 (69.1)
BMI, kg/m²		26.24	3.74	26 (18-36.7)	
Chalson comorbidity index w/o age		1.42	1.38	1 (0-7)	
Preoperative Cre, mg/dL		1.18	0.63	0.98 (0.5-4.6)	
Preoperative Alb, mg/dL		3.93	0.53	4.00 (2.69-4.84)	
Preoparative Hb, g/dL		12.6	2.23	13 (7.6-17.7)	

Y: Year, n: Number, M: Male, F: Female, Cre: Creatinine, Alb: Albumine, Hb: Hemoglobine, SD: Standard deviation, BMI: Body mass index

Table 2. Preoperative, opeative, and postoperative results of extraperitoneal versus transperitoneal groups				
		Extraperitoneal n=58	**Transperitoneal n=52**	**p**
Age, y		65.4±7.6	64.1±8.8	0.40
Gender, n (%)	**M**	55 (50.0)	49 (44.5)	1.0
	F	3 (2.7)	3 (2.7)	
Smoking history, n (%)		41 (70.6)	35 (67.3)	0.44
BMI, kg/m²		26.2±4.0	26.2±3.4	0.99
Chalson comorbidity index w/o age [median (minimum-maximum)]		1 (0-7)	1 (0-6)	0.81
Preoperative Cre, mg/dL		1.07±0.34	1.29±084	0.08
Postoperative Cre (highest), mg/dL		1.45±0.64	1.33±0.61	0.34
Cre on the day 90th, mg/dL		1.00±3.78	1.19±0.54	0.07
Preoperative Alb, mg/dL		3.93±0.50	3.79±0.92	0.44
Postoperative Alb, mg/dL		2.49±0.32	2.60±0.35	0.10
Preoparative Hb, g/dL		12.62±2.30	12.65±2.11	0.93
Postoperative Hb, g/dL		10.2±1.84	10.08±1.68	0.50
Intravesical treatment, n (%)		10 (17.2)	8 (15.3)	0.79
Tumor grade, n (%)	**HG**	56 (51.4)	46 (42.2)	0.24
	LG	2 (1.8)	5 (4.6)	
CIS, n (%)		19 (32.7)	17 (32.6)	0.84
cT, n (%)	**<T2**	35 (31.8)	34 (30.9)	0.93
	T3-T4	23 (20.9)	19 (17.2)	
cN, n (%)		2 (3.4)	8 (15.3)	**0.03**
cM, n (%)		0 (0)	1 (100.0)	0.47
Abdominal surgery history, n (%)		8 (38.1)	13 (61.9)	0.13
Neoadjuvant chemoterapy, n (%)		3 (33.3)	6 (66.7)	0.20
Operation time, min		270±45	245±60	0.35
Hospital stay, d		10.8±3.5	11.3±4.4	0.50
Erytrocyte transfusion, n (%)		16 (27.5)	24 (46.1)	**0.04**
Clavien-Dindo classification system, n (%)	**1 and 2**	53 (48.2)	43 (39.1)	0.17
	>3	5 (4.5)	9 (8.2)	
Surgical region infection, n (%)		14 (24.1)	10 (19.2)	0.38
Ileus, conservative treatment, n (%)		1 (1.9)	8 (13.7)	**0.02**
Ileus, surgical treatment, n (%)		1 (1.7)	4 (7.6)	0.18
Urinary leakage, n (%)		0 (0)	1 (1.9)	0.47
Postoperative emergency admission, in the first 30 days, n (%)		12 (20.7)	11 (21.1)	0.84
Surgical margin positivity, n (%)		2 (3.4)	0 (0)	0.49
Local recurrence, n (%)		2 (3.4)	3 (5.7)	0.48
Total excision of LN,		12.3±3.8	14.0±4.4	0.12
Pathological LN positivity, n (%)		15 (25.8)	15 (28.8)	0.49
Follow-up, m		15.01±14.1	12.7±13.2	0.39

y: Year, d: Day, Min: Minute, n: Number, m: Month, M: Male, F: Female, Cre: Creatinine, Alb: Albumine, Hb: Hemoglobine, HG: High grade, LG: Low grade, cT: Clinical T stage, cN: Clinical N stage, cM: Clinical M stage, BMI: Body mass index, CIS: Carcinoma in situ. Categorical variables and quantitative data expressed as mean ± SD and n (%), respectively. Chi-square test and t-test were performed to examine the difference between groups. The value of $p<0.05$ was considered statistically significant and marked in bold

Discussion

Radical cystectomy is a challenging surgical procedure with high morbidity and mortality due to perioperative complications. Although the perioperative mortality rate of radical cystectomy is steady-state for the last decade (1-3%), the morbidity rate of radical cystectomy is still about 50% (8,9). Some techniques have been tried to develop to decrease this kind of perioperative morbidity. Extraperitonealization of ileal conduit separates the uretero-ileal anastomosis in front of the contaminated small bowel anastomosis and enables local management of infectious complications which lead to deterioration of the healing process of anastomosis. Furthermore, the importance of the extraperitoneal approach decreases an ileus not only due to the fluid loss of intestines which are exposed to more atmosphere during radical cystectomy but also adherents in case of any urinary leakage that leads to affect the gastrointestinal system (9). In this study, we detected fewer gastrointestinal complications especially postoperative ileus treated conservatively in extraperitoneal approach radical cystectomy which was highlighted by our study and brought popularity into consideration.

Postoperative bowel motility issue is the most frequent complication of radical cystectomy (3). It is thought that keeping the integrity of the peritoneal cavity in extraperitoneal approach may prevent the inflammatory process and help the functional recovery of the bowel. Some advantages like management of postoperative ileus or urinary leakage in intraperitonealization of an ileal segment and the extraperitoneal approach in radical cystectomy have been reported (5,10,11). In the retrospective analysis of Kulkarni's study at least five-year follow-up, the statistically significant difference in ileus (5% vs 15.8%) and reoperation due to urinary or bowel leaks (6.1% vs 12%) have been reported (9). Another beneficial effect of early bowel recovery is early enteral feeding and a decrease in electrolyte disturbances which positively reinforce the bowel movement. Zaytoun et al. (12) reported that the extraperitoneal approach had faster peristalsis (36 hours vs 12 hours, $p<0.001$), flatus (72 hours vs 36 hours, $p=0.001$), and stool passage (120 hours vs 96 hours, $p=0.06$) (12). Although there was no difference in the urinary leak (0% vs 1.9%, $p=0.47$) and ileus need for surgical intervention (1.7% vs 7.6%, $p=0.18$), our study is compatible with the previous studies in terms of ileus treated conservatively in an extraperitoneal approach increases the importance of keeping peritoneal integrity in radical cystectomy.

Since urologists have been performing radical prostatectomy through an extraperitoneal approach for years, they have anatomically dominated this field. Although it offers a narrower surgical area, it provides better surgical exposure since the area is not invaded by the intestines. Also, ligation of the dorsal vein complex decreases the blood loss and allows better surgical exposure in operation (12). In our study, the need for erythrocyte transfusion in a perioperative period is less in the extraperitoneal group supports this theory (27.5% vs 46.1%, $p=0.04$). Although in transperitoneal approach has better surgical space for dissection of pelvic LNs, we did find a similar number of extracted LNs and pathological LN positivity. Furthermore, surgical margin results and local recurrence are also key principles in oncological surgery in which our results demonstrate that the extraperitoneal approach is comparable to the transperitoneal approach in terms of oncological safety and efficacy ($p=0.49$ and 0.48, respectively).

Study Limitations

We have also some limitations in our study. First of all, this is a study of retrospective nature with a relatively low number of patients and a short follow-up period. We did not analyze the exact feeding day and electrolyte results of patients which may offer the opportunity to compare between groups. We did not focus on the overall complication rates in the early postoperative period. However, we included only ileal loop patients to eliminate the differences in surgical technique which is the strength of our study.

Conclusion

In conclusion, besides the extraperitoneal approach radical cystectomy and retroperitonealization of the ileal loop is safe and effective on oncological surgical principles, it may also provides better functional outcomes for gastrointestinal motility after surgery.

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Ethics

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Authorship Contributions

Critical Review: E.G., Supervision: E.G., Data Collection or Processing: K.G.Ş., O.Ö., Analysis-Interpreation: E.S., Literature Review: E.S., O.Ö., Writing: E.S.

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Investigation of Factors Influencing the Prognosis in Prostate Cancer Patients with Isolated Bone Metastasis

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Abstract

Objective: Bone metastases, which show a milder course compared with visceral disease, are among the most common metastatic sites in prostate cancer. In the present study, we aimed to investigate the prognostic factors that influence the survival time in the castration-sensitive phase in patients diagnosed with prostate adenocarcinoma with isolated bone metastasis.

Materials and Methods: The prognostic effects of the clinical (performance status, number of bone metastases) and laboratory parameters of a total of 217 patients, of whom the data could be accessed, on survival in the castration-sensitive phase were evaluated.

Results: Of the 217 patients included in our study, 144 (66.4%) were metastatic at presentation. The mean age of the patients was 68.4 (42-88) years. The mean follow-up duration was 44 months. Of our 217 patients, 125 (57.6%) were included in the castration-sensitive group and 92 (42.4%) in the castration-resistant group. In multivariate analyses; lactate dehydrogenase, alkaline phosphatase (ALP) levels and the number of bone metastases were independent prognostic factors with a strong correlation with time to castration-resistant prostate cancer. The evaluation of these three parameters within the framework of a prognostic index and subsequent risk stratification revealed median progression-free survival times of 91, 36, 20 and 12 months for the very low-risk, low-risk, intermediate-risk and high-risk groups, respectively.

Conclusion: Lactate dehydrogenase, ALP levels and the number of bone metastases were determined as strong and useful prognostic factors in predicting time to castration-resistant prostate cancer in metastatic prostate cancer.

Keywords: Bone metastasis, prostate cancer, prognostic factors

Introduction

Prostate cancer constitutes the second most frequent cause of cancer-related mortality in males (1). The bones are among the most common metastatic sites in prostate cancer. Most of the time, the patient loses the chance of curative treatment in the presence of bone metastasis (2). Although it is known that there is a strong interaction between cancer cells and the microenvironment in bone metastases, that osteocytes, which play a leading role in bone remodeling and formation, interact with cancer cells; the form and magnitude of this interaction is not yet elucidated (3,4). In the case of bone metastasis, bone mineralization due to elevated osteoblastic activity and, as an indicator of this, elevated alkaline phosphatase (ALP) levels are encountered (5). However, the induced osteoblastic activity leads to the formation of bones of low quality that are at risk of fracture (6).

Another common condition in cancer patients is anemia encountered at diagnosis or developing later (7). The prevalence of anemia was reported to vary between 19% and 75% across different cancer diagnoses (8). Among the proposed theses are that anemia diminishes treatment response by creating tumor hypoxia and that it causes an increase in angiogenesis (9). Anemia has been reported as a poor prognostic factor in prostate cancer (10). The risk of anemia increases approximately three-fold in patients receiving androgen deprivation therapy (ADT) in prostate cancer (11).

To date, many prognostic models have been produced that can predict the course of the disease in metastatic prostate cancer. The first model was developed by Glass et at. (12) in non-castrate metastatic prostate cancer patients based on performance status, prostate specific antigen (PSA) level, localization of bone metastases and Gleason score (GS). Later studies revealed ALP levels to be a significant indicator of overall survival (OS) (13). According to the current literature; a high GS, large tumor size, high ALP and PSA levels constitute an independent risk factor for bone metastasis (14). The scores that have been devised were mostly based on castration-resistant patients.

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In this study, we aimed to investigate the prognostic factors that will predict the time to castration-resistant prostate cancer (CRPC) in patients diagnosed with prostate adenocarcinoma with bone-only metastasis in light of the literature and to assess the role of these factors in a prognostic index that will offer convenient clinical use.

Materials and Methods

In this study, data of patients diagnosed with prostate adenocarcinoma who presented to the Medical Oncology Clinic of Dicle University, Faculty of Medicine between 2010-2020 were retrospectively examined. In total, 349 (43.9%) of the 795 patients diagnosed with prostate cancer had metastatic disease. Of the patients who developed metastases, 132 (43.9%) had visceral organ metastasis and 217 (62.2%) had isolated bone metastasis. Our study included patients diagnosed with prostate adenocarcinoma with isolated bone metastasis. Patients with visceral organ metastases were not included in the study. The clinical characteristics of patients' [age, GS, number of bone metastases, Eastern Cooperative Oncology Group performance status (ECOG PS), lymph node metastasis], total PSA (tPSA), mean platelet volume (MPV), lactate dehydrogenase (LDH), ALP, hemoglobin (Hg) and albumin levels at diagnosis, treatments received during the hormone-sensitive phase were recorded. The relationships of these parameters in the castration-sensitive phase with time to CRPC were investigated.

Castration-resistant disease was accepted as; clinical, radiological and biochemical progression of the disease despite castration-level testosterone levels (<50 ng/dL). The diagnosis of metastatic disease was made using the following methods: Magnetic resonance imaging, computed tomography, bone scintigraphy or positron emission tomography/prostate-specific membrane antigen. Treatment response was evaluated every three months, based on clinical results, PSA levels and radiological imaging. Radiological response was evaluated according to the Response Evaluation Criteria in Solid Tumors criteria.

All analyses were performed in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the Ethics Committee of Dicle University Medical Faculty for the study (decision number: 127, date: 25.02.2021).

Statistical Analysis

SPSS 18.0 package program was used for statistical analysis of the data. Descriptive statistics were used to evaluate patient characteristics and the frequencies of the parameters, student's t-test was used for normally distributed numeric variables, and the Mann-Whitney U test was used for the analyses of non-normally distributed variables. As ten clinical and laboratory parameters at the first metastatic diagnosis; age (15), tPSA (16), albumin (15), LDH (15), MPV (17), ALP levels (15), number of bone metastases (18), treatments received during the hormone-sensitive phase (19), GS (20) and ECOG PS (15) were defined as independent variables based on previous studies. The Kaplan-Meier method (Tarone-Ware tests, Breslow, Log-rank) was used for survival analysis. OS was calculated as the duration of time from the diagnosis to mortality, metastatic OS as the duration of time from metastatic progression to mortality, and time to CRPC as the duration of time from ADT initiation to the development of refractory disease. Receiver operating characteristic (ROC) analysis was used to determine cut-off values for the quantitative parameters with high sensitivity and specificity. In univariate analysis, chi-square test, the t-test, Mann-Whitney U tests and Fisher's Exact were used. The parameters that had prognostic significance in the univariate analysis were introduced to the Cox regression model to determine the parameters with prognostic value for time to CRPC in prostate cancer patients with isolated bone metastases. A 95% confidence interval and a p significance level <0.05 were adopted.

Results

This study included a total of 217 patients diagnosed with prostate adenocarcinoma who had isolated bone metastases. Of our patients, 125 (57.6%) were included in the castration-sensitive group and 92 (42.4%) in the castration-resistant group. One-hundred and forty-four patients (66.4%) were metastatic at initial diagnosis. Seventy-three patients (33.6%) who initially presented at a localized stage and later developed metastasis had received primary radiotherapy or radical prostatectomy at the localized stage. The mean age of the patients was 68.4±8.3 years. The median follow-up duration was 33 (2-217) months [32 (2-216) months for castration-sensitive patients and 34 (2-217) months for castration-resistant patients]. In the castration-sensitive phase, 198 (91.2%) patients were given ADT [bilateral orchiectomy or gonadotropin-releasing hormone agonist (leuprolide, goserelin) ± bicalutamide] and 19 (8.8%) patients were given ADT + docetaxel therapy. Hormone refractory disease occurred during the follow-up of our 125 (57.6%) patients. The baseline characteristics of the patients are presented in Table 1.

In patients who developed castration resistance, the median time to castration resistance was 25 months [95% confidence interval (CI): 20.6-29.3]. The median survival time from diagnosis was 42 months (95% CI: 32.1-51.8), the OS time from metastatic progression was 31 (95% CI: 26.0-33.9) months, the median survival time after the development of castration-resistance was 10 (95% CI: 8.6-11.4) months. For our patients in the castration-sensitive and castration-resistant groups, the median OS times from diagnosis were 51 months and 41 months (p=0.38), respectively. The median OS times from metastatic progression were 31 and 30 months (p=0.62). The progression-free survival times of our patients with the treatments given in the hormone-sensitive phase were 11 months (95% CI: 8.6-13.3) and 28 months (95% CI: 22.7-33.2) for patients who received ADT + Docetaxel and patients who received ADT alone (p<0.001), respectively. Of our 125 castration-resistant patients, 91 (41.9%) had received one-line, 27 (12.4%) had received two lines, 5 (2.3%) had received three lines of therapy.

ROC analysis results and cut-off values concerning the following identified clinical and laboratory variables are presented in Table 2: LDH, ALP, MPV, tPSA and number of bone metastases. Cut-off values were determined as follows: MPV ≥8 fl [Area under curve (AUC): 0.618 (0.239-0.698), p=0.005], LDH ≥300 U/L (AUC: 0.600 (0.519-0.681), p=0.018), ALP ≥140 U/L [AUC: 0.609 (0.529-0.690), p=0.010], tPSA ≥100 ng/dL (AUC: 0.634 (0.555-0.713), p=0.001), number of bone metastases ≥5 [AUC:

Table 1. Baseline characteristics of patients at initial of metastatic disease

Characteristic	All patients (n=217) n (%)	Castration resistant (n=125) n (%)	Castration sensitive (n=92) n (%)	P value
Age (years)				
Mean ± SD	68.4±8.3	68.1±8.7	68.7±7.9	0.91***
ECOG PS				**0.048***
0-1	178 (82)	97 (54.5)	81 (45.5)	
≥2	39 (18)	28 (71.8)	11 (28.2)	
Gleason score				0.728*
<8	112 (53.8)	65 (58)	47 (42)	
≥8	96 (46.2)	58 (60.4)	38 (39.6)	
Lymph node metastasis				**0.016***
Yes	79 (36.7)	54 (68.4)	25 (31.6)	
No	136 (63.3)	70 (51.5)	66 (48.5)	
Co-morbidities				0.818*
Yes	75 (34.6)	44 (58.7)	31 (41.3)	
No	142 (65.4)	81(57)	61 (43)	
First treatment options				0.318*
ADT	198 (91.2)	112 (56.6)	86 (43.4)	
ADT + docetaxel	19 (8.8)	13 (68.4)	6 (31.6)	
Lactate dehydrogenase (U/L)				**0.018****
Median (range)	252 (112-1845)	292 (135-1845)	237 (112-1837)	
Alkaline phosphatase (U/L)				**0.010****
Median (range)	126 (36-4541)	168 (49-2254)	102 (36-4541)	
Albumin (gr/dL)				0.95***
Mean ± SD	3.39±0.65	3.39±0.64	3.38±0.66	
Hemoglobin (gr/dL)				0.19***
Mean ± SD	12.3±2.1	12.1±2.1	12.5±2.1	
Baseline PSA level (ng/dL)				**0.001****
Median (range)	90 (0.1-5000)	100 (0.1-5000)	38 (1-4217)	
Mean platelet volume				**0.005*****
Mean ± SD	7.8±1.5	7.6±1.5	8.2±1.5	
Number of bone metastases				**<0.001****
Median (range)	5 (1-21)	6 (1-21)	3 (1-20)	

ADT: Androgen deprivation therapy, ECOG PS: Eastern Cooperative Oncology Group performance status *Chi-Square test, **Mann-Whitney U test ***Student t-test, SD: Standard deviation

0.648 (0.574-0.723), p<0.001]. Among these variables; number of bone metastases, ≥5, LDH ≥300 U/L, ALP ≥140 U/L, MPV ≤8fl and tPSA ≥100 ng/dL were determined as strong prognostic values.

Univariate analyses revealed a statistically significant difference between the castration-sensitive and -resistant groups in terms of the number of bone metastases, LDH, ALP, MPV and PSA levels and lymph node involvement; and multivariate analyses determined a statistically significant association between the number of bone metastases (p=0.002), LDH (p=0.003) and ALP (p=0.004) variables and time to CRPC (Table 1, Table 3).

These three parameters (number of bone metastases, ALP and LDH) were defined as independent factors predicting time to CRPC. The number of bone metastases, ALP and LDH parameters were evaluated within the framework of a prognostic index. Patients with five or more bone metastases were given a score of 1, those with fewer than five bone metastases were given a score of 0, those with an ALP level of 140 U/L or above were given a score of 1, those with an ALP level below 140 U/L were given a score of 0, those with an LDH level of 300 U/L or above were given a score of 1, those with an LDH level below 300 U/L were given a score of 0. When all scores were summed to obtain a total score; those with a score of 0 were categorized into the very low-risk group, those with a score of 1 into the low-risk group, those with a score of 2 into the intermediate-risk group, and those with a score

Table 2. ROC analysis results for cut-off value							
Variables	**Cut-off value**	**AUC**	**95% CI**	**P value**	**sensitivity**	**1-spesifity**	**State variable**
Mean platelet volume (fl)	≥8	0.618	0.239-0.698	**0.005***	0.494	0.327	Castration sensitive
Lactate dehydrogenase (U/L)	≥300	0.600	0.519-0.681	**0.018***	0.487	0.291	Castration resistant
Alkaline phosphatase (U/L)	≥140	0.609	0.529-0.690	**0.010***	0.539	0.291	Castration resistant
Baseline PSA level (ng/dL)	≥100	0.634	0.555-0.713	**0.001***	0.567	0.354	Castration resistant
Number of bone metastases	≥5	0.648	0.574-0.723	**<0.001***	0.675	0.413	Castration resistant
ROC: Receiver operating characteristic, AUC: Area under curve, CI: Confidence interval *statistically significant							

Table 3. Multivariate analysis of factors affecting time to castration resistant prostate cancer			
	Multivariate analysis		
Variables	**HR**	**95% CI**	**P value**
Performance status (0-1. ≥2)	1.043	0.650-1.674	0.862
Mean platelet volume (fl) (<8. ≥8)	0.855	0.561-1.302	0.465
Lactate dehydrogenase (U/L) (<300. ≥300)	1.939	1.244-3.023	**0.003***
Alkaline phosphatase (U/L) (<140. ≥140)	1.988	1.252-3.157	**0.004***
Baseline PSA level (ng/dL) (<100. ≥100)	1.092	0.695-1.715	0.703
Lymph node metastasis (No. yes)	1.155	0.776-1.719	0.479
Number of bone metastases (<5. ≥5)	2.066	1.313-3.250	**0.002***
First treatment options (ADT. ADT+ docetaxel)	1.489	0.739-3.001	0.265
*Statistically significant, ADT: Androgen deprivation therapy, HR: Hazard ratio, CI: Confidence interval, PSA: Prostate specific antigen			

of 3 into the high-risk group. The number of patients, whose complete data could be obtained, and who were included in the prognostic index, was 190. The distribution of the patients across risk groups was as follows: 56 (29.5%) patients in the very low-risk group, 44 (23.3%) in the low-risk group, 46 (24.2%) in the intermediate-risk group, and 22 (23.2%) in the high-risk group. Time to CRPC values of the groups when ordered from the very low-risk group to the high-risk group were 91, 36, 20 and 12 months, respectively (p<0.001). There was a statistically significant difference between the groups in terms of time to CRPC (Table 4, Figure 1). The percentage of patients who developed castration resistance over time in each risk group is shown as a scale (Figure 2).

Discussion

In light of the literature, we investigated in this study the clinical and laboratory parameters predicting time to CRPC in patients diagnosed with prostate cancer with bone metastasis that would offer ease of use in practice. As is known, ADT or, in patients with a high tumor burden, ADT + docetaxel/second generation antiandrogen therapies can be used as the initial treatment in metastatic castration-naive prostate adenocarcinoma (19). In all patients included in our study, castration was obtained with ADT in the metastatic period. Patients with a high tumor burden and without chemotherapy rejection or contraindications who had appropriate performance status [n=19, (8.8%)] were given ADT + docetaxel. Time to CRPC was 28 months in the group that received only ADT [n=198 (91.2%)], while it was

Table 4. Prognostic index for time to CRPC in castration sensitive prostate cancer with isolated bone metastases						
			Time to CRPC (months)			
Risk groups	**n=190**	**Total score**	**Median**	**95% CI**	**HR (95% CI)**	**P value**
Very low	56	0	91	34.1-147.8	Reference	**<0.001***
Low	44	1	36	15.4-56.5	1.883 (1.055-3.361)	**0.032***
Intermediate	46	2	20	15.0-24.9	4.693 (2.62-8.402)	**<0.001***
High	44	3	12	10.1-13.8	9.843 (5.363-18.065)	**<0.001***
LDH ≥300 U/L=1			**LDH <300 U/L=0**			
ALP ≥140 U/L=1			**ALP <140 U/L=0**			
NBM ≥5=1			**NBM <5=0**			
*Statistically significant, CRPC: Castration resistant prostate cancer, LDH: Lactate dehydrogenase, ALP: Alkaline phosphatase, NBM: Number of bone metastases, CI: Confidence interval, HR: Hazard ratio						

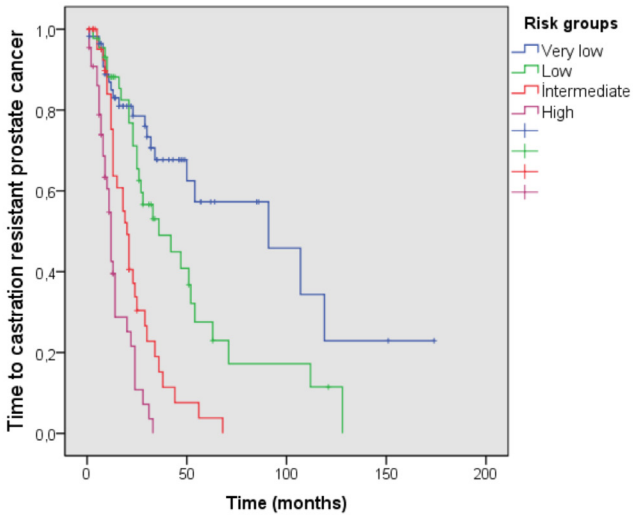

Figure 1. Time to castration resistant prostate cancer according to risk groups

Time to CRPC values of the groups when ordered from the very low-risk group to the high-risk group were 91, 36, 20 and 12 months, respectively (p<0.001)

CRPC: Castration-resistant prostate cancer

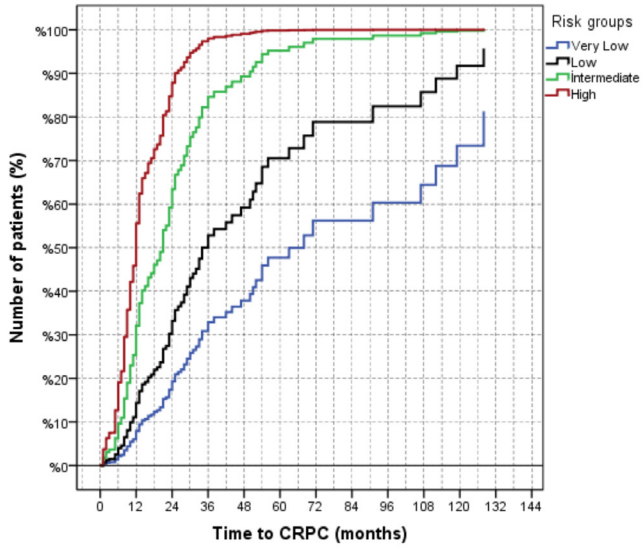

Figure 2. Castration resistant risk scale according to time

The percentage of patients who developed castration resistance over time in risk groups is shown on the scale

CRPC: Castration-resistant prostate cancer

11 months in the group that used ADT + docetaxel (p<0.001). There was a statistically significant difference between the two groups in terms of time to CRPC. We reasoned that this was because patients with a more aggressive clinical course and higher tumor burden were included in the chemotherapy arm.

Factors influencing survival, such as tumor metastasis sizes, radiological and laboratory parameters have been investigated in prostate cancer, particularly in the castration-resistant phase. In metastatic castration-resistant prostate cancer (mCRPC), the survival times for patients with only lymph node involvement, bone metastasis, lung and liver metastasis were reported as 31.6, 21.3, 19.4 and 13.5 months, respectively (21). Our study included prostate cancer patients with isolated bone metastases. For the patient group that remained castration-sensitive and the group that developed castration resistance, the median OS from diagnosis were 51 and 41 months, respectively (p=0.38). Meanwhile, the median OS from metastatic progression were 31 and 30 months for the two groups, respectively (p=0.62). There was no statistically significant difference between the two groups with regard to OS. However, the median survival times of our patients were longer compared with the values reported in the literature (21). Two-year and five-year biochemical progression-free survival rates of castration-sensitive patients were reported as 23- 64% and 6-31% (22). In our study, patients who developed castration resistance had a PFS of 25 months in the castration-sensitive phase. After the development of castration resistance, the median survival time of the patients in this group was 10 months.

The prediction of progression in castration-sensitive patients mostly involves genomic-based approaches such as Decipher (23) and Oncotype Dx (24). In the literature, prognostic factors such as a poor performance status, high LDH and ALP levels, low Hg and albumin levels, localization of bone metastases and presence of visceral organ metastasis were inspected predominantly in castration-resistant patients. OS values for risk groups were attempted to be estimated using nomograms in mCRPC patients (15).

When this matter is inspected along with the literature; it is found that 12- and 24-month survival rates and median OS times of patients with castration-resistant bone metastases were evaluated in a study by Fizazi et al. (16) using a nomogram including clinical and laboratory parameters such as skeletal-related events and the state of development of visceral metastasis, age, pain and performance status, time to first bone metastasis, Hg, ALP and PSA. In another study, it was reported that the volume of bone metastasis could be a prognostic marker of OS in mCRPC (25). Armstrong et al. (26) investigated the relationship between the automated bone scan index (BSI) and survival in CRPC patients with bone metastases in a prospective randomized study. In this study, ALP, PSA and LDH levels were determined to be correlated with the extent of bone involvement. There are also studies showing that the metastatic site, metastatic extent and pain are prognostic markers (27). In non-castrate metastatic prostate cancer; age, body mass index, pain status, Hg, LDH and ALP levels were reported to be prognostic markers indicating OS and, particularly, high ALP levels were found to be a strong predictor of OS (13).

With regard the castration-sensitive phase; Akamatsu et al. (28) evaluated the relationship of high LDH, GS, extent of disease with the OS in treatment-naive metastatic castration-sensitive prostate cancer and developed a risk stratification system. Besides GS, PSA and T-stage, other studies have also examined the BSI as an important prognostic marker during the ADT period (20) and as an independent predictor factor of time to

castration resistance (29). In a study conducted in Japan, Miyoshi et al. (30) constructed a nomogram involving age, T-stage, extent of the disease, GS and PSA levels in order to estimate 1-, 3- and 5-year survival in Japanese patients diagnosed with prostate cancer with bone metastasis. MPV, which is another parameter evaluated in the present study, has been studied in the literature as a prognostic marker in various diseases and was also evaluated in prostate diseases (31). However, it was not used as a prognostic marker in prostate cancer before. Studies have reported elevated MPV levels in males diagnosed with hypogonadotropic hypogonadism and reduced MPV levels in the presence of hyperandrogenemia in women diagnosed with polycystic ovary syndrome (17,32). This brings to mind the thesis that MPV is an indirect marker of androgen activity in the body.

In the present study, the parameters that have been used in the literature under various titles and, as described above, in different combinations, in order to predict the prognosis in prostate cancer were evaluated in prostate cancer patients with isolated bone metastases. As independent variables; we examined age, ECOG, PS, GS, tPSA, Hg, albumin, MPV, LDH, ALP, lymph node involvement and number of bone metastases.

In the evaluation of GSs and tPSA levels; no statistically significant difference was found between the castration resistant and castration-sensitive groups with regard to GSs (p=0.72), while PSA levels at metastatic onset were higher in the group that developed castration resistance, with statistical significance (p=0.001).

As specified in detail in Table 1; primarily, the number of bone metastases, MPV, ALP and LDH levels, as well as lymph node involvement and ECOG performance were significantly different between the groups in univariate analysis. Our results were consistent with the studies previously reported in the literature. MPV levels were lower in the castration-resistant group, with statistical significance. This appears to corroborate the studies reporting a relationship between androgens and MPV (17,32). In contrast with the nomograms reported in mCRPC patients in the literature; age, Hg and albumin levels were comparable between the castration-sensitive and -resistant groups in our study (15). When the prognostic parameters, for which cut-off values were determined using ROC analysis (Table 2), were evaluated using multivariate analyses, time to CRPC did not have a statistically significant correlation with ECOG PS, tPSA and MPV values. Number of bone metastases ≥5 (p=0.002), LDH ≥300 U/L (p=0.003), ALP ≥140 U/L (p=0.004) were statistically significant variables predicting time to CRPC in castration-sensitive metastatic prostate cancer. Excluding the parameters that did not have a statistically significant relationship with time to CRPC in multivariate analysis, the three parameters that were determined to have a strong statistical correlation with time to CRPC (number of bone metastases, LDH, ALP) were evaluated within the framework of an index. A score of 1 was recorded for each parameter meeting the following conditions: Number of bone metastases ≥5, LDH ≥300 U/L, ALP ≥140 U/L. When the total scores were computed from these three groups; the group with a score of 0 was defined as the very low-risk group, that with a score of 1 as the low-risk group, that with a score of 2 as the intermediate-risk group, and that with a score of 3 as the high-risk group. According to the comparison of these groups in terms of time to CRPC; the median time to CRPC values for the very low-, low-, intermediate- and high-risk groups were 91 months, 36 months, 20 months, 12 months, respectively (log rank p<0.001). There was a statistically significant difference between the groups in terms of ADT-T (Table 4, Figure 1). We observed that the number of bone metastases, ALP and LDH levels at diagnosis were important and strong prognostic factors predicting time to CRPC in non-visceral metastatic prostate cancer. The Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) study reported that complementing ADT with chemotherapy was associated with a survival advantage in high-volume metastatic castration-sensitive prostate cancer (18). In the CHAARTED study, high-volume disease was defined as the presence of visceral metastasis or the presence of at least 4 bone metastases with one outside of the pelvis and/or vertebral column (18). For some patient groups with isolated bone metastasis and no visceral organ metastasis, the factors described in the CHAARTED study are not sufficient by themselves for the chemotherapy decision. Our view is that the parameters we determined in this study in castration-sensitive prostate cancer with isolated bone metastasis can serve as predictor factors in the planning of the treatment, particularly with respect to the risk groups. We think that these three useful parameters that are easily accessible in practice, which were evaluated within the framework of an index, can assist and guide clinicians in the management of the patients and the prediction of time to CRPC in castration-sensitive metastatic prostate cancer.

Study Limitations

The limitations of our study were that the study was single-centered and retrospective and the number of patients was small.

Conclusion

Prostate cancer is a prevalent disease at advanced ages and various factors such as performance status, co-morbidities, life expectancy and histological characteristics of the disease play a role in the planning of the treatment. There is a need for predictive and prognostic markers that will indicate survival in the castration-sensitive phase and determine the treatment approach in prostate cancer patients with isolated bone metastases. We believe that the prognostic index specified in this study, which is composed of the number of bone metastases, LDH and ALP levels will be a practical tool useful in the prediction of time to CRPC in prostate cancer patients with isolated bone metastases.

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Ethics

Ethics Committee Approval: Approval was obtained from the Ethics Committee of Dicle University Medical Faculty for the study (decision number: 127, date: 25.02.2021).

Informed Consent: Retrospective study.

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Authorship Contributions

Concept: S.E., Z.O., Z.U., M.A.K., M.K., A.I., Design: Supervision: S.E., Z.O., Z.U., M.A.K., M.K., A.I., Data Collection-Processing: S.E., Z.O., Z.U., M.A.K., M.K., A.I., Analysis-Interpretation: S.E., Z.O., Z.U., M.A.K., M.K., A.I., Literature Review: S.E., Z.O., Z.U., M.A.K., M.K., A.I., Writing: S.E., Z.O., Z.U., M.A.K., M.K., A.I., Critical Review: S.E., Z.O., Z.U., M.A.K., M.K., A.I.

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Original Article

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Treatment and Management in Relapsed/Refractory Malignant Somatic Transformation

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Abstract

Objective: To demonstrate treatment responses, survival analysis and treatment-related mortality characteristics of patients with malignant somatic transformation (MST).

Materials and Methods: In this retrospective cross-sectional study, patients with relapsed and refractory MST who had previously received multiple-line chemotherapy were evaluated. Clinical features and follow-up data of relapsed/refractory MST patients were recorded from the patients' registration database at the hospital. Age, clinical stage at initial diagnosis, serum tumour marker levels, visceral metastasis status, previous treatment protocols and follow-up times were recorded. This study aims to demonstrate demographic and disease-related characteristics, best response to systemic therapy, and overall survival (OS) results.

Results: The study included 14 patients. Mean age at diagnosis was 29.6 years for the whole group. The most-common sarcoma subtype was Ewing sarcoma (44.4% in the sarcoma group). In half the patients, the best response to systemic treatment was determined as a complete response. Median OS for the sarcoma group was 19.72 months [interquartile range (IQR) 29.18 months], and in the adenocarcinoma group, it was determined as 136.24 months (IQR 131.92 months) (p=0.006). The median OS for the whole group was 28.12 months (IQR 99 months). No significant difference in survival was found between synchronous and relapsed cases [median (IQR) 24.09 (91.23) months vs 43.54 (113.51) months, p=0.606].

Conclusions: Germ cell tumour patients with MST should be treated according to the somatic component. Poor responses to cisplatin-based chemotherapy have been found in this cohort. Patients with sarcomatous components were found to have significantly shorter OS.

Keywords: Germ cell tumour, malignant somatic transformation, teratoma, testicular cancer

Introduction

Germ cell tumours (GCTs) are one of the most-common solid malignancies in the male population, especially in the second and third decades of life (1). Even if patients are diagnosed at an advanced stage, a very good response can be obtained, especially with the platinum-based treatment approach. The five-year overall survival (OS) for advanced disease is 80-90% (2).

By contrast, it is known that, rarely, testicular teratomas can undergo malignant somatic transformation (MST) (3). MST is a phenomenon seen in 2.7-8.6% of non-seminomatous GCTs. The most-common transformed histologic types include rhabdomyosarcoma, adenocarcinoma, and primitive neuroectodermal tumour (4,5). MST is a difficult clinical entity to treat because of its chemoresistance to platinum-based therapies and frequent recurrence. Despite all oncological treatment options, survival rates are low even in reference health centers (6).

Since studies on this subject are limited to case reports, it is difficult to understand the prognostic factors of cases with MST and to manage the treatment process. No significant difference in survival has been reported between secondary histopathological subgroups in most studies (5,7). To the best of our knowledge, in relation to our country, anecdotal case series of MST patients have been reported.

We retrospectively evaluated the clinical features of all cases with MST treated at University of Health Sciences Turkey, Gülhane Training and Research Hospital in Ankara, Turkey. We focused on the presentation differences between the histological subtypes of MST, the time frame in which MST occurs, and the therapeutic approach used to understand the response to treatment. We aimed to show the prognostic factor differences and survival difference between sarcomatous transformation and carcinomatous transformation.

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Materials and Methods

We conducted this study by retrospectively reviewing the medical records of outpatients and inpatients with MST from a tertiary clinic from January 2017 through June 2021. The inclusion criteria were age ≥18 years, a histologically confirmed metastatic testicular cancer, imaging-proven metastases and confirmed somatic transformation at diagnosis or at recurrence. The exclusion criteria were age <18 years and insufficient clinical data.

We identified a total of 14 patients. Age at diagnosis, synchronous vs metachronous detection of MST, localization of primary lesion, localization of MST, histopathological subtypes of MST, serum tumour marker status at first diagnosis, International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification at initial diagnosis, visceral metastasis status, treatments for MST (surgery, radiotherapy and systemic treatments), survival after MST diagnosis and OS time from first diagnosis were retrieved from medical records (8). Time from initial diagnosis to the patient's last hospital admission or death was defined as OS. The University of Health Sciences Turkey, Gülhane Training and Research Hospital Clinical Research Ethics Committee approved the study protocol (decision number: 2021/57).

Complete remission was defined as the disappearance of all clinically and radiologically detectable lesions and the normalization of tumour markers. More than 20% reduction in tumour burden was defined as a partial response. Tumour growth greater than 20% was defined as progressive disease. Any other response was classified as stable disease.

Statistical Analysis

Descriptive statistics are presented as a percentage of the total. Uniformity of continuous variables to normal distribution was examined using the Kolmogorov-Smirnov test. Normally distributed continuous data are expressed as mean ± standard deviation, and data not normally distributed are expressed as median [interquartile range (IQR)]. Differences between groups according to distribution and type of variable were tested with Pearson's chi-squared test, Student's t-test or Mann-Whitney U test. A p-value less than 0.05 was considered statistically significant. We performed statistical analyses using SPSS 22.0 software (SPSS Inc., Chicago, Illinois).

Results

The mean age of the group at initial diagnosis was 29.6 years, and the most-common localization of the primary tumour was the testicles (78.6%). Patients were often identified as stage 3C at the time of initial diagnosis (71.4%). Most patients had a sarcomatous histological subtype (64.2%), and also in most patients, MST was detected at the time of relapse (57.1%). The most-common sarcoma subtype was Ewing sarcoma (44.4%). Colon cancer was the most-common adenocarcinoma subtype (40%). At the diagnosis, serum tumour marker level at S3 was detected in 42.9% of the patients. In the IGCCCG risk classification evaluation, the majority of patients were included in the "poor" risk group (78.6%). Orchiectomy was performed in all patients with primary testicular cancer (Table 1). Surgery to the MST lesion was performed in most patients (64.3%). Half the patients with MST lesions received radiotherapy with or without surgery. All patients received systemic chemotherapy. In half the patients, a complete response was obtained as the best response. Median OS for the sarcoma group was 19.72 months (IQR 29.18 months). In the adenocarcinoma group, it was determined as 136.24 months (IQR 131.92 months) (p=0.006). Mean OS for the whole group was 28.12 months (IQR 99 months) (Table 2 and Figure 1). No significant difference in survival was observed between synchronous and relapsed cases [median (IQR) 24.09 (91.23) months vs 43.54 (113.51) months, p=0.606].

Table 1. The demographic and disease-related characteristics of the patients

Features	Sarcoma (n=9)	Adenocarcinoma (n=5)	Total (n=14)
Age, median (range), years	23 (18-40)	42 (20-49)	26.5 (18-49)
Location of primary, n (%)			
Testes	7 (77.7)	4 (80)	11 (78.6)
Retroperitoneal	1 (11.1)	1 (20)	2 (14.3)
Mediastinal	1 (11.1)	0 (0)	1 (7.1)
Time of diagnosis of MST, n (%)			
Synchronus	5 (55.5)	1 (20)	6 (42.9)
Relapse	4 (44.4)	4 (80)	8 (57.1)
Clinical stage (AJCC, 8th), n (%)			
II B	2 (22.2)	0 (0)	2 (14.3)
II C	2 (22.2)	0 (0)	2 (14.3)
III C	5 (22.2)	5 (100)	10 (71.4)
Serum tumor markers, n (%)			
S0	5 (55.5)	1 (20)	6 (42.9)
S1	1 (11.1)	1 (20)	2 (14.3)
S2	0 (0)	0 (0)	-
S3	3 (33.3)	3 (60)	6 (42.9)
IGCCCG risk groups, n (%)			
Good risk	1 (11.1)	0 (0)	1 (7.1)
Intermediate risk	2 (22.2)	0 (0)	2 (14.3)
Poor risk	6 (66.6)	5 (100)	11 (78.6)
Visceral metastasis, n (%)			
Lung	5 (55.5)	4 (80)	9 (64.3)
Liver	4 (44.4)	3 (60)	7 (50)
Bone	2 (22.2)	1 (20)	3 (21.4)
Orchiectomy	7 (77.7)	4 (80)	11 (78.6)

MST: Malignant somatic transformation, AJCC: The American Joint Committee on Cancer, S1: Lactate dehydrogenase (LDH) <1.5 × Upper limit of normal (ULN) and human chorionic gonadotropin (hCG) (mIU/mL) <5000 and alpha-fetoprotein (AFP) (ng/mL) <1000. S2: LDH 1.5 to 10 × ULN or hCG (mIU/mL) 5000 to 50,000 or AFP (ng/mL) 1000 to 10,000. S3: LDH >10 × ULN or hCG (mIU/mL) >50,000 or AFP (ng/mL) >10,000. IGCCCG: The International Germ Cell Cancer Collaborative Group

Discussion

The development of MST in GCT patients is a very rare condition. Because of this, there is a lack of data on MST and, therefore, a lack of a general approach. Widespread differences in inclusion criteria in the reported case series preclude generalization of study findings for this already-small number of patients.

MST, which develops from different germinal layers as its histological origin, is considered to be a clinical entity that exacerbates the prognosis. It is a phenomenon with a tendency to transform into systemic disease and invade local tissues. MST is often resistant to the chemotherapy used to treat GCTs. Therefore, in a significant proportion of patients, surgical resection remains the only potentially curative approach (9,10).

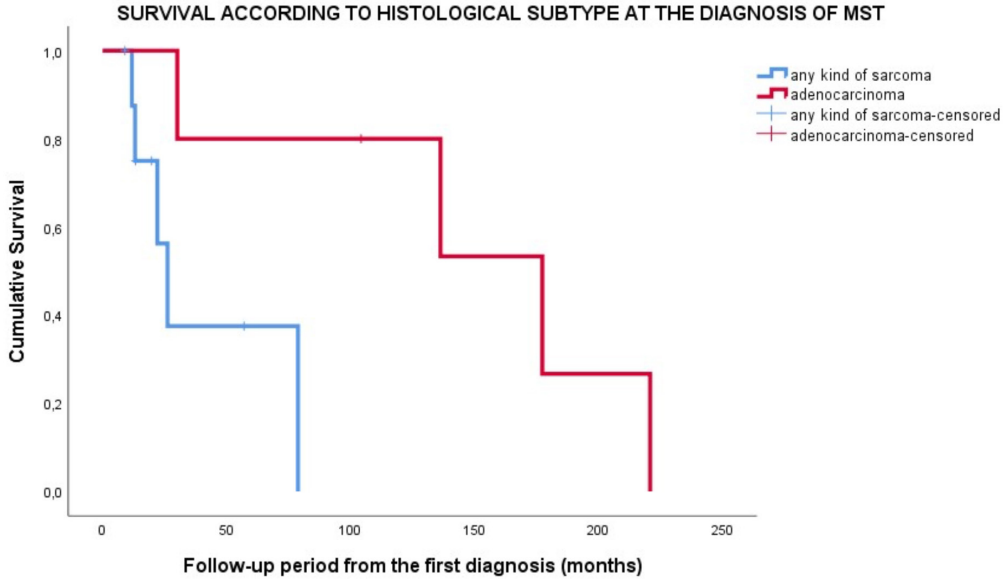

Figure 1. Survival according to histological subtype at the diagnosis of MST

MST: Malignant somatic transformation

Table 2. Treatment-related characteristics of the patients

Features	Sarcoma (n=9), n	Adenocarcinoma (n=5), n	Total (n=14), n (%)
Surgery to MST, n (%)	7 (77.7)	2 (40)	9 (64.3)
Radiotherapy to MST, n (%)	5 (55.5)	2 (40)	7 (50)
Systemic treatment of MST, n (%)	9 (100)	5 (100)	14 (100)
First line systemic treatment for MST, n (%)			
ICE	2 (22.2)	1 (20)	3 (21.4)
VAC-IE	4 (44.4)	0 (0)	4 (28.6)
FLOT	0 (0)	1 (20)	1 (7.1)
FOLFOXIRI-bevacizumab	0 (0)	1 (20)	1 (7.1)
Cisplatin + gemcitabine	0 (0)	1 (20)	1 (7.1)
IMA	2 (22.2)	0 (0)	2 (14.3)
VAC	1 (11.1)	0 (0)	1 (7.1)
FOLFOX	0 (0)	1 (20)	1 (7.1)
Best response to systemic treatment for MST, n (%)			
Complete response	6 (66.6)	1 (20)	7 (50)
Partial response	0 (0)	2 (40)	2 (14.3)
Stable disease	1 (11.1)	2 (40)	3 (21.4)
Median overall survival, median (IQR), months	**19.72 (29.18)**	**136.24 (131.92)**	**28.12 (99)**

MST: Malignant somatic transformation, ICE: Ifosfamide, carboplatin, etoposide, VAC-IE: Vincristine, adriamycin, cyclophosphamide, ifosfamide, etoposide, FLOT: Fluorouracil, oxaliplatin, docetaxel, FOLFOXIRI: Fluorouracil, oxaliplatin, irinotecan, IMA: Ifosfamide mesna adriamycin, VAC: Vincristine, adriamycin, cyclophosphamide, FOLFOX: Fluorourasil, oxaliplatin, IQR: Interquartile range

As in the previously reported case series, sarcomatous transformation was mostly detected in our patients. While rhabdomyosarcoma is the dominant component in case series, the most-common sarcomatous component in our series is Ewing sarcoma (11). Primary tumour location was predominantly in the testes. Scheckel et al. (6) also reported the most-common primary site as the testicles in a case series of 24 patients. The effect of the detection of synchronous or relapsed MST on survival has been the subject of ongoing speculation. Rice et al. (11) reported one of the largest series on this subject and stated that MST detected at relapse had a shorter cancer-specific survival. In our cases, although the survival difference was numerically shown in the synchronous and relapsed patient groups, no significant results were identified.

It has been reported in previous series that clinical staging and IGCCCG classification, which are the leading schemes showing the prognosis used in GCT, are not effective for use in the case of MST (11,12). Instead, the histological grade of the sarcomatous transformation and MST detection in relapse have been associated with prognosis (3,13). However, Colecchia et al. (14) found the stage at initial diagnosis to be a strong prognostic factor associated with the disease in their series of 40 patients. The patients in our study were detected in the advanced clinical stage according to the American Joint Committee on Cancer. This may be the reason we could not detect a survival difference between the groups.

For MST, the presence of visceral metastases is considered a poor prognostic factor for a condition that is already considered chemoresistant. In a series of 33 cases reported by Guo et al. (7), the presence of metastases in MST was shown to be associated with a higher mortality rate.

Surgical resection is considered the main element of treatment, and access to centers that can provide advanced surgical care is important. There are also reports suggesting that, if the MST is limited to the primary testicular GCT, there may be no difference in survival between GCTs with MST and GCTs (15). It can be considered advantageous to provide direct local treatment by performing orchiectomy, especially in the detected testicular mass.

Administration of chemotherapy after resection is widely accepted, but in contrast to highly curable testicular GCTs, chemoresistance to standard cisplatin-based regimens is common in MST (16). Therefore, the main factor that guides systemic treatment in MST is the histologically dominant component. In our cases, adriamycin-containing regimens were generally used with patients with sarcomatous transformation, whereas fluorouracil-containing regimens were preferred in cases with adenocarcinoma since they were generally of gastrointestinal origin (16,17).

There are discrepancies in the data on survival of patients with MST. Some reports have stated that histological subtype has no effect on survival. Others have reported that the carcinoma subtype results in better survival than sarcomatous transformation (5,18). In our cases, we found that the adenocarcinoma group had a significantly longer survival than the sarcomatous group.

Study Limitations

This paper has several limitations. First, the number of cases is limited. Although the time interval in which the series reported in the literature were collected is much wider than our time interval, we present one of the largest case series from our country as a single center, to the best of our knowledge. MST is an extremely rare clinical entity. Even in clinics that follow a high percentage of GCT patients, few cases are seen. We believe that we will be able to present new evaluations in the future with the follow-up and increase of our cases in this regard. Second, because our study is a retrospective analysis, the assurance of the accuracy of the records is limited. Such studies may involve bias in record-keeping ability. Third, the present study has a cross-sectional design. Therefore, the results cannot be assumed to be causal. Additionally, our study includes GCTs of mixed tissue origin, such as the mediastinum, retroperitoneum, and testes, which are known to have different clinical outcomes. Finally, although a significant difference in OS was detected between the groups, the small sample size limits definitive results.

Conclusion

Our cases primarily highlight the difficulty in the follow-up and treatment of patients with MST and GCT, as well as the need for a multidisciplinary treatment approach as the basis for successful management. The study aimed to contribute to the literature in this field, which consists of anecdotal case series, in general, from the Turkish patient population.

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Ethics

Ethics Committee Approval: The University of Health Sciences Turkey, Gülhane Research and Training Hospital Clinical Research Ethics Committee approved the study protocol (decision number: 2021/57).

Informed Consent: Retrospective cross-sectional study.

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Authorship Contributions

Concept: M.B.A., N.K., Design: M.B.A., R.A., Supervision: B.Y., İ.E., N.K., Data Collection-Processing: G.S.Y., N.İ., Analysis-Interpretation: M.B.A., Literature Review: G.S.Y., N.İ., R.A., Writing: M.B.A., Critical Review: B.Y., İ.E., N.K.

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Case Report

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A Pregnant Female with a Rare Entity: Giant Adrenal Cyst

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Abstract

Diagnosis of an adrenal cyst is not a frequent conclusion. Being usually small in size and asymptomatic, may make them underdiagnosed. Although adrenal cysts are thought to be found in all ages, a total of only 18 pregnant patients having adrenal cysts were reported until now. In this article, a pregnant woman with a 184x132 mm adrenal cyst filling the right suprarenal area is presented and the relevant literature is reviewed.
Keywords: Adrenal cyst, pregnant, laparoscopy, giant

Introduction

It was considered that Greiselius described the first benign adrenal cyst, in 1670. The desription was based on autopsy findings of a 45-year old patient who had rupture of the cyst (1). Adrenal cysts, being uncommon, are predominantly small and asymptomatic, and can be found in any age (2). Pregnant females, reported to have adrenal cysts, were very rare, with only a total of 18 pregnant patients having adrenal cysts were presented until now (3). Here, we present a pregnant woman with a giant adrenal cyst.

Case Report

The obstetrician of the 31-year old patient having 27 weeks of gestation found a large mass in the upper right quadrant of the abdomen. The patient was referred to urology for further work-up. In physical examination, besides the findings related to pregnancy, a large mass in the upper right quadrant of the abdomen was palpated. Blood chemistry was totally normal and endocrinological values showed no abnormality. Ultrasonographic examination was commented as a hemorrhagic cyst, possibly of liver origin. An magnetic resonance imaging (MRI) study was conducted and revealed a 184x132 mm cyst in right adrenal area, displacing the right kidney, concluding to a diagnosis of giant adrenal cyst (Figure 1, 2). With no signs related to a malignant potential, with no endocrinological activity and with no symptoms, the patient was offered a delayed intervention to be performed in the period after delivery with close follow-up of the cyst.

The following 12 weeks, in which a scheme of routine physical examination and serum electrolyte measurements and ultrasonographic examinations in every 4th week was chosen as the follow-up method, were uneventful, and no significant volume change of the cyst was observed in three consecutive examinations. At the 39th week of gestation, the patient gave birth to a live female child with a mass of 2940 grams. Six weeks after the delivery, without a suspicion for hydatid disease, a laparoscopic operation was planned and performed. Due to the size of the cyst, a Hutchinson approach was thought to be appropriate. The cyst was found to be related to the adrenal gland but not related to neither the kidney nor the liver. A total excision of the cystic lesion with sucking of all the cystic fluid of 4250 mL, accompanied by a partial adrenalectomy was completed during the surgical procedure. The patient was hospitalized for three days. The results of the cytological and histopathological examinations were consistent with the diagnosis of an adrenal cyst. The results obtained from histochemical staining were as follows: calretinin (+), synaptophysin [focal (+)], rcc (-), CK7 (-), CD31 [(-) except vessel walls], concluding to a diagnosis of an adrenal pseudocyst.

The patient was held on follow-up, the last visit being on the 18th month of the operation with no problems.

Informed consent was obtained from the patient.

Discussion

Less than 500 cases of adrenal cyst were reported in the literature (3). Only 18 of them were diagnosed during pregnancy. The

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increase in the use of imaging modalities during medical visits, led to an increase in incidental diagnosis of adrenal cyts (4). Adrenal cysts, being asymptomatic usually, are predominantly diagnosed incidentally, nowadays and are evaluated in four categories: parasitic cysts, endothelial cysts, epithelial cysts, and pseudocysts (5). Symptomatic cases may have the symptoms because of the dimension or the localisation of the cysts. Only a very small group of patients was found to be endocrinologically active. Also, not so often, a malignant lesion was described (6).

In cases with a cystic lesion with a suspicion about being adrenal cyst, the first step was described to be excluding malignant potential. Later, an endocrinological activity was to be ruled out. Symptomatic patients may need intervention, as well as an asymptomatic patient with a cyst with a huge diameter. Adrenal cysts with a diameter of 10 cm or more were accepted as giant adrenal cysts, necessiating surgical intervention.

The patient, presented here, had no suspicion of a malignant lesion and had no endocrinological activity. She was asymptomatic, but with a giant adrenal cyst. The intervention was an unavoidable situation, with the pregnancy of the patient kept in mind. In order not to risk the fetus and the mother, a postponed surgery was offered to the patient, who accepted to be in close follow-up. Literature review showed that 3 of the 18 pregnant patients had delayed intervention, while the remaining 15 had the surgical procedure during pregnancy period. Worth to mention that half of the 18 patients had a preoperative diagnosis other than an adrenal cyst, having the diagnosis through histopathological examination (3,7). Similar findings led to a conclusion that pregnant females with cystic lesion should undergo an MRI study to reveal the pathology (8). It was stated that in male patients or in female patients without pregnancy, a computed tomography study may have high accuracy for the diagnosis (9).

Data about a volume change in an adrenal cyst during pregnancy period is lacking, and also a scheme for a follow-up during the mentioned period is not approved. We tried to manage the follow-up period with ultrasonograhic examinations in every 4th week until delivery accompanied by routine physical examinations and serum electrolyte measurements. In a patient with a decision of delayed surgical intervention, a follow-up scheme seems necessary, while immediate surgical intervention during the pregnancy period may be another choice necessiating no follow-up scheme. Trauffer and Malee (10) reported that surgical interventions related to adrenal cysts had no negative effect on the course of pregnancy. On the other hand, Tait et al. (11) reported a case with adrenal cyst surgery, ending with premature delivery of a 995 grams baby who was discharged from hospital after a three-month period with bronchopulmonary dysplasia. It must be kept in mind that emergency laparotomy procedures in the pregnancy period had a 40% premature delivery or abortus rate (12). We found no signs related to a malignant potential and no endocrinological activity in the presented patient. Also, she was neither hypertensive nor hypokalemic and was free from symptoms of a cardiac failure. So, she was offered a delayed intervention to be performed in the period after delivery but with close follow-up. We, as the group managing the presented patient, felt satisfied keeping her away from intervention during the pregnancy period and performing the definitive treatment as soon as puerperal period ended with no problems.

The histopathological examination of the excised lesion have utmost importance in excluding a malignant activity and in categorising the cystic lesion. The findings of the presented patient; with synaptophysin positivity leading us to a neuroendocrine origin, with calretinin positivity leading us to an adrenocortical origin while excluding pheochromocytoma and renal cell carcinoma, with rcc negativity excluding renal cell carcinoma, with CD31 negativity excluding an endothelial origin, with CK7 negativity excluding an epithelial origin, made us conclude the diagnosis as an adrenal pseudocyst.

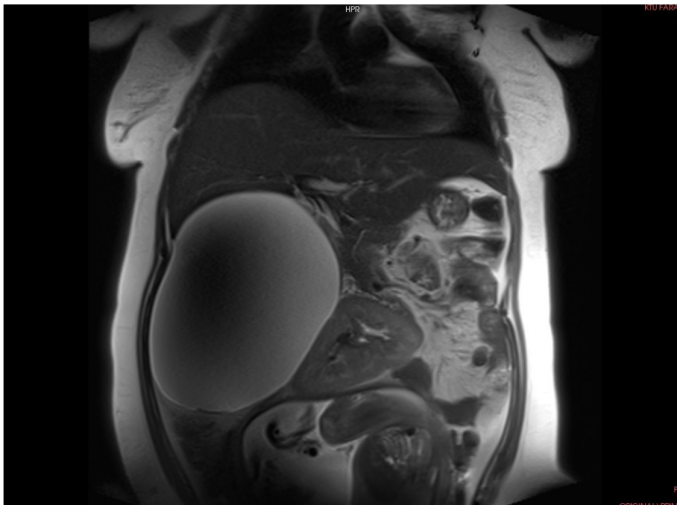

Figure 1. Coronal image of the adrenal cyst, displacing the right kidney (obtained from MRI studies)

MRI: Magnetic resonance imaging

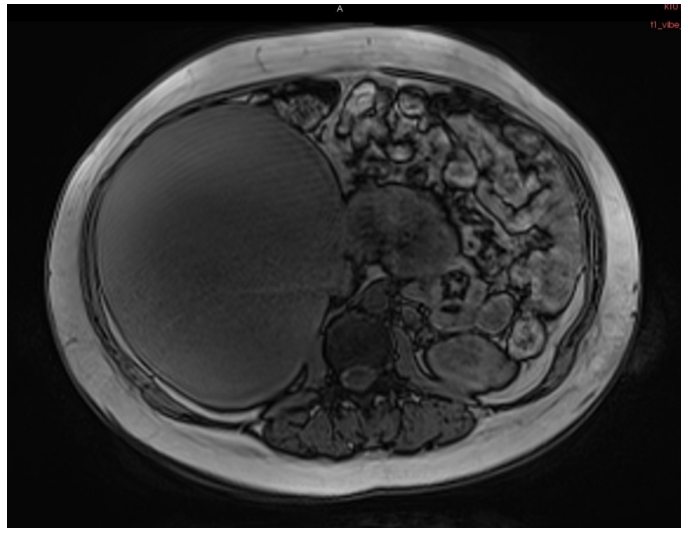

Figure 2. Axial image of the adrenal cyst, filling the right half of the abdomen (obtained from MRI studies)

MRI: Magnetic resonance imaging

Conclusion

Abdominal masses, discovered during pregnancy, needs complete evaluation in order to find the true origin. Ultrasonographic studies may present valuable data. However, MRI study of the abdomen is highly recommended in pregnant females. The definitive treatment for adrenal cysts, diagnosed during pregnancy, with no suspicion of malignancy and with no endocrinological activity, may be postponed, but with close follow-up, to decrease the risks for the fetus and the mother.

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