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The Bulletin of Urooncology is The Official Journal of Urooncology Association of Turkey. The Bulletin is an independent, peer-reviewed, international journal published quarterly in March, June, September, and December.

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

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

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

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

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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.

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

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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Manuscripts are submitted online at www.uroonkolojibulteni.com. If you are unable to successfully upload the files, please contact the editorial office by e-mail or through the online submission system. Rejected manuscripts are not sent back to the authors except for art work.

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.

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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.

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-Introduction

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

-Conclusions

-References

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

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

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

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

Submissions must include according to the following sequence:

A-Original Article

1) Copyright Transfer and Author Declaration Statement Form

2) Title Page

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

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

4) Table(s)

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B. Case Reports

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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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Contents

Review

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Contemporary Trends in Adrenal Sparing Surgery

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Abstract

Adrenal gland surgery has been practiced by the urologists ever increasingly in line with their interest in this particular field. Total adrenalectomy which is the classical approach for adrenal masses, is replaced by the organ-sparing surgery as soon as the significance of the organ sparing approach is understood as in the case of the renal masses. The partial adrenalectomy which has been in use through open surgery method since 1950's, was adapted to adrenal surgery by Gagner in 1991 and technical advancement was achieved since then with the introduction of the laparoscopic adrenalectomy by Janetschek six years later. Although it is increasingly being used, there still exist ambiguities concerning the technique and indications of the adrenal sparing surgery. In this review, the updated status of the adrenal sparing surgery is discussed with the current literature.
Keywords: Adrenalectomy, partial adrenalectomy, organ-sparing surgery, adrenal mass

Introduction

Adrenal glands are known to be associated with several diseases. In autopsy series, it has been reported that there are anomalies in the adrenal glands at a rate of 9% (1-3). With the widespread use of the computerized tomography (CT), adrenal lesions have been encountered at an approximate rate of 5% in CT scans (1). The rate of detection of the adrenal masses most of which are incidental, varies depending on the age, and the rate is 0.4% at the age of 20 which turns out to be about 7% at the age of 70 (4). It is almost never seen during childhood period. Thus, the adrenal tumors are defined incidentally through the radiological methods in progress and gradually becoming widespread. On the other hand, upon being aware of the symptoms, the tumors are diagnosed during the early stage when the patients consult with the doctor. Such tumors are detected when they are smaller in size when compared with the past (5). The reasons and frequencies of the adrenal masses are given in Table 1 (4,6). There is an increase in rate of diagnosing the adrenal masses by the time. Also, relatively smaller adrenal masses are detected with and a gradual decrease in the preliminary diagnosis of malignity. Hence, the adrenal sparing surgeries are supported in line with the evolutions experienced in the surgeries of the other organs (7). For the patients with high surgical risk, ablative methods have been defined but this is not included within the scope of this article.

Upon execution of the first adrenalectomy by Thornton in 1889, the progresses have been made in adrenalectomy while adrenal sparing surgery was first applied in 1950's for ACHT dependent Cushings' syndrome and bilateral pheochromocytoma thereafter (8). A patient who underwent adrenal sparing surgery in 1950's due to pheochromocytoma showed recurrence after 30 years of partial adrenalectomy in 1984 (9). The first laparoscopic partial adrenelectomy (PA) was made by Janetschek in 1997 with transperitoneal approach and by Walz one year later through retroperitoneal approach (10). Robotic PA was introduced in 2006 while Kumar applied robotic PA for adrenal metastases in 2009 soon after (1,2).

Indications and Contraindications of the Adrenal Sparing Surgery

The traditional method for adrenal masses is the total adrenalectomy (TA). The primary reason for this may include the easiness of this surgical procedure as it is also efficient and safe that the adrenal is the dual functional organ. Since the adrenal diseases show specific behavior, the results may not always be the same. The indications of the adrenal sparing surgery include unifocal, small and unilateral masses on one side, and multifocal, hereditary masses with high recurrence risks on the other side. Ishıdoya et al. (11) showed that more than one adenoma may be observed within the adrenal at a rate of 27% and that the final pathology may not display similar clinical and radiological corelation. The masses greater than 4cm are not deemed to be surgical responsive for adrenal sparing surgery due to the malignity risks and technical reasons. All these reasons display the difficulties and question marks as far

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as the adrenal sparing surgery is concerned and emphasize the significance of the selection of the patients with due diligence along with the preoperative assessment. The indications and techniques of the adrenal sparing surgery have not been fully standardized. Despite the advantages for the patients with solitary adrenal or bilateral involvement, optimal treatment of the small hormonal masses where the other adrenal is normal has not yet been clear while on the other hand the arguments for partial adrenalectomy are not sound. When deciding for adrenal sparing surgery, there should be some sort of balance among the complications similar to the kidney cancer, risk of recurrence and functional and long term results (7).

1- Bilateral adrenal mass

2- Mass on the solitary adrenal

3- Risk of metachromo multiple adrenal tumor.

4- Unilateral, sporadicmasses *

The followings are the current indications for the adrenal sparing surgery:

* (Since the response to stress subsequent to bilateral adrenalectomy is most often failed, PA may be applicable for the unilateral sporadic patients as well as the patients with small mass while the surgical indications gradually increase).

Out of the contraindications of the adrenal sparing surgery, the following can be listed in addition to the contraindications of the laparoscopy:

- Masses larger than 4 cm.

- Metastatic masses

- Doubt of invasive malignity

- Adrenal vein/vena cava inferiorinvolvement

Why Adrenal Sparing Surgery?

Adrenal sparing surgery has been placed in the first priority due to the bilateral involvement of the masses at varying rates, suboptimal response against the stress after the bilateral adrenalectomy, and the risk of Addison crisis -which may be mortal at a rate of 4 %- stemming from failures after the surgery where bilateral adrenalectomy is needed to be done. Many of the adrenal lesions which include especially the hereditary forms such as Von Hippel Lindau (VHL) and MEN-2 syndromestend to be observed in bilateral, multifocal and recurrent forms. On the other hand, the in some cases of pheochromocytoma with nonadrenal residence TA may be insufficient and even insignificant. The rate of bilateral nature of the adrenal masses varies and although it is higher in familial diseases, it is rated to be 7.8% for incidentalome, 35 to 80% for familial MEN syndrome and 40 to 60% for VHL. Table 2 shows the rates of bilateral frequencies of adrenal masses. It should be taken into consideration that the multifunctionality of the adrenal gland and relatively small and fragile nature give way tothe risk of distortion of the adrenal gland in the rest of life. The probability of the lifelong distortion depending on the infections on the adrenal gland, infiltrative diseases, adrenal metastases and such other reasons is only 1% and this rate does not include the adrenal wise distortions during nephrostoma (7). This supports the idea of the use of the adrenal sparing surgery in an appropriate manner. The reasons why the adrenal sparing surgery is of importance are the lifelong replacement requisite due to adrenal failure, hospitalization at a rate of 1/3, the risk of Addison crisis at a rate of 30%. Besides, the risks of serious diseases like osteoporosis, infections and diabetes and insufficient response against stress in the case of bilateral adrenalectomy may also have an impact despite the normality of the other adrenal where no postoperative replacement is required. Therefore, organ sparing approach which gains popularity as time pass by and can be sampled through other urologic tumors, should be prioritized for the adrenal gland.

Technique

One of the most advantageous urologic surgeries is the adrenal surgery where laparoscopy is superior to open surgery. Some studies reveal that minimal invasive approaches such as laparoscopy and robotic laparoscopy used in the adrenal sparing surgery are superior to the open surgery in view of the postoperative pains, complications and cosmetic results as in the case of TA (4,12,13). The recent robotic devices used in the adrenal sparing surgery provide some benefits. The advantages of the robotic surgery may include the minimal mobilization of the normal adrenal tissue during rotatable resection of the entophytic adrenal mass and better control of the adrenal bleeding (14).

Laparoscopic surgery techniques will be summarized here. The position of the patient in laparoscopic partial adrenalectomy and the port locations are almost the same with the laparoscopic adrenalectomy. Based on the experience of the surgeon, the process may be transperitoneal or retroperitoneal. The widely used approach is the transperitoneal approach (4). Prior to dissection of the adrenal gland, inspection is made and the location, dimension of the mass are defined along with the proximity to the adrenal vein. The intraoperative ultrasonography provides benefit for the assessment of the adrenal masses during PA and the intraoperative planning and it is particularly recommended to minimize the risk of residual masses for the diseases with multi nodularity such as pheochromocytoma (15,16). Another method which may assist to define the limits of the masses is the indocyanine green (ICG). There exist very few studies showing the use of the ICG in adrenal sparing surgery. While the pheochromocytoma and lypoadenoma was imaging fluorescent, cortex-induced lesions such as Cushing syndrome imaged hyper fluorescent and this may provide benefits in the complete resection of the mass (17,18). Upon defining the mass and its limits, the adrenal gland and especially the area with the mass are cleared using haemostatic devices such as harmonic scissor, bipolar shutter-cutter. It is recommended to provide protection for the main adrenal vein to the extent possible based on the location of the mass (12). In case the main adrenal vein cannot be protected, it should be resected, however, in such a case, only the location with the mass should be dissected in order not to give way any damage to the minor plexus within the retroperitoneal area to keep the adrenal functionality in order. On the other hand the appropriate section should be mobilized to the extent possible (13,19). Connecting the adrenal vein at the initial stage of the operation has been proven to be preventing the hypertension attacks which are observed more frequently in

PA for pheochromocytoma (20). Some authors suggest direct resection of the mass without dealing with the mobilization of the adrenal gland and the veins (19,20). Walz et al. (21) argued that the most important point to preserve the functionality of the adrenal gland during PA is the protection of the adrenal tissues to the extent possible. The protection of the sound adrenal tissues as much as it can be during PA is sought while the complete excision of the mass is of particular importance. Although there exist studies reporting that 2-3 mm distance as surgical limit is sufficient, in general terms the acceptable distance has always been 5 mm (19,20,22,23). An effective hemorrhage control is made subsequent to excision. During hemostatis the normal adrenal tissue is diligently spared. Hemostatic agents may be used to minimize the potential postoperative hemorrhage

There is no consensus concerning the quantity of the remaining adrenal tissue for the continuity of the physiological functions. There exist some studies suggesting the sparing of 1/3 of the remaining adrenal tissue while some other studies report that 20% of the well perfuzed adrenal is sufficient for preservation (19,24-26).

Results

The most important factors which may have an impact on the options to be made between the TA and the adrenal sparing surgery for the patients with adrenal mass are the ratio of the complications, oncologic results and functional outcomes (trifecta). These are summarized as follows:

Complications

One of the most important points which should be taken into consideration in the case of the patients who are to undergo adrenal sparing surgery is the complications. The complications may be in relation with the overall medical condition of the patient and applicable anesthesia and surgical techniques. The most frequent and significant complication encountered during perioperative and postoperative periods is bleeding (27). It is followed by open wound infection and pneumonia and laxity of the abdominal Wall (28). The study by Walz et al. (21) compared a total of 325 patients who underwent total and partial adrenalectomy. It was observed that average operation time was 80 min with amount of bleeding 29 mL for PA and that no expressive difference was noted when compared with TA Fu et al. (29), in their study with 212 similar cases, reported that there observed no significant difference between the groups in view of the operation time and rates of complication. Wang et al. (27), in their retroperitoneoscopic PA study for adrenal masses of 1 cm and smaller masses, no long term complication was observed and no recurrence was determined over a follow up period of 41 months. The larger the dimension of the mass, the more difficult the PA technique would be. It has been proven that this would have negative effect on the duration of the operation and the amount of hemorrhage. In a recent study comparing the total and partial adrenalectomy made applicable through transperitoneal and retroperitoneoscopic approach for the adrenal masses smaller or larger than five centimeters, it has been observed statistically that the operation period is longer (102.68±30.92 min/9.64±28.39 min, p=0.02) and hemorrhage is higher (451.9±186.3 mL / 286.0±217.5 mL, p=0.02) during retroperitoneoscopic PA for the tumors larger than five centimeters (30). The ratio of transition from PA to TA was determined to be 2.5% in the contents of the study conducted by Kaye et al. (28) with 417 cases. The ratios of perioperative blood transfusion and perioperative complication have been found to be 7.3%, and it was reported that perioperative results are as good as TA.

In case the literature regarding the PA complications are evaluated, it can be argued that although the amount of hemorrhage and duration of the operations are a bit more than the envisaged amount the complications are similar to that of the TA and can be an applicable technique at the experienced medical organizations while it may not always be applicable and possible for every patient.

Oncologic Results

The concerns for oncologic results are the most important factor which may have an effect on the selection of PA by the patients. As specified above, in the case and doubt of the malignity, adrenal sparing surgeryis contraindicated and applied only in benign pathologies despite recurrences observed.

The studies showed the differences in the recurrence rates based on the diseases (9,12,31-33). In particular, it is reported that the rate of recurrence of familial pheochromocytoma tend to be bilateral varies at a wide range like 0% - 100% (9,27,31-33). Referring to the study released by Castinetti et al. (34) in 2016, the rate of recurrence of the hereditary pheochromocytoma is between 0% - 21%. It was stated by Castinetti et al. (34) in their comparative study that the rates of recurrence in the long term follow up is 2.6% for PA and 1.5% for TA while the time for recurrence is stated to 9.5 years (35). The study by Amar et al. (36) regarding the factors affecting the recurrences in pheochromocytoma shows that recurrence is impacted by the dimensions of the tumor, affected location (right side is more likely than the left side) and diagnosis age (recurrence is much more observed amongst the youth). Walz et al. (37), in their study dated back to 2018 in which an assessment was made for the minimal invasive TA and PA for 70 adrenal masses observed on the patients involving 42 children and adolescents with pheochromocytoma and/or paraganlioma, (26 with pheochromocytoma, 11 PGL and 5 pheochromocytoma + PGL) reported that 31 of the patients with pheochromocytoma underwent PA while excision was made for the patients with PGL. During the follow up period of 8.5 years as an average, recurrence was observed in two patients with VHL syndrome in the case of PA and out of five PGL patients with recurrence, four patients had to undergo another operation. As for the Adenoma Secreting Aldosterone (ASA), the rate of recurrence varies between 0% and 2% (7). Out of 212 patients, Fu et al. (29) applied TA on 108 patients and PA on 104 patients and they reported that no recurrence was observed within 96-months follow up period. Kaye et al. (28) reported the overall recurrence rate as 3% in the metaanalysis of the 22 studies they have conducted for the different adrenal diseases. As is seen, the recurrence observed in the benign masses especially the new series are at acceptably low levels except for

the familial pheochromocytoma. In case the patients who may suffer multi-focal cases are assessed carefully and if the adrenal mass is excised through the responsive surgical technique using the intraoperative ancillary technologies (intraoperative ultrasonography, ICG etc.), the oncologic results for PA may be satisfactory.

Functional Results

The functional results of the adrenal sparing surgery can be assessed in two aspects. The first is the recovery of the diseases such as hypertension caused by the hormonal functions of the adrenal mass and the second is the prevention of the steroid dependence of the adrenal function. Ishidoya et al. (11), in their study in the contents of which they compared the results of the TA and PA on 174 patients suffering aldosteronamia, reported that only 2 (6.9%) patients suffered hypertension in view of PA. It has been observed in the study conducted by Fu et al. (29) that the hypertensions of all of the patients suffering ASA in the two groups on whom TA and PA was applied tend to have been recovered while the plasma rennin activities and serum aldosterone levels normalized within the period of 6-months follow up. In both of the groups no Addison crisis was observed and no steroid replacement was deemed to be necessary. Gupta et al. (24) reported that out of 121 cases with PA applied on the pheochromocytoma patients (10 of such surgeries 8 patients with concurrent multiple pheochromocytoma on the similar location), there observed recoveries on the symptoms of all of the patients after 12 months while steroid replacement was a requisite for only one patient with solitary adrenal. In the contents of the study conducted by Chen et al. (30) no hormone replacement was necessary as far as the PA was concerned, while out of 27 patients, replacement was a requisite for 13 patients who underwent TA r (0%/48.15%, p=0.002). In another study, 16 PA and 47 TA for 63 adrenal masses were compared and recuperation was observed in the plasma rennin activity on both side by the end of the year. However, 43.8% of the patients had to undergo anti hypertension treatment for PA. No steroid replacement was deemed to be a requisite on both sides (25). For the durability of the functionality of the adrenal gland, there exist divergent opinions concerning the significance of the preservation of the adrenal vein during PA. The fact that some of the researchers are in the thought that the main adrenal vein should be spared for the continuity of its functions, in the study of Walz et al. (21), it has been argued that the adrenal vein should not be preserved while sufficient adrenal tissue should be spared as possible as it can be, as stated in this study under the title of "Technique". It is observed that the PA and TA results are similar in view of the recovery of the symptoms of the hormonal function of the mass. If examined in view of the preservation of the adrenal functions, PA seems to be advantageous, it should be kept in mind that postoperative replacement may be necessary for the patients with solitary adrenal.

Follow Up

Although recurrence risk after PA does not seem to be statistically higher than TA, more studies should be conducted to find out the time relapsed for recurrence for the patients with pheochromocytoma in particular and the probability for such recurrence. Therefore, periodical biochemical assessments should be made after the surgery as well as the clinical follow-up (6,22). Within 24 hours after the surgical operation, metabolites such as catecholamine and metanephrine fractioned with urine are reviewed and such reviews are repeated for the patients followed up clinically 6 months. Although there exists no consensus concerning the follow-up period, long term follow up protocols are suggested since it can be recurred even after 10 years (28).

Conclusion

Adrenal sparing surgery presents outcome which are similar with TA both in view of the complications and the oncologic results. When reviewed in line with the functional results, it is observed through several studies that despite ongoing antihypertension treatments subsequent to PA, hypertension after PA decreases significantly and steroidplasma is seldom required. Therefore, it can be concluded that the functional results for PA are better than the TA. The adrenal sparing surgery has always been a better surgical alternative for not only the patients with bilateral adrenal mass or solitary adrenal mass along with the patients suffering Familial syndrome with the risk of recurrence and patients with unilateral adrenal mass. Upon completion of the successful preoperative preparations, open surgery or laparoscopic or robotic methods which provide some advantages in comparison with the open surgery, may be applicable.

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Appendix 1. None

Questions

1) Which of the following is not an indication of adrenal sparing surgery?

a. Bilateral adrenal tumor
b. Tumor on the solitary adrenal
c. Metachoronous multiple adrenal tumor risk
d. Uni lateral sporadic tumors
e. Adrenal tumors larger than 4 cm

Correct answer: e

2) Which of the following is false?

a. Open surgery is superior to the minimal invasive methods in adrenal sparing surgery
b. The widely used technique varies based on the experience of the surgeon but it is the laparoscopic transperitoneal approach.
c. It is still being discussed whether or not the adrenal vein is spared during adrenal surgery
d. Minimal mobilization of the adrenal tissueis recommended for the maintenance of the adrenal functions during adrenal sparing surgery.

Correct answer: a

3) Which of the following is true?

a. 1 mm surgical limit is sufficient in adrenal sparing surgery
b. Adrenal sparing surgery is indicated even in the case of any doubt of malignity
c. Recurrence is quite likely after adrenal sparing surgery in the case of ASA.
d. Dependence on the steroid after adrenal sparing surgery is rated to be higher than the total adrenalectomy.
e. For the tumors with multi nodularity such as pheochromocytoma, the devices such as intraoperative ultrasonography helps a lot during adrenal sparing surgery

Correct answer: e

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Original Article

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Is Laparoscopic Adrenalectomy Safe in Large Adrenal Masses?

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Abstract

Objective: We aimed to investigate the reliability and effectiveness of laparoscopic adrenalectomy (LA) in large adrenal masses by comparing LA results for large- and small-volume (<5 cm) masses.

Materials and Methods: Patients who underwent LA due to adrenal mass between February 2004 and December 2018 in our clinic were retrospectively analyzed. The patients were divided into two groups as mass size <5 cm (group I) and ≥5 cm (group II). Patients who underwent open adrenalectomy and whose data were not available were excluded from the study. Perioperative data, postoperative results, complications, and histopathological results were examined.

Results: There were 62 patients who underwent LA. Thirty-three patients (53.2%) had a left adrenal mass, and 29 patients (46.8%) had a right adrenal mass. Of the 62 adrenal masses, 46 (74.2%) had a diameter of <5 cm (group I), and 16 (25.8%) were ≥5 cm (group II). The mean tumor size was 3.2±0.15 and 6.4±3.5 cm in group I and group II, respectively. There was no statistically significant difference between the groups in terms of age, operative time, and blood loss. The average length of hospital stay was 37.6±20.9 hours in group I, while it was 49.8±22.9 hours in group II and was significantly longer in group II ($p<0.05$). Intraoperative blood pressure elevation occurred in one patient in group I and II. In a patient with suspected malignancy in group II, the surgery was shifted to open surgery as the capsule over the mass was opened. Hypopotasemia was observed in one patient, and atelectasis was observed in one patient in group I, and pneumonia was observed in one patient in group II.

Conclusion: LA is a minimally invasive surgical method that can be applied safely in experienced centers in masses larger than 5 cm with no suspected invasion in preoperative imaging.

Keywords: Adrenal mass, laparoscopy, laparoscopic adrenalectomy, large adrenal masses

Introduction

In 1992, laparoscopic adrenalectomy (LA) was first used by Gagner et al. (1) in a patient with Cushing's syndrome. Developing to date, it has been the preferred method of surgical treatment of various adrenal masses, including dysfunctional adenoma, pheochromocytoma, Cushing's disease, aldosteronoma, myelolipoma, and cysts (2,3).

Laparoscopic treatment of large adrenal masses is alarming due to the risk of malignancy and technical difficulties (4,5). The size criterion is one of the main issues discussed for the laparoscopic approach in adrenal lesions. For LA, an exact upper limit has not been defined in terms of mass size. Data obtained in the last 15 years show that the laparoscopic approach is feasible and successful for lesions smaller than 5 cm (6). It has been reported that the size of the adrenal mass in preoperative imaging should not be the primary factor in determining laparoscopic indication (7). In this study, we aimed to investigate the reliability and effectiveness of LA in large adrenal masses by comparing the perioperative and postoperative results of patients with a mass of <5 cm and those with a mass of ≥5 cm, who underwent LA.

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Materials and Methods

Sixty-two patients who underwent LA due to adrenal mass in our clinic between February 2004 and December 2018 were retrospectively reviewed. Detailed anamnesis was obtained from all patients, and a physical examination was performed. Patients were evaluated with computed tomography (CT) and/or magnetic resonance imaging (MRI) and F-18 FDG positron-emission tomography/CT imaging, if necessary. All patients were consulted with the Endocrinology Clinic to evaluate the function of the adrenal mass. In addition to the complete blood count and routine biochemical tests, serum electrolytes, adrenocorticotropic hormone, cortisol, aldosterone, renin, dehydroepiandrosterone sulfate, arterial blood gas, and 5-hydroxy indole acetic acid, metanephrine, normetanephrine, homovanilic acid, vanyl mandelic acid, adrenaline and noradrenaline in 24-hour urine were performed according to the clinical features of the patients to determine whether the adrenal mass was functional or not. Plasma metanephrine levels were evaluated in patients with high catecholamine degradation products in 24 hours of urine. All patients underwent a 1 mg dexamethasone suppression test. 24-hour urine cortisol levels were also examined in patients with suspected Cushing's disease. Patients with surgical indications (hormone active, suspicious of malignancy, or mass larger than four centimeters) underwent LA by an experienced team.

The patients were divided into two groups as mass size <5 (group I) and ≥5cm (group II). Patients who had open adrenalectomy and whose data could not be accessed were excluded from the study. All intraoperative and postoperative parameters were retrieved from adrenalectomy data and hospital information systems, where data has been recorded regularly since 2004 and evaluated retrospectively. Demographic features, tumor sizes, duration of surgery, intraoperative and postoperative complications, length of hospital stay, and histopathological features were examined.

Ethics committee approval was received for this study from the Ethics Committee of Çukurova University (approval number: June 2019, 89/49).

Laparoscopic Adrenalectomy Technique

All patients underwent LA by transperitoneal route after obtaining informed consent. On the day before the operation, intestinal preparation was made with a clear liquid diet and laxatives. For pre-diagnosed functional pheochromocytoma, beta-blocker (propranolol 1x40 mg or metoprolol succinate 2x50 mg) and alpha-blocker (doxazosin 2x4 mg) treatment were started two weeks before the surgery. In these cases, phentolamine (alpha 1 + alpha 2 adrenergic blocker) was available for a possible hypertensive crisis during the surgery. In all cases, prophylactic first-generation cephalosporin was administered one hour before surgery, and general anesthesia with endotracheal intubation was performed. Modified (60°) lateral decubitus position was used in patients with right adrenal mass, and lateral decubitus position was used in patients with a left adrenal mass. The upper arm was fixed to the patient's posterolateral to protect the brachial plexus. The patients were covered so that we could switch to open surgery if necessary. On the pararectal line, a 1.2 cm long transverse incision was made to the 2-5 cm cranial of the umbilicus, and the abdomen was entered with a Veress needle. Carbon dioxide pneumoperitoneum was created so that intraperitoneal pressure was 16-18 mm Hg (12-14 mm Hg in those with suspected pheochromocytoma). An 11 mm port was inserted bluntly by canceling the blade in the umbilicus through the incision to accommodate the camera. Thirty degree lenses were used in surgeries.

For left adrenalectomy, two subcostal 5 mm ports are placed; one in the midclavicular line and the other in the pararectal line. After the trocars were placed, the working pressure was set to 12 mmHg (10 mmHg for those with suspected pheochromocytoma).

On the left, the Toldt line was first incised. The phrenocolic and splenocolic ligaments were cut, and the colon was reflected medially. Posterior peritoneal dissection was carried out between the lateral spleen and upper stomach. The dissection was completed by incising the splenorenal ligament, and the spleen was allowed to fall away cranially with its own weight. At this stage, the upper part of the adrenal gland was freed entirely from the spleen and superomedially from the pancreas, the entire upper dissection was completed from the posterior diaphragm to the quadratus lumborum muscle, and the upper part of the adrenal gland was released. The upper pole of the kidney and renal hilum were visualized. The left adrenal vein pouring into the renal vein was found and clipped. The inferior part of the adrenal gland was freed entirely by opening the Gerot's fascia and dissecting between the adrenal gland and the upper pole of the kidney, and then adrenalectomy was completed by medial, posterior, and lateral dissection.

In the right adrenalectomy, after the triangular ligament was cut, a 5 mm trocar was placed 1-2 cm below the xiphoid for liver retraction in addition to the ports on the left. A laparoscopic locking grasper was placed in a way to retract the inferior edge of the liver anterosuperiorly and was locked to the lateral wall of the abdomen. In the posterior peritoneum, an incision was made starting from the cecum at the bottom and lateral of the ascending colon and extending to the posteroinferior edge of the liver along the lateral edge of the duodenum. The duodenum was reflected medially, and vena cava and right renal vein were visualized. After the inferomedial corner of the adrenal gland was mobilized by dissection at the junction of the renal vein and vena cava, the surgery was extended to the liver by dissection between the lateral edge of the vena cava and the medial edge of the adrenal gland. After finding the right adrenal vein in the posterolateral side of vena cava, it was clipped and cut. Lateral dissection was performed between the inferior edge of the liver and the superior edge of the adrenal gland, and then the posterior part of the adrenal gland was freed. Finally, adrenalectomy was completed by dissection from medial to the lateral between the superior pole of the kidney and the inferior edge of the adrenal gland. In cases diagnosed with pheochromocytoma, the adrenal vein was clipped as early as possible on both sides.

The adrenal gland was placed in the specimen bag and was removed by enlarging the 11 mm trocar incision or by making

an incision at the lateral end of the Pfannenstiel incision in female patients who had a previous cesarean section. In cases where the surgeon did not need, a drain was not placed, and one drain was placed in the others.

In the postoperative period, patients were mobilized as early as possible, analgesics were applied when necessary, and oral feeding was initiated according to intestinal functions. Patients without problems were discharged on the first postoperative first day after their drains were removed. They were followed by the departments of urology and endocrinology, according to the histopathological examination results and clinical status.

Statistical Analysis

SPSS 23 was used for statistical analysis of the data. Categorical data were summarized as numbers, while numerical data were summarized as mean and standard deviation. A chi-square test was used to compare categorical data between groups. The Kolmogorov-Smirnov test determined whether the numerical data met the normal distribution assumption. Independent samples t-test was used for comparison of numerical data between groups if assumptions were met, and the Mann-Whitney-U test was used if assumptions were not met. The statistical significance level was set as <0.05 in all tests.

Results

Of the 62 patients undergoing LA, 43 (69.3%) were female, and 19 (30.7%) were male. Thirty-three patients (53.2%) had a left adrenal mass, and 29 patients (46.8%) had a right adrenal mass. Of the 62 adrenal masses, 46 (74.2%) were <5 cm in diameter (group I), and 16 (25.8%) were ≥5 cm (group II). The demographic data of patients in the groups are summarized in Table 1. The mean tumor size was 3.2±0.15 cm (range: 1-4.9 cm) and 6.4±3.5 cm (range: 5-10 cm) in group I and group II, respectively (Table 1). Surgical indications in group I were mass size in 11 patients (23.9%), functional mass in 21 patients (45.6%), and suspicion of malignancy in 14 patients (30.4%). Surgical indications in group II were mass size in 10 patients (62.5%), functional mass in three patients (18.7%), and suspicion of malignancy in three patients (18.7%).

Table 1. The demographic data of patients in the groups

	<5 cm	≥5 cm	p
Number of the patients	46 (74.2%)	16 (25.8%)	-
Gender n (%)			
Male	34 (73.9%)	9 (56.2%)	0.22
Female	12 (26.0%)	7 (43.7)	
Side			
Right	19 (41.3%)	10 (62.5%)	0.16
Left	27 (58.6%)	6 (37.5%)	
Age (year)	46.1±12.7	47±12.5	0.83
BMI* (kg/m²)	27.5±3.8	30.4±7.3	0.62
Size of the tumor (cm)	3.2±0.15	6.4±3.5	**0.01**

*BMI: Body mass index

The mean operative time was 101.2±21.8 and 107.4±25.4 minutes in group I and group II, respectively, and there was no statistically significant difference between the groups in terms of mean operative time (p=0.31) (Table 2). The mean amount of bleeding was 49.5±12.7 and 94.3±40.2 in group I and group II, respectively (Table 2). The bleeding amount of group II was higher than group I, but there was no statistically significant difference (p=0.14). Only one of the patients in group II received one unit of blood transfusion in the perioperative period. The mean length of hospital-stay in group I was 37.6±20.9 hours, while it was 49.8±22.9 hours in group II and was statistically significantly longer in group II (p<0.05) (Table 2).

One of the patients in group I also underwent simultaneous partial nephrectomy due to the ipsilateral renal mass. In group II, one of the patients underwent simultaneous renal cyst excision, and one of the patients underwent simultaneous psoas abscess drainage.

Complications are shown in Table 3. According to the modified Clavien-Dindo Classification, there were two grade 2 complications in group I and one grade 2 complications in group II. Intraoperative blood pressure elevation occurred in one patient in each group. Blood pressure returned to typical values after the adrenal vein was clipped. In a patient with suspected malignancy in group II, the surgery was shifted to open surgery as the capsule of the mass was opened. One patient in group I developed hypopotasemia, and one patient had atelectasis, and one patient in group II developed pneumonia.

Histopathological results in both groups are shown in Table 4. According to histopathology reports, there were 42 benign (91.3%), three malignant (6.5%) lesions and one borderline (2.1%) lesion in group I, and 14 benign (87.5%) and two malignant (12.5%) lesions in group II. When the two groups were compared in terms of malignancy, there was no statistically significant difference (p=0.46).

A patient with adrenal cortical carcinoma had a reported capsule invasion as a result of histopathology, and the patient

Table 2. Difference between the groups in terms of mean operative time

	<5 cm	≥5 cm	p
Duration of the operation (min)	101.2±21.8	107.4±25.4	0.3
Amount of bleeding (mL)	49.5	94.3	0.14
Blood tranfusion, n (%)	0	1 (6.25%)	0.08
Discharge time (min)	37.6±20.9	49.8±22.9	**0.05**

Table 3. Complications

	<5 cm	≥5 cm
Perioperative complications, n (%)	1 (2.1%)	2 (12.5%)
Perioperative hypertension	1 (2.1%)	1 (6.2%)
Opening the capsule	0	1 (6.2%)
Postoperative complications, n (%)	2 (4.3%)	1 (6.2%)
Hypopotassemia	1 (2.1%)	0
Atelectasis	1 (2.1%)	0
Pneumonia	0	1 (6.2%)

Table 4. Histopathological results in both groups		
Histopathology	**<5 cm**	**≥5 cm**
Adrenale cortical neoplasia, n (%)	18 (39.1%)	3 (18.7%)
Adrenale hyperplasia, n (%)	11 (23.9%)	0
Phaeochromocytoma, n (%)	6 (13.0%)	2 (12.5%)
Myelolipoma, n (%)	4 (8,6%)	5 (31.2%)
Adrenale cortical carcinoma, n (%)	1 (2.1%)	1 (6.2%)
Metastasic renal cell carcinoma, n (%)	1 (2.1%)	0
Oncocytic adrenale cortical neoplasia, n (%)	1 (2.1%)	0
Vascular cyst, n (%)	1 (2.1%)	0
Ganglioneuroblastoma, n (%)	1 (2.1%)	0
Epithelial cyst, n (%)	1 (2.1%)	0
Simple kist, n (%)	1 (2.1%)	0
Hemangioma, n (%)	0	2 (12.5%)
Metastasic urethral carcinoma, n (%)	0	1 (6.2%)
Hemorrhagic cyst, n (%)	0	1 (6.2%)
Endothelial cyst, n (%)	0	1 (6.2%)

was followed up closely, and no recurrence was observed during follow-up. Adjuvant radiotherapy and chemotherapy were initiated in the histopathology report of the patient, who was shifted to open surgery due to opening the capsule, upon microscopic invasion at the surgical margins. The patient's chemotherapy is still ongoing. Other patients had no postoperative margin positivity as a result of histopathology. Our mean follow-up was 2.3±1.8 years. Twenty-one patients did not attend regular follow-up. No problems were encountered in the patients during follow-up.

Discussion

LA has rapidly gained popularity since its description by Gagner et al. (1). LA offers less perioperative morbidity and mortality, shorter hospital-stay, better cosmetics, and better clinical results compared to the open technique (8). However, LA remains a challenging operation for large adrenal masses. Although data obtained in the past 15 years have shown that the laparoscopic approach is feasible and successful for lesions <5 centimeters, size criteria are a current discussion topic for laparoscopic approaches in adrenal lesions (6,9,10). Due to technical difficulties, local recurrence due to possible capsular rupture and risks of incomplete resection, most surgeons are rightly concerned about applying LA for large adrenal masses (11).

In a study where they examined the LA results in adrenal masses larger than 5 cm, Hemal et al. (7) reported that the size of the adrenal mass in preoperative imaging alone should not be the primary factor in determining laparoscopy indication; and that LA for adrenocortical cancers could be performed safely and effectively in a selected group. Tsuru et al. (12) compared LA results in ≥5 cm and <5 cm tumors and stated that the operative time, blood loss, and oral feeding onset times were similar, but that the postoperative recovery period was significantly longer in large tumors. Parnaby et al. (13) compared LA results applied to adrenal masses larger and smaller than 6 cm in 101 patients and concluded that LA results were comparable if there was no local invasion detected by preoperative imaging methods. They stated that local invasion of adrenal masses could be accurately evaluated with CT and MRI and that open adrenalectomy was appropriate in case of local invasion (13). In a study by Novitsky et al. (14) with 24 patients who underwent LA for adrenal masses larger than 5 cm, the mean mass diameter was 6.8 cm, and the mean operative time was 178 (range: 120-300) minutes and no shift to open surgery was reported. The authors found that the advantages that were advocated as a classic for LA were preserved despite the increase in mass size. The authors concluded that LA is indicated for large tumors of 5-10 cm in the absence of adhesions or infiltration (12).

In the study of Bozkurt et al. (11) in adrenal masses larger than 8 cm undergoing LA, one surgery was shifted to open surgery, two patients had spleen capsule laceration, and one patient had a liver capsule laceration. They reported Clavien grade 1 postoperative complications in two patients and Clavien grade 2 complications in two patients. In their study in masses larger than 6 cm, Agrusa et al. (10) reported that there was bleeding due to spleen injury in one patient and perirenal hematoma in one patient. In our study, one LA surgery in group II was shifted to open surgery due to the opening of the capsule, intraoperative blood pressure increased in one patient, and Clavien grade 2 complication occurred in one patient. Our results were found to be compatible with the literature.

There are many multicenter studies comparing transperitoneal and retroperitoneal LA surgical results, and both techniques have been reported to have their own advantages and disadvantages (15,16,17,18). The transperitoneal approach has advantages such as providing a wide surgical area and direct access to the adrenal vessels. In this approach, the risk of injury in the intraperitoneal organs is higher. In the retroperitoneal approach, it is advantageous that there is no relation with the intraabdominal organs, and the narrowness of the area and the lack of distinctive anatomical areas during surgery are the disadvantages of this method (19). The retroperitoneal approach is recommended for small adrenal adenomas (20). In the study of Hemal et al. (7), despite the retroperitoneal approach in seven patients, it was stated that the transperitoneal approach was suitable for large adrenal tumors and adrenal carcinomas. In our study, all surgeries were performed with a transperitoneal approach. In this approach, we think that the larger viewing area of the adrenal gland and its surroundings and direct access angles of hand tools compared to the retroperitoneoscopic approach increase the ease of work and safety.

According to the National Institute of Health consensus, the incidence of adrenal cortical carcinoma is 2% in tumors <4 cm, 6% in tumors 41-60 mm, and 25% for tumors larger than 6 cm (21). In our study, histopathology of adrenal masses larger than 5 cm revealed pheochromocytoma in two patients (12.5%) and malignancy in two patients (12.5%). Malignancy rates in our study seem to be consistent with the literature. It has been reported in different series that 74-95% of pheochromocytomas are benign (22). In this case, adopting only the size of the mass as a criterion in the selection of the most appropriate surgical approach may lead to unnecessarily open adrenalectomy in many patients with a benign adrenal mass. The results of our study showed that laparoscopic approach indications in large adrenal masses could vary depending on the surgeon's

experience and skill and that the mass size alone was not an absolute criterion for laparoscopy.

The limitations of the study were that the study was retrospective and single-centered.

Conclusions

LA is a minimally invasive surgical method that can be applied safely in experienced centers for masses larger than 5 cm and where there is no doubt of invasion in preoperative imaging.

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Ethics

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Authorship Contributions

Concept: M.D., Design: M.D., Y.B., V.İ., Data Collection or Processing: M.D., M.A., N.A., Analysis or Interpretation: M.D., Y.B., V.İ., M.Z.T., Literature Search: M.D., M.A., N.A., Writing: M.D.

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Evaluation of the Risk of Falls in the Patients Hospitalized in A Urology Inpatient Clinic

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Abstract

Objective: Falls are a significant cause of morbidity and mortality, particularly in hospitalized patients. In this study, we aimed to evaluate the risk of falls in the patients hospitalized in a urology clinic.

Materials and Methods: The study included patients that were hospitalized in a urology clinic between November and December 2018. All the patients were administered both Itaki Fall Risk scale (IFS) and Morse Fall scale (MFS). Demographic and clinical characteristics, history of falls within the past six months, type of surgery, primary diagnosis (urooncological vs non-urooncological), and the department/unit from which the patients were referred [outpatient clinic vs emergency service/intensive care unit (ICU)] were recorded.

Results: The risk of falls was significantly higher in the patients with urooncological diseases compared to the patients with non-urooncological diseases ($p<0.001$) and in the patients referred from emergency service/ICU compared to the patients referred from outpatient clinics ($p<0.001$). Moreover, the patients with a history of falls within the past six months were found to be at higher risk of falls compared to the patients with no history of falls both on IFS and MFS ($p=0.002$, $p=0.01$, respectively).

Conclusion: Hospitalized patients should be closely followed due to the risk of falls, particularly the cancer patients and the patients referred from the emergency service or ICU.

Keywords: Fall, urology, risk

Introduction

A fall is defined by the World Health Organization as an event that results in a person coming to rest inadvertently on the ground or floor or other lower level, mostly due to the carelessness of the person or an accident (1). Falls are a significant cause of morbidity and mortality, particularly in old-age patients (aged 65 years or older). About one-third of these individuals experience falls each year, with 10-20% of the falls resulting in severe injury (2). However, young individuals also have a risk of falls, and it has been shown that about 16% of young adults experience fall injuries due to various reasons (3).

In hospitalized patients, on the other hand, falls can result in injuries and loss of functions, thereby leading to prolonged hospital stays, increased treatment costs, and reduced quality of life. Moreover, these falls may also result in the development of anxiety and fear both in the patients and the healthcare staff (4). In previous studies, the rates of falls in hospitalized patients have been reported to range between 2.9-13 falls per 1,000 bed days (5).

Common urological factors associated with increased risk of falls include overactive bladder, nocturia associated with benign prostatic hyperplasia, lower urinary symptoms (such as pollakiuria), urological malignancies, and alpha-blocker therapy (3,6,7,8,9,10). Additionally, the risk of falls is increased in patients undergoing urological surgeries and, in the patients, hospitalized in the urology clinic, as in other types of surgeries and other clinics. On the other hand, in patients undergoing surgery, some other factors can also increase the risk of postoperative falls, such as patient-related causes, duration of surgery, anesthetic management, changes in fluid-electrolyte balance, and blood flow, and pain (11).

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The aim of this prospective study was to evaluate the risk of falls and to determine the groups with a high risk of falls in patients hospitalized in a urology inpatient clinic.

Materials and Methods

Patient Selection and Study Design

The study included patients that were hospitalized in Kayseri City Hospital Urology Department Inpatient Clinic between November and December 2018. Patients with a malignancy other than urological malignancies and patients aged less than 18 years were excluded from the study. The patients were administered both Itaki Fall Risk scale (IFS) and Morse Fall scale (MFS). Moreover, each patient was queried as to whether they had experienced any falls within the past six months. Age, body mass index, types of surgery, and the reason for hospitalization (surgical treatment vs medical follow-up) were recorded for each patient. The surgical types were divided into six categories: (I) scrotal surgeries (varicocelectomy, hydrocelectomy, orchiectomy), (II) transurethral resection of bladder tumor (TURBT), (III) transurethral resection of the prostate, (IV) radical surgeries (radical cystectomy, radical/partial nephrectomy, radical prostatectomy), (V) urinary stone surgeries (ureterorenoscopy, percutaneous nephrolithotomy, cystolithotripsy), and (VI) other urological surgeries (urogynecological surgeries, reconstructive surgeries, trauma surgeries). The patients were divided into two groups as (a) patients hospitalized electively (i.e., referred from polyclinics) and (b) patients hospitalized under emergency conditions [i.e., referred from emergency service or an intensive care unit (ICU))]. Additionally, the patients were divided into two groups based on their diagnoses: (i) urooncological (UO) and (ii) non-urooncological (NUO). The total length of hospital stay was recorded for each patient. The risks of falling were determined and compared among the groups based on the IFS and MFS scores.

Itaki Fall Risk Scale (IFS): This scale was introduced by the Republic of Turkey Ministry of Health Performance Management and Quality Improvement Directory in 2011. The scale consists of 19 items regarding the main risk factors related to falls in patients, including 11 minor and nine major risk factors. Each minor factor is scored as 1 point and each major factor is scored as 5 points. Based on the total score, the patients are categorized as being at low or high risk of falls, with a score of <5 indicating low risk and a score of >5 indicating a high risk. Accordingly, higher scores demonstrate a higher risk of falls (12).

Morse Fall Scale (MFS): This scale was first introduced in 1985 and consisted of six subscales: a history of falling, secondary diagnosis, ambulatory aid, IV/heparin lock, gait/transferring, and mental status. Based on the total score obtained on MFS, the patients are determined to be at low, moderate, or high risk of falls. The scale was revised in 2009 (13).

Ethical Approval

The study was approved by the Ministry of Health, Kayseri City Hospital Medical Specialty Committee and the Erciyes University Faculty of Medicine Ethics Committee (approval no: 2018/531).

Statistical Analysis

Data were analyzed using SPSS for Windows version 22.0 (IBM Corp., Armonk, NY, USA). Normality tests were performed using a Shapiro-Wilk test and histograms. Continuous variables with normal distribution were expressed as mean ± standard deviation. Continuous variables with non-normal distribution were expressed as median (25^{th}-75^{th} percentiles) and were compared using the Mann-Whitney U test. Categorical variables were compared using the chi-square test. A p value of <0.05 was considered significant.

Results

The study included a total of 368 patients. The demographic and clinical characteristics of the patients are presented in Table 1. The most common surgical procedures performed in the patients were urinary stone surgeries (27.7%). Of the 368 patients, 126 (34.2%) of them had UO, and 242 (65.8%) had NUO diseases. For each patient, four parameters included Itaki score (Is), Itaki risk level (Ir), Morse score (Ms), and Morse risk level (Mr) were determined, which indicated that the UO group had a significantly higher risk of falls compared to the NUO group. In order to decrease the effect of "age" on fall risk and to obtain a more homogenous age group, patients between the ages of 41-65, who could be defined as middle age group, were evaluated for fall risk. Similarly, the risk of falling was significantly

Table 1. Demographic and clinical characteristics

Parameter	**Mean (range or percentile)**
Age (years)	62.00 (36.00-69.75)
Gender (n, %)	
Female	48 (13%)
Male	320 (87%)
Body mass index (kg/m²)	24.1 (22.3-26.5)
Primary diagnosis (n, %)	
Urooncological	126 (34.2%)
Non-urooncological	242 (65.8%)
Department/Unit of referral (n, %)	
Polyclinic	301 (82%)
Emergency	47 (13%)
ICU	20 (5%)
Hospital stay (days)	2.0 (2.0-3.0)
Surgical procedure (n, %)	
Urinary stone surgery	102 (27.7%)
Transurethral resection of bladder tumor	97 (26.4%)
Scrotal surgery	60 (16.3%)
Transurethral resection of the prostate	59 (16%)
Radical surgeries	22 (6%)
Others	16 (4.3%)
Medical follow-up	12 (3.3%)

ICU: Intensive care unit, n: Number

higher in the UO group when the patients aged 41-65 years were examined (Table 2). Eleven percent of all patients (41 out of 368) had a history of at least one fall in the past one year, which was significantly higher in the UO group (17%; 21 out of 126) compared to the NUO group (8%; 20 out of 242) (p=0.015). Moreover, the Is, Ir, Ms, and Mr results indicated that the risk of falls was significantly higher in the patients with a history of at least one fall compared to the patients with no history of falls (Table 3). Of the 368 patients, 301 (82%) of them were hospitalized electively, and 67 (18%) were hospitalized under emergency conditions (emergency service or ICU), and the risk of falls was significantly higher in the patients hospitalized electively compared to the patients hospitalized under emergency conditions (Table 4). However, no significant difference was found between emergency service and ICU groups with regard to the Is, Ir, Ms, and Mr results (p=0.069, p=0.251, p=0.409, p=0110, respectively). No fall occurred in any patient in the Urology inpatient clinic throughout the study period.

Table 3. Comparison of the risk of falls based on the history of falls within the past six months

	History of falls within the past six months		
Parameter	**Yes (n=41)**	**No (n=347)**	**p**
Age (years)	67.0 (54.0-77.0)	61.0 (36.0-69.0)	0.007
Itaki score	7.0 (1.0-9.5)	2.0 (0.0-8.0)	0.004
MFS score	25.0 (5.0-50.0)	15.0 (0.0-25.0)	0.002
Itaki level			0.010
Low risk	36.6%	57.8%	
High risk	63.4%	42.2%	
MFS level			0.002
Low risk	41.5%	66.7%	
Moderate risk	39.0%	26.0%	
High risk	19.5%	7.3%	

MFS: Morse Fall scale, n: Number of the patients

Table 4. Comparison of the risk of falls based on the department/unit of referral

	Department/Unit of referral		
Parameter	**Polyclinic (n=301)**	**Emergency service/ICU (n=67)**	**p**
Age (years)	55.0 (33.0-68.0)	78.0 (68.0-81.0)	<0.001
Itaki score	1.0 (0.0-6.0)	9.0 (8.0-10.0)	<0.001
MFS score	0.0 (0.0-25.0)	50.0 (25.0-75.0)	<0.001
Itaki level			<0.001
Low risk	66.8%	4.5%	
High risk	33.2%	95.5%	
MFS level			<0.001
Low risk	74.8%	14.9%	
Moderate risk	21.3%	55.2%	
High risk	4.0%	29.9%	

MFS: Morse Fall scale, ICU: Intensive care unit, n: Number of the patients

Discussion

The most important finding of this study was that the risk of falls was lower in the patients hospitalized electively compared to those hospitalized under emergency conditions. Another important finding was that the patients with urological malignancies had a significantly higher risk of falls and a significantly higher incidence of a history of falls compared to patients without urological malignancies.

Urolithiasis is a highly prevalent health problem encountered in Europe and Turkey (14,15), with a reported prevalence of 15% in Turkey (15). As consistent with the literature, urinary stone surgeries were the most common surgeries performed in our clinic throughout the study period (27.7%). Bladder cancer is a common urological malignancy, and its treatment requires repeat cystoscopy and TURBT, particularly at the early stages of the tumor (16). In our study, TURBT was the second most common surgical procedure performed in our patients.

Of the 368 patients in our study, the frequency of a history of falls within the past six months was significantly higher

Table 2. Comparison of the risk of falls based on the primary diagnosis

	Primary diagnosis (for all patients)			Primary diagnosis (for 41-65 years old)		
Parameter	UO (n=126)	NUO (n=242)	p	UO (n=32)	NUO (n=66)	p
Age (years)	69.00 (62.00-79.00)	44.00 (30.75-66.00)	<0.001	58.50 (55.00-62.00)	60.00 (47.50-62.00)	0.122
Itaki score	8.0 (5.0-9.0)	1.0 (0.0-3.0)	<0.001	5.0 (5.0-7.0)	1.0 (0.8-2.0)	<0.001
MFS score	25.0 (15.0-50.0)	0.0 (0.0-15.0)	<0.001	15.0 (15.0-25.0)	0.0 (0.0-15.0)	<0.001
Itaki level			<0.001			<0.001
Low risk	8.7%	79.8%		15.6%	83.7%	
High risk	91.3%	20.2%		84.4%	16.3%	
MFS level			<0.001			0.001
Low risk	29.4%	81.8%		59.4%	89.4%	
Moderate risk	49.2%	16.1%		40.6%	10.6%	
High risk	21.4%	2.1%		-	-	

UO: Urooncological, NUO: Non-urooncological, MFS: Morse fall scale, n: Number of the patients

in the UO group compared to the NUO group (18% vs 8%) (p=0.015). Moreover, the Is, Ir, Ms, and Mr results were significantly higher in the UO group compared to the NUO group (p<0.001). However, as expected, cancer patients were older than NUO patients, and a homogeneous group of age could not be obtained. In order to decrease the effect of ''age'' on fall risk and to obtain a more homogenous age group, patients between the ages of 41-65, who could be defined as middle age group, were evaluated for fall risk. Similarly, UO patients between 41-65 years of age were found to have a higher risk of falling. According to these results, it can be said that cancer increases the risk of falling regardless of the age effect. A recent retrospective study evaluated a cohort of 304 cancer patients with urological, hematological, breast, lung, and gynecological cancers over a follow-up period of 6 months and reported that 35.8% of the patients had a history of at least one fall. The study concluded that old age and cancer patients have a significantly higher risk of falls compared to the general population (9). However, unlike our study, that study evaluated patients aged 65 years or older as well. In a more recent study, Wildes et al. (17) evaluated a cohort of 498 cancer patients aged 65 years or older and reported that 18.2% of the patients had a history of at least one fall within the past six months. Similarly, another study that was conducted in 2017 evaluated 280 patients with prostate cancer and revealed that 28% of the patients had a history of at least one fall within the past one year (18). However, this high rate of falls could have been related to the fact that the study had a longer study period compared to that of our study. On the other hand, two recent systematic reviews suggested that cancer patients have a significantly higher risk of falls compared to the general population (19,20). Taken together, all these findings implicate that the findings of our study are consistent with those reported in the literature.

In our study, the risk of falls was lower in the patients hospitalized electively compared to those hospitalized under emergency conditions. In a study conducted in 2016, Demir et al. (21) reported that 66.6% of the patients hospitalized in the internal disease's ICU had a relatively higher risk of falls. Çinarli et al. (22) reported that the risk of falls was higher, particularly in the patients aged 75 years or older, patients with chronic diseases, and patients with a history of falls. Several factors are directly associated with an increased risk of falls, including muscle weakness, behavioral disturbance, agitation, or confusion, and postural hypotension or syncope (23,24). Accordingly, our finding that indicated that the patients hospitalized under emergency conditions had a significantly higher risk of falls compared to those hospitalized electively could be explained by these factors.

Urbanetto et al. (25) analyzed the risk prediction capability and validity of the Brazilian version of MFS and found that MFS can appropriately predict the risk of falls. Similarly, in a Korean study, Baek et al. (26) evaluated the validity of MFS in 151 patients with a history of falls and 694 patients with no history of falls and revealed a sensitivity of 0.72 and a specificity of 0.91 for MFS. In our study, we evaluated the risk of falls over six months, and we found that among the patients with a history of falls, the proportions of the patients classified as being at moderate and high risk of falls on MFS were higher than those classified as being at low risk (Table 3). Additionally, although similar outcomes were obtained on the IFS, which is a national scale administered in Turkey, the outcomes of this scale could not be used for obtaining definitive evaluations since there are no international studies validating the reliability of this scale.

Study Limitations

The primary limitation of our study was that it only evaluated the history and risk of falls but did not include a long-term, prospective analysis of the falls. Furthermore, the fact that the patients in the UO group and the patients hospitalized under emergency conditions were significantly older than the other patients led to controversial findings. Old-age patients are typically expected to have an increased risk and frequency of falls; however, aging and cancer development cannot be distinguished from each other. In order to minimize this effect, a homogeneous group consisting of only patients aged 41-65 years was formed, but the small patient number of these groups is a limitation of our study. Additionally, hospitalization of older patients in ICUs and emergency services is inevitable, and thus, the hospitalization of these patients is directly associated with aging. However, it remains controversial whether there is an association between the high risk of falls in such patients and the age or clinical characteristics of these patients. Meaningfully, the absence of such an analysis was another limitation of our study. Finally, despite the rapid patient circulation in urology inpatient clinics, our study had a relatively short duration of the study period and a relatively smaller patient population.

Conclusions

Patients hospitalized in inpatient clinics should be closely followed due to the risk of falls. In particular, utmost care should be taken for cancer patients and the patients referred from the emergency service or ICU. Further multi-center studies with larger patient series and longer follow-up periods are needed.

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Ethics

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Informed Consent: Retrospective study.

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Authorship Contributions

Concept: A.D., M.A.K., Design: A.D., M.A.K., Data Collection or Processing: Ş.T.T., Analysis or Interpretation: G.S., M.K., Literature Search: Ş.T.T., Writing: G.S.

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Original Article

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"Atypical Cell'' Parameter in Automated Urine Analysis for the Diagnosis of Bladder Cancer: A Retrospective Pilot Study

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Abstract

Objective: To evaluate the application of an automated urine analyzer (AUA) for the diagnosis of bladder cancer (BC)
Materials and Methods: A retrospective data analysis of 2365 urine specimens from the department of urology has been performed and matched with those patients, who have undergone cystoscopic evaluation or surgical treatment for different urological pathologies during 2018. After matching, clinical records of the patients has been further evaluated in order to select patients with recent or previous BC diagnosis. To assess the diagnostic efficacy of AUA, patients were divided into five groups according to the patient history of BC and healthy controls.
Results: A total of 106 patients are included in this study and the majority (69.8%) of the patients are follow-up patients with previous diagnosis and treatment of non-muscle invasive BC (NMIBC). For patients with low-risk NMIBC (n=27), the sensitivity and specificity were calculated as 75% and 100%. For patients with high-risk NMIBC (n=47), who were previously treated with intravesical BCG, the sensitivity and specificity were calculated as 54.5% and 83.3%. All patients in radical cystectomy group (n=7) with muscle invasive BC had positive urine analyses results for atypical cells. And none of the patients in the control group (n=8) had positive AUA results and cystoscopic evaluation also did not show any bladder mass suspicious for BC.
Conclusion: The results of this retrospective pilot study showed acceptable sensitivity and specificity rates of the "fluorescence flow cytometry" based AUA and the results of the low-risk group are especially valuable regarding its potential use to decide on performing a follow-up cystoscopy or not. A prospective study is currently on progress to validate the findings of the current study.
Keywords: Bladder cancer, automated urine analysis, diagnosis

Introduction

Bladder cancer (BC) is the 9th most lethal malignancy with a worldwide age-standardized incidence rate (per 100,000 people/years) of 9.0 for men and 2.2 for women (1). Cystoscopy, with a sensitivity of 90%, is the golden standard for the diagnosis and follow-up of BC. However, it is an invasive approach that sometimes overlooks small tumors within the bladder (2). There are currently six Food and Drug Administration (FDA) approved urine tests, and although the sensitivity of these kits for BC diagnosis ranges from 57-82% to 74-88%, it increases with increasing stage and degree of the BC (3). There is certainly a need for a non-invasive tool to replace surveillance cystoscopies.

The fully automated urine formed element analyzer (UF-5000 SYSMEX Corporation, Kobe, JAPAN), which was launched in 2015, is capable of classifying and quantifying epithelial cells in greater detail with its "nucleic acid content" detecting

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"fluorescence flow cytometry" technology (4). Epithelial cells, predominantly with high nucleic acid contents for their cell size, are counted as atypical (a research parameter) by the analyzer. A previous study from Japan reported a high ability of the analyzer to predict the results of microscopic analysis of atypical cells in patients with urinary tract tumors; however, the type of the cancer cells is not specifically identified (5).

In this retrospective pilot study, we aimed to evaluate the application of an automated urine analyzer (AUA) for the diagnosis of BC.

Materials and Methods

A retrospective data analysis of 2365 urine samples from the department of urology has been performed. We selected the samples of patients, who underwent cystoscopic evaluation or surgical treatment for various urological pathologies during 2018. Clinical records of these patients were further evaluated in order to select patients with recent or previous BC diagnosis. Out of 2365 urine samples, a total of 98 samples (one sample per patient) were evaluated within the preoperative two weeks before the cystoscopy in patients with BC diagnosis. A total of eight samples were selected from patients who underwent cystoscopic evaluation for non-cancerous etiologies (control group).

To assess the diagnostic efficacy of AUA, patients were divided into five groups according to the patient history of BC risk groups, which are defined by the international guidelines (6,7):

Group 1– follow-up cystoscopy low-risk non-muscle invasive BC (NMIBC)

Group 2– follow-up cystoscopy high-risk NMIBC with previous intravesical Bacillus Calmette-Guerin (BCG) treatment (induction and at least 1-year maintenance treatment)

Group 3– transurethral resection for a newly diagnosed bladder mass without previous BC history

Group 4– radical cystectomy for muscle-invasive BC

Group 5– cystoscopic evaluation for non-cancerous etiologies (control group)

Epithelial cells, predominantly with high nucleic acid contents for their cell size, are counted as atypical (a research parameter) by the analyzer, and these cells in the atypical cell zone are reported as "atypical cell in µL" of the urine specimen.

Statistical Analysis

Data analysis was executed with SPSS version 20.0 (Chicago, IL, USA), and for the purpose of this pilot study, only the sensitivity and specificity analyses were performed.

Results

A total of 106 patients were included in this study, and the majority (69.8%) of the patients were follow-up patients with previous diagnosis and treatment of NMIBC. For patients with low-risk NMIBC (n=27), sensitivity and specificity were calculated as 75% and 100%. Results of the urine analyses, cystoscopic evaluation, and pathologic characterization of the tumors are present in Table 1.

For patients with high-risk NMIBC (n=47), who were previously treated with intravesical BCG, the sensitivity and specificity were calculated as 54.5% and 83.3%, respectively. Results of the urine analyses, cystoscopic evaluation, and pathologic characterization of the tumors are present in Table 2.

For Group three patients (n=17), who underwent transurethral resection for a newly diagnosed bladder mass and without previous BC history, the sensitivity and specificity were calculated as 50% and 100%, respectively. Results of the urine analyses, cystoscopic evaluation, and pathologic characterization of the tumors are present in Table 3.

All patients in the radical cystectomy group (n=7) with muscle-invasive BC had positive urine analysis results for atypical cells. Furthermore, none of the patients in the control group (n=8) had positive AUA results, and cystoscopic evaluation also did not show any bladder mass suspicious for BC.

Discussion

The results of this study showed acceptable sensitivity and specificity rates of the "fluorescence flow cytometry" based AUA compared to the current FDA approved urine tests. The results of the low-risk group are especially valuable regarding its potential use to decide on performing a follow-up cystoscopy or not. Such an application might be useful for avoiding an invasive procedure on the patient side together with additional economic savings considering the costs of the follow-up cystoscopies.

Table 1. Low risk NMIBC-control cystoscopy

SYSMEX result	Cystoscopy result			
	Negative	LMPUN	*pTaLG*	Total
Negative	23	0	1	24
Positive	0	2	1	3
Total	23	2	2	27

NMIBC: Non-muscle invasive bladder cancer, LMPUN: Papillary urothelial neoplasia with low malignant potential

Table 2. High risk NMIBC-control cystoscopy

SYSMEX Result	Cystoscopy result						
	Negative	LMPUN	*pTaLG*	*pTaHG*	*pT1HG*	MIBC	Total
Negative	30	3	1	1	0	0	35
Positive	6	1	2	0	2	1	12
Total	36	4	3	1	2	1	47

NMIBC: Non-muscle invasive bladder cancer, MIBC: Muscle invasive bladder cancer, LMPUN: Papillary urothelial neoplasia with low malignant potential

Table 3. First time TUR for a newly diagnosed bladder tumor

SYSMEX result	Cystoscopy result						
	Negative	LMPUN	*pTaLG*	*pTaHG*	*pT1HG*	MIBC	Total
Negative	1	1	4	1	1	1	9
Positive	0	0	1	1	5	1	8
Total	1	1	5	2	6	2	17

TUR: Transurethral resection, MIBC: Muscle invasive bladder cancer, LMPUN: Papillary urothelial neoplasia with low malignant potential

There are limited reports of the atypical cell counts with AUA for the diagnosis of BC. Ergüder et al. (8) analyzed 12900 urine samples retrospectively and included 1060 samples with the atypical parameter >0.1 in their study. The mean "atypical cell" count was significantly higher in patients with BC compared to other pathologies (1.61 vs 0.31). However, they did not report the pathological details of the tumors.

Shukuya et al. (5) analyzed the urine of 44 patients, who likely to have urinary tract tumors. In 41 patients, atypical cells were detected, and urinary tract tumors diagnosed. They reported the sensitivity as 81.0% and specificity as 88.0%, however no data regarding the pathological details of the tumors. Our data showed sensitivity and specificity as 75% and 100% for patients with low-risk NMIBC. This group of patients is of interest to active surveillance, and an alternative approach with such a urine analyzer can contribute to the current efforts (9).

Almost half (44.3%) of our study group included high-risk NMIBC patients who were treated with intravesical BCG. This group received at least 1-year maintenance treatment, which is the minimum recommended duration for intravesical treatment for high-risk patients. Cytology is useful, particularly as an adjunct to cystoscopy, in patients with high-risk tumors, and the sensitivity and specificity of the urine cytology were reported ranging from 30% and 86% to 83% and 43% in various studies, respectively (7). For this group, the sensitivity and specificity of the urine analyzer were calculated as 54.5% and 83.3%.

Study Limitations

The present study is limited by its retrospective nature. A significant limitation is that we did not have another parameter such as urine cytology in all patients to compare with urine analyzer. Another limitation is the absence of information regarding the timing of the collection of the urine. According to the developers of the analyzer, the ideal urine should last at least 4 hours within the bladder or, most ideally, the first urine in the morning. Another potential limitation is that our study included a relatively small number of patients. However, compared to the limited reports, our data includes a relatively heterogeneous BC patient population that consisted of patients with different disease stages.

Conclusions

The results of this retrospective pilot study showed acceptable sensitivity and specificity rates of the ''fluorescence flow cytometry'' based AUA, and the results of the low-risk group are especially valuable regarding its potential use to decide on performing a follow-up cystoscopy or not. A prospective study is currently on progress to validate the findings of the current study.

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Ethics

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Informed Consent: Retrospective study.

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Authorship Contributions

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

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Predictive Value of Different Parameters for Estimating the First 90-days and Long-term Survival Following Radical Cystectomy

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Abstract

Objective: We aimed to define the prognostic risk factors which may have an impact on the survival by assessing the effects of the different clinical parameters and several comorbidity classifications on the oncologic outcomes within the first 90 days and long-term follow-up after radical cystectomy.

Materials and Methods: Fifty-two patients who underwent radical cystectomy between June 2013-and June 2017 due to bladder tumors and whose data were fully accessible, have been assessed retrospectively. The demographical, clinical and pathologic data of the patients were recorded along with the progression and mortality rates within the first 90 days follow up period and the subsequent long-term follow-up. Age-adjusted Charlson Comorbidity index (ACCI), Eastern Cooperative Oncology Group (ECOG) score, American Society of Anesthesiologists (ASA) score, Framingham risk score, Preoperative Score to Predict Postoperative Mortality, Rockwood frailty index, preoperative serum hemogram parameters and estimated glomerular filtration rate (eGFR) were all calculated and recorded.

Results: Out of the 52 patients the average age was 68.21±6.47, distant metastasis was observed in 17 (32.7%) patients during monthly follow ups at an average of 37.52±26.15 [minimum (min)=1, maximum (max)= 96], while morbidity was observed in 23 patients (44.2%). According to receiver operativing characteristic analysis, the two parameters as the most reliable tool in the prediction of the mortality during long term follow up were eGFR [area under the curve (AUC)=0.754, $p<0.001$] and Framingham score (AUC=0.782, $p=0.001$). It has also been observed in multivariate analysis that Framingham score and Clavien-Dindo classification was the most meaningful predictive factor in the estimation of the mortality in the first 90 days period, progression free survival (PFS) and overall survival (OS); eGFR for PFS and OS; ECOG score for PFS; ASA score for OS; monazite/lymphocyte rate for the estimation of the mortality in the first 90 days period. In addition, pT3-4 stage has been observed to be much more meaningful in the prediction of PFS, non-transitional cell carcinoma pathology for PFS and OS, and, lymph node positivity for OS.

Conclusion: Radical cystectomy is a surgical procedure with high morbidity and mortality due to perioperative complications both in the first 90-days of the postoperative period and long-term follow-up.We found that Framingham score and eGFR were superior and easily applicable parameters in prediction of PFS and OS, whereas Framingham score and MLR were better in prediction of the first 90-days mortality. In this way, we think that we can identify patients who are more suitable for cystectomy, so we can provide more successful postoperative follow-up and treatment management.

Keywords: eGFR, Framingham risk score, monocyte/lymphocyte ratio, oncologic outcomes, radical cystectomy

Introduction

Out of the cancers, the bladder cancer is the sixth malignity which is encountered widely while it is ranked to be the second frequency out of the urologic tumors (1). It is the fifth cancer type which gives way to death in all around the world (2). By the time of diagnosis, 70% of the bladder cancer is supposed to be at the non-invasive stage while the remaining 30% is at the invasive and metastatic stage (3). The diagnosis for muscle invasive cancer could be made through the transurethral

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resection (TUR) and the proposed treatment for stage T2-T4a N0-Nx M0 is the radical cystectomy subsequent to clinical evaluation (3). In addition, as far as the non-muscle invasive bladder cancers (NMIBC) are concerned, radical cystectomy is one of the options for the treatment of the cases with resistance against intravesical treatments or the presence of low-grade diffusive tumors which cannot be resected completely (3).

Since the median age of the patients during diagnosis is 70, the rate of postoperative complications reaches to 60% due to the high morbidity rates of the surgical operation with the effects of the elder age and the accompanying diseases (4). The mortality rates observed within the first 90 days of the postoperative period vary between 2.6% to 7.9%. (4). The preoperative assessment of the short and long-term mortality for the geriatric population (>70 age) is of particular importance in this respect (5). Hence, the patients and their families will be informed of the potential risks and the approaches to protect the bladder will perhaps be brought forward for the patients with higher morbidity. However, we come to an understanding that there exists no consensus for the nomogram or scoring system which may be the best for comorbidity of such patients, if we have a look at the literature (6).

In this study, we aimed to define the prognostic risk factors which may have an impact on the survivals taking into account the effects of the various clinical parameters and different comorbidity classifications on the oncologic assessments to be made within the first 90 days follow period subsequent to cystectomy and the long term follow period as well.

Materials and Methods

The data of 65 elder people who underwent radical cystectomy was applied by a primary surgeon due to a bladder tumor between June 2013 and June 2017 at our clinic were assessed retrospectively. Nine of the patients on whom no extended lymph node dissection application was performed and four patients data of whom were inaccessible were excluded from the study. Radical cystectomy for curative purposes, bilateral lymph node dissection and ileal conduit as urinary diversion were applied on 52 patients included in this study.

The demographical data of the patients involved, body mass index (BMI), preoperative hydronephrosis status, TUR pathology, cystectomy pathology, atypical variant histology were all recorded. Prior to cystectomy, the estimated glomerular filtration rate (eGFR) was calculated and kept under the records. For this particular calculation, Modification of Diet in Renal Disease formula which includes the parameters e.g preoperative creatinin, age, gender, and race, was used. Based on the patients' data obtained during the preoperative period, Age - adjusted Charlson comorbidity index (ACCI), Eastern Cooperative Oncology Group (ECOG) performance score, ECOG score, Framingham risk score, Preoperative Score to Predict Postoperative Mortality (POSPOM) and Rockwood frailty index (RFI) were calculated. The serum hemogram parameters [(neutrophile/lymphocyte rate (NLR), platelet/lymphocyte rate (PLR), monocyte/lymphocyte rate (MLR), average platelet volume (MPV), red cell distribution width (RDW)] taken one week before the cystectomy were calculated individually and recorded.

The follow-up period of the patients subsequent to cystectomy, postoperative complications according to Clavien-Dindo classification, progression and mortality rates were all recorded.

Age-adjusted Charlson Comorbidity Index

This scoring is used to predict the 30 days mortality in traumatic cases or the diseases which require emergency radical surgery (7). Scoring is based on the severity of the comorbidity (lmild, moderate or severe) in the case of cardiovascular, pulmonary, gastrointestinal, urologic, neurologic and hematologic diseases. Out of 19 parameters as a total, for each parameter score between 1 to 6 is assigned to attain to the total score. For each case above 50 years of age, one more point is added against 10 years increase.

Eastern Cooperative Oncology Group Performance Score

Eastern Cooperative Oncology Group performance score is scaled between 0 and 5 to assess the general performance status of the oncology patients where zero point shows good performance and five points shows death (8).

American Society of Anesthesiologists Score

American Society of Anesthesiologists (ASA) score is the primordial scoring system between 1 and 4 based on the perioperative risks based on the physical conditions of the patients during preoperative period as defined by the ASA in 1940 (9).

Framingham Risk Score

It is a nomogram that calculates the ten-year risk of cardiovascular disease development and associated mortality. The parameters used in this scoring systems are age, gender, blood pressure value, total cholesterol, high density lipoprotein (HDL) level smoking and diabetes. Scores are assigned against each of such parameters and the total score is thus calculated. The probability of the occurrence of any cardiovascular disease for the ten years period can be found out for each of the gender in pursuance with the percentile corresponding to the scores obtained. Accordingly, <10% shows low-risk, 10-19% intermediate risk, and ≥20% high risk (10).

Preoperative Score to Predict Postoperative Mortality

It is the risk score which not only predicts the potentiality of the mortality at the hospital for the patents who are to undergo surgical operation but also makes risk assessment in order to reach to a clinical solution. In this scoring system, a total of seventeen predictive factors which include age, cardiovascular, cerebra-vascular, renal, urologic, endocrine, and oncologic pathologies are defined. In case the total score assigned for each of such factors is more than 28, it then shows the poor prognosis (7).

Rockwood Frailty Index

Frailty can be characterized through external factors which may lead to physical stress. By the time the fragile individuals within the geriatric population are followed up at the hospital,

the risks for drops, delirium and disability increase. RFI is the nomogram used to predict the duration of hospitalization and the development of the major complications for the postoperative patients (11). Scores between 1 and 4 mean to be "no fragility", 5 and 6 "mild to moderate degree", and 7 and 9 "severe fragility "

Statistical Analysis

After evaluating the normality status with the Kolmogorov-Smirnov and Shapiro-Wilk tests, while identifying the characteristics of all patients, the continuous variables with normal distribution were shown as mean ± standard deviation, the non-normally distributed variables were shown as median (25th percentile-75th percentile), and categorical variables were shown as number (percent). To define the estimated value used to predict the mortality during long-term follow-up period subsequent to radical cystectomy, receiver operating characteristic curve analysis were made. Kaplan-Meier method was used for the survival analysis and the differences amongst the patient sub groups were defined through log rank test. Cox Regression analysis was used to define the variables which may have an impact on the mortality, progression free survival (PFS) and overall survival (OS) in the first 90 days. The analyses were made through IBM SPSS Statistics 21 (IBM, Armonk, NY USA) software. $p < 0.05$ value is considered statistically significant.

Results

The average age of the patients included in our study is 68.21±6.47 (min=50, max=78) while 48 patients (92.3%) were male and four patients (7.7%) were female. During the 37.52±26.15 (min=1, max=96) months follow-up period, distant metastasis was observed on 17 patients (2.7%) with the death of 23 (44.2%) patients. Distant metastasis has been defined in the lymph nodes of four patients, the lungs of eight patients, bones of two patients and the liver of three patients. The demographical, clinical, pathological, and oncologic outcomes for the patients are shown in Table 1.

Table 2 shows the estimated values of the parameters to be used in the prediction of the mortality in the long-term subsequent to cystectomy. Out of such values, the eGFR [area under the curve (AUC)= 0.754, $p<0.001$] and Framingham score (AUC=0.782, p=0.001) have been observed to be the most reliable two parameters. According to the Framingham score which makes an assessment on the risk of development of cardiovascular disease over the ten years if we classify the patients in the manner that (<10%) is low risk, (10-19%) is medium risk, and (≥20%) is high risk, the group observed with mortality, includes high risk patients more than the other group (53.8% vs 23.5%) and the patients under high risk have been observed to be assigned higher mortality (61.9%) while we have found out that much more reliable results could be attained in the prediction of the mortality if the estimated value for Framingham score is set to be 14.5. (Table 2, Figure 1-2).

Age, gender, BMI, smoking history, cystectomy pathology, atypical variant histology in cystectomy specimen, presence of carcinoma in situ, lymphovascular invasion, presence of upstaging / downstaging, surgical margin positivity, pathological

Table 1. Patients' demographical, clinical and pathological data and oncologic results

Parameters	Total (n=52)
Age	68.21±6.47
Body mass index	25.78±3.72
Gender (n, %)	
Male	48 (92.3)
Female	4 (7.7)
Smoking history (n, %)	
Yes	30 (57.7)
No	22 (42.3)
TUR-BT pathology (n, %)	
-T2G3	47 (90.4)
- Non-TCC	5 (9.6)
Cystectomy pathology (n, %)	
-T0	6 (11.5)
-Ta	1 (1.9)
-T2	21 (40.4)
-T3	12 (23.1)
-T4	7 (13.5)
- Non-TCC	5 (9.6)
Atypical variant histology (n, %)	
-Micro papillary	4 (7.7)
-Sarcomatoid	10 (19.2)
- No atypical variant histology	38 (73.1)
Upstaging after cystectomy (n, %)	
Yes	23 (44.2)
No	29 (55.8)
Downstaging after cystectomy (n, %)	
Yes	7 (13.5)
No	45 (86.5)
Accompanying CIS (N, %)	
Yes	13 (25.0)
No	39 (75.0)
Positive surgical margin (n, %)	
Yes	10 (19.2)
No	42 (80.8)
Lymph vascular invasion (n, %)	
Yes	7 (13.4)
No	45 (86.6)
Positive lymph node (pN+) (n, %)	
Yes	20 (38.5)
No	32 (61.5)
Preoperative hydronephrosis (n, %)	
Yes	27 (51.9)
No	25 (48.1)
eGFR (mL/dk/1.73 m^2)	74.84±9.92

ACCI	5.25±2.37
Neo-adjuvant chemotherapy (n, %)	
Yes	9 (17.3)
No	43 (82.7)
Adjuvant chemotherapy (n, %)	
Yes	12 (23.1)
No	40 (76.9)
ECOG score	2 (2-3)
POSPOM score	27.17±9.92
Framingham score	17.02±8.10
Framingham risk classification	
Low risk	12 (23.1)
Intermediate risk	19 (36.5)
High risk	21 (40.4)
ASA score	2 (2-3)
RFI	5.83±1.86
NLR	2.23±0.72
PLR	113.18±28.37
MLR	0.27±0.09
MPV	3.61±0.99
RDW	13.61±0.99
Clavien-Dindo classification (n, %)	
-1	22 (42.3)
-2	17 (32.7)
-3a	6 (11.5)
-3b	6 (11.5)
-4b	1 (1.9)
Follow up period (month)	37.52±26.15
Rate of metastasis during follow up (n, %)	17 (32.7)
Rate of mortality in the first 90 days (n, %)	6 (11.5)
General mortality rate (%)	23 (44.2)

BMI Body/Mass index, TUR-BT: Transurethral resection of the bladder tumor, TCC: Transitional cell carcinoma, CIS: Carcinoma in situ, eGFR: Estimated glomerular filtration rate, ACCI: Age Adjusted Charlson Comorbidity Index, ECOG: Eastern Cooperative Oncology Group, POSPOM: Preoperative Score to Predict Postoperative Mortality, ASA: American society of anesthesiologists, RFI: Rockwood frailty index, NLR: Neutrophile/lymphocyte rate, PLR: Platelet/lymphocyte rate, MLR: Monocyte/lymphocyte rate, MPV: Average platelet volume, RDW: Erythrocyte distribution width

lymph node positivity, preoperative hydronephrosis status, neoadjuvant/adjuvant chemotherapy, status POSPOM, Framingham score, RFI, NLR, PLR, MLR and Clavien-Dindo classification were used, univariate and multivariate survival analyzes were performed to include these data as independent variables. Since no meaningful estimated value has been defined for MPV (AUC=0.601, p=0.214) and RDW (AUC=0.645, p=0.074) in receiver operating characteristic analysis, these two parameters have not been included in the univariate and multivariate analysis.

The predictive factors for PFS and OS within the follow-up period in the long-term, and the first 90 days mortality subsequent to radical cystectomy according to the univariate and multivariate analyses are shown in Table 3A-C. Kaplan-Meier curve for the parameters used in the prediction of the OS in accordance with the multivariate analysis is shown in Figure 1-7.

Discussion

Radical cystectomy is the surgical procedure with high morbidity and mortality both in the course of the first 90 days of the postoperative period and the follow-ups in the long-term due to the perioperative complications (7). Different publications

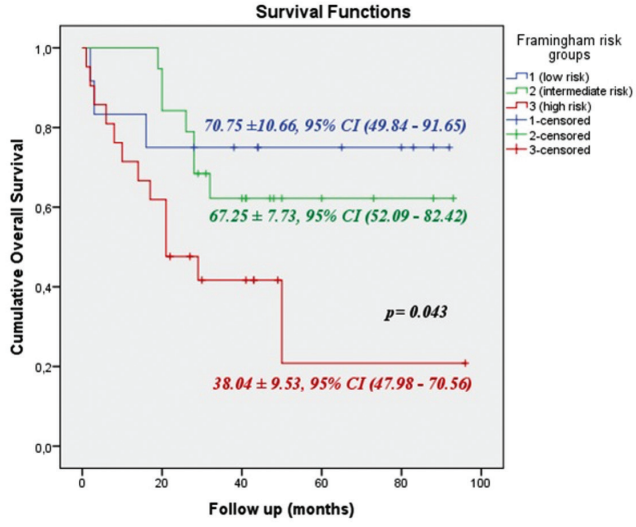

Figure 1. Kaplan-Meier plot of overall survival times predicted for Framingham risk groups

CI: Confidence interval

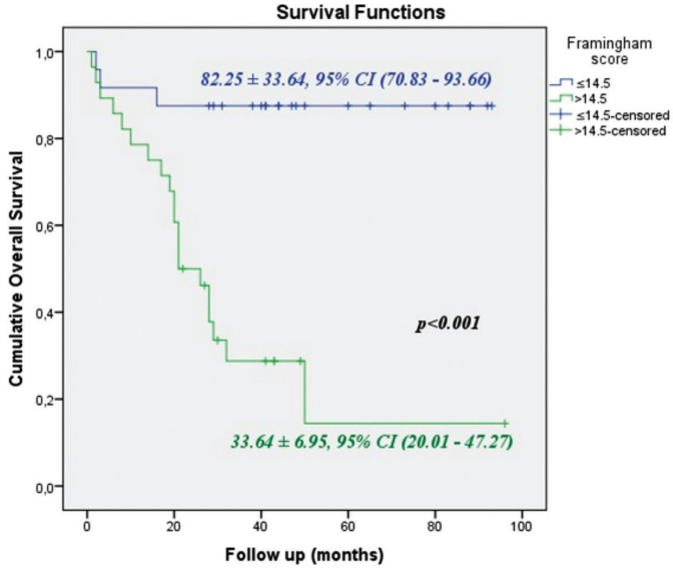

Figure 2. Kaplan-Meier plot of overall survival times predicted by Framingham risk score

CI: Confidence interval

Table 2. Cut-off values for the parameters used to predict the mortality in the long-term follow-up subsequent to radical cystectomy

	ACCI	POSPOM	Framingham score	RFI	NLR	MLR	PLR	eGFR
Cut-off value	5.5	25.5	14.5	5.5	2.13	0.26	110.36	74.10
Sensitivity (%)	60.9	65.2	87.0	73.9	60.9	73.9	73.9	82.6
Specificity (%)	69.0	65.5	72.4	51.7	55.2	65.5	65.5	69.0
PPV (%)	66.2	67.2	75.9	60.4	57.6	68.1	68.1	72.7
NPV (%)	63.8	65.3	84.7	66.4	58.8	71.5	71.5	79.8
AUC	0.705	0.713	0.782	0.697	0.666	0.726	0.669	0.754
p	0.012*	0.009*	0.001*	0.015*	0.042*	0.022*	0.037*	<0.001*

ACCI: Age-adjusted Charlson Comorbidity index, RFI: Rockwood frailty index, , POSPOM: Preoperative Score to Predict Postoperative Mortality, NLR: Neutrophile/lymphocyte rate, MLR: Monocyte/lymphocyte rate, PLR: Platelet/lymphocyte rate, eGFR: Estimated glomerular filtration rate, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve *p<0.05 (There is a significant difference between the groups)

have specified that the perioperative mortality ratio is 2-13% and general survival percentage for five years is 50-60% (12). We have observed that the said ratios are respectively 11.5% and 44.2% in accordance with the literature. Multimodal treatments for the protection of the bladders or radiotherapy for palliative purposes may be an option for the patients with high morbidity especially the elder patients, to get rid of the surgical risks despite the fact that such treatments are not deemed to be the alternatives to the cystectomy in view of curative treatment. Therefore, it is of particular concern to define the patients with high mortality ratio and morbidity associated with cystectomy (13).

There exists surplus of studies which pertain to the comorbidity index to be used in the prediction of the OS in the follow up in the long term and the perioperative mortality of 90 days for the patients on which radical cystectomy is planned due to bladder tumors (4,12,13,14). Different studies have shown that the elder age, angina pectoris, smoking history, chronic lung diseases and Diabetes Mellitus were used as independent prognostic factors to predict the 10-year mortality subsequent to cystectomy (13,15). However, instead of evaluating the comorbid conditions individually, it is thought to be more valuable to use nomograms that examine the total morbidity burden (2).

According to the updated guidelines of the European Association of Urology (EAU), it is suggested to make an evaluation for the morbidity of the potential patients who are to undergo radical cystectomy preoperatively (3). For this purpose, the widely used scoring systems are ACCI and ASA and it has been observed that they are much more beneficial for the prediction of the complications which may develop in the elder patients during the first 30 days after the operation and the cancer free mortality in the first 90 days (13,14). It has been reported that the prognostic value of ACCI may be higher in the estimation of five-year mortality due to all causes (12).

It is obvious that the predicted values of the survival analyses of the scoring systems vary in every study (4,12,16). As a matter of fact elder age (≥75), it has been reported that progressive cancer stages (T3-4) and high ASA score (≥3), increase the perioperative mortality within the 90 days period (4); make a negative impact of the five-years OS ratios through ACCI (17) and ECOG score has no additional contribution for the prediction of the 90 days mortality (4). According to Boorjian et. al (12), ASA and ECOG scores make an impact on both the 90-days perioperative mortality and the five years OS, on the other hand ACCI predicts the OS in a much more meaningful manner. Froehner et al. (16) have specified that ACCI and ASA scores fail to predict the short and long-term mortality for the patients aged 80 and more, after cystectomy. According to the multivariate analysis in our study, we observed that advanced tumor stage (T3-4) and ECOG score affect PFS more significantly, and ASA score affects OS more significantly, while we could not determine the effect of patient age on oncological results. In addition, we have found out that non-transitional cell crcinoma pathology is much more deterministic in the prediction of the PFS and OS while positive lymph node is a determinant for the prediction of the OS. Being distinct from the publications listed in the literature we have also observed that Framingham score and Clavien-Dindo classification are the predictive factors which are much more meaningful in the determination of the first 90 days mortality, PFS and OS and eGFR is for the PFS and OS.

RFI has been in use for the estimation of the duration of hospitalization and development of major complications during postoperative period especially within the geriatric population. There exists no study showing the use of the same for the old population who underwent cystectomy (18). In our study in which we have found out that high RFI (>5.5) values decreases the OS at a rate of 2.32 in the case univariate analysis and that RFI has no meaningful impact on OS in the multi variate analysis..

Froehner et al. (5) reported that systemic disease load is effective on the survival in the long-term subsequent to cystectomy. POSPOM is one of the disease-counting classifications that can be used to predict this. In our study, although high POSPOM (> 25.5) scores decreased PFS at a rate of 2.94 times and OS at a rate of 2.37 times in univariate analysis, it did not have a significant effect in multivariate analysis.

While 28 (53.8%) of 52 patients who underwent cystectomy in our study were 70 years old and under, 24 (46.2%) were over 70 years old. Although we found that the patient's age did not affect oncological results, the rate of patients who underwent cystectomy over 75 years of age was 11.5% in accordance with the literature. Even for the cases with low ASA score (≤2), it is observed that radical cystectomy was applicable on the patients older than 75 years old, at a lesser rate (21% vs 49%) (19).

Nevertheless, Boorjian et al. (12), has stated that the elder age of the patients has no impact on the perioperative mortality and that the age is not the sole determinant for the decision to apply cystectomy In our study, 28 patients (53.8%) aged 70 or younger, out of 52 patients received cystectomy while 24 patients (46.2) were older than 70. Although we have found out that the age of the patients had no impact on the oncologic results, the percentile of the patients who under cystectomy and aged 75 and older is 11.5 % in compatible with the literature.

The updated EAU guidelines suggest the use of the Cumulative Illness Score Rating-Geriatrics (CISR-G) in the assessment of the general medical condition of the patients and when defining the most appropriate treatment alternative for the geriatric group in the case of prostate cancer (20). We consider that this scoring system may not only be used for the patients diagnosed with prostate cancer in daily practice but also for defining the geriatric patients who are to undergo cystectomy. However, the fact that this scale includes many detailed queries concerning the systemic diseases, it is neither practical nor it is possible to apply the same within the scope of the retrospective studies. Therefore, it seems much more convenient to use it in the prospective studies concerning the follow ups on the patients on whom cystectomy was applied. Froehner et al. (15) has reported that ACCI, when compared to CISR-G, is much easier to apply and is at acceptable levels to predict the postoperative mortality.

Since the use of angina pectoris classification of the New York Heart Association (NYHA) and Canadian Cardiovascular Society (CCS) for the prediction of pre-cystectomy cardiac mortality

Table 3A. Predictive factors for the first 90 days mortality in the long term follow up subsequent to radical cystectomy

First 90 days mortality	Uni variate model				Multi variate model			
	HR	95% CI		p	HR	95% CI		p
		Lower	Upper			Lower	Upper	
Age	1.010	0.941	1.084	0.770	-	-	-	-
Gender (male)	1.333	0.176	10.101	0.780	-	-	-	-
BMI	1.087	0.971	1.217	0.146	-	-	-	-
Smoking history	1.373	0.604	3.115	0.449	-	-	-	-
Atypical variant histology	1.372	0.561	3.355	0.488	-	-	-	-
Cystectomy pathology (T3-4)	1.158	0.501	2.676	0.732	-	-	-	-
Cystectomy pathology (TCC/nonTCC)	2.890	0.943	8.849	0.063	-	-	-	-
Upstaging	1.852	0.809	4.242	0.145	-	-	-	-
Downstaging	1.262	0.429	3.715	0.672	-	-	-	-
CIS presence	1.813	0.765	4.295	0.176	-	-	-	-
Positive surgical margin	1.549	0.610	3.931	0.357	-	-	-	-
Positive lymph node	1.579	0.676	3.685	0.291	-	-	-	-
Lymph vascular invasion	1.667	0.618	4.494	0.313	-	-	-	-
Preoperative hydronephrosis	1.497	0.631	3.553	0.361	-	-	-	-
Neo-adjuvant chemotherapy	2.027	0.517	3.097	0.235	-	-	-	-
Adjuvant chemotherapy	2.333	0.888	6.130	0.086	-	-	-	-
eGFR <74.10	2.702	0.981	7.462	0.044*	-	-	-	-
ACCI >5.5	1.576	0.673	3.695	0.295	-	-	-	-
ECOG >2	2.068	0.884	4.840	0.094	-	-	-	-
ASA >2	2.279	1.332	3.311	0.034*	-	-	-	-
POSPOM >25.5	2.401	1.010	5.708	0.055	-	-	-	-
Framingham score >14.5	5.064	1.500	17.095	0.009*	5.064	1.500	17.095	0.009*
RFI >5.5	1.781	0.701	4.523	0.225	-	-	-	-
NLR >2.13	1.470	0.636	3.396	0.038*	-	-	-	-
PLR >110.36	1.965	0.755	5.110	0.046*	-	-	-	-
MLR >0.26	2.541	0.628	4.590	0.042*	2.357	1.226	4.156	0.039*
Clavien-Dindo (>2)	1.444	1.045	1.994	0.026*	1.093	0.882	2.857	0.041*

BMI: Body mass index, TCC: Transitional cell carcinoma, CIS: Carcinoma *in situ*, eGFR: Estimated glomerular filtration rate, ACCI: Age-adjusted Charlson Comorbidity index, ECOG: Eastern Cooperative Oncology Group, POSPOM: Preoperative Score to Predict Postoperative Mortality, RFI: Rockwood frailty index, NLR: Neutrophile/lymphocyte rate, PLR: Platelet/lymphocyte rate, MLR: Monocyte/lymphocyte rate, MPV: Average platelet volume, HR: Hazard ratio, CI: Confidence interval
*p<0.05 shows the statistically significant difference, Cox regression analysis

Table 3B. Predictive factors for progression free survival in the long-term follow-up subsequent to radical cystectomy									
	Uni variate model				Multi variate model				
Survival without progression	HR	95% CI		p	HR	95% CI		p	
		Lower	Upper			Lower	Upper		
Age	1.002	0.915	1.096	0.972	-	-	-	-	
Gender (male)	1.440	0.329	6.308	0.629	-	-	-	-	
BMI	1.035	0.913	1.173	0.590	-	-	-	-	
Smoking history	1.308	0.503	3.401	0.581	-	-	-	-	
Atypical variant histology	1.925	0.709	5.232	0.199	-	-	-	-	
Cystectomy pathology (T3-4)	1.569	0.605	4.070	0.034*	1.354	0.917	3.332	0.034*	
Cystectomy pathology (TCC/nonTCC)	4.756	2.044	12.232	0.002*	3.756	1.044	13.222	0.002*	
Upstaging	2.878	1.060	7.813	0.038*	-	-	-	-	
Down staging	2.724	0.761	7.408	0.331	-	-	-	-	
CIS presence	2.553	0.967	6.739	0.059	-	-	-	-	
Positive surgical margin	1.827	0.642	5.195	0.259	-	-	-	-	
Positive lymph node	1.924	0.739	5.015	0.180	-	-	-	-	
Lymph vascular invasion	2.649	0.858	8.176	0.090	-	-	-	-	
Preoperative hydronephrosis	2.116	0.781	5.734	0.141	-	-	-	-	
Neo-adjuvant chemotherapy	3.303	0.837	6.835	0.168	-	-	-	-	
Adjuvant chemotherapy	1.688	0.589	4.837	0.329	-	-	-	-	
eGFR<74.10	4.739	1.540	14.705	0.007*	4.504	1.443	14.084	0.002*	
ACCI >5.5	5.672	1.840	17.481	0.003*	-	-	-	-	
ECOG >2	2.993	1.102	8.128	0.031*	3.036	1.003	9.190	0.049*	
ASA >2	3.419	1.259	9.283	0.016*	-	-	-	-	-
POSPOM >25.5	2.941	1.032	8.385	0.044*	-	-	-	-	-
Framingham score >14.5	5.845	1.661	20.573	0.006*	4.466	1.128	107.684	0.033*	-
RFİ>5.5	1.523	0.562	4.132	0.408	-	-	-	-	-
NLR>2.13	1.825	0.675	4.936	0.036*	-	-	-	-	-
PLR>110.36	2.534	1.172	8.842	<0.001*	-	-	-	-	-
MLR > 0.26	2.452	1.843	6.591	0.004*	-	-	-	-	-
Clavien-Dindo (>2)	3.409	1.230	9.451	0.018*	-	2.442	1.346	6.773	0.024*

BMI: Body mass index, TCC: Transitional cell carcinoma, CIS: Carcinoma *in situ*, eGFR: Estimated glomerular filtration rate, ACCI: Age-adjusted Charlson Comorbidity index, ECOG: Eastern Cooperative Oncology Group, POSPOM: Preoperative Score to Predict Postoperative Mortality, RFI: Rockwood frailty index, NLR: Neutrophile/lymphocyte rate, PLR: Platelet/lymphocyte rate, MLR: Monocyte/lymphocyte rate, MPV: Average platelet volume, HR: Hazard ratio, CI: Confidence interval
*p<0.05 shows the statistically significant difference, Cox regression analysis

may vary both due to the requirement for clinical familiarity and the estimation of the mortality risk of any given patient, it seems much appropriate to make use of ASA score and ACCI in lieu of these (21). We have observed in our study that the Framingham risk scores which predict the cardiovascular mortality over a period of 10 years is much more successful in the prediction of the first 90 days mortality, PFS and OS when compared with ASA, ECOG, ACCI, RFI and POSPOM. Hence, we consider that Framingham risk score which is much more practical method of calculation in comparison with the ACCI, NYHA and CCS angina pectoris classification, is much easier to use in the analysis to be made to predict the survival after cystectomy.

Out of the other mortality indices for survival after cystectomy in the literature are the Elixhauser index, Lee mortality index and Adult Comorbidity Evaluation-27 which all are more popular. (4,12,15). However, none of such indices has superiority over ACCI, ECOG and ASA in view of easiness in the application and high prediction rates (4). Although we have found out that ACCI, ECOG and ASA predicted the first 90 days mortality, PFS and OS in the univariate analysis in a meaningful manner, the ECOG score has predicted the PFS and ASA score has predicted the OS in a meaningful manner in the multi variate analysis.

In the literature, it has been reported that decreased preoperative eGFR values negatively affect GS in renal cell carcinoma by increasing cancer-specific survival (CSS), recurrence-free survival and cardiovascular risk (22,23). Matsumoto et al. (24) has reported that there observed a distinct decrease in eGFR levels subsequent to radical cystectomy, in case the eGFR value is <45 mL/min/1.73 m^2 the PFS and CSS decreases significantly. In the multivariate analysis, we observed that preoperatively decreased eGFR levels (<74.10 mL /min/1.73 m^2) decreased PFS by 4.73 times and OS by 4.10 times after cystectomy. In

Table 3C. Predictive factors for general survival in the long-term follow-up subsequent to radical cystectomy								
	Uni variate model				Multi variate model			
General survival	HR	95% CI		p	HR	95% CI		p
		Lower	Upper			Lower	Upper	
Age	1.064	0.973	1.164	0.171	-	-	-	-
Gender (male)	2.074	0.278	15.384	0.477	-	-	-	-
BMI	1.048	0.942	1.166	0.389	-	-	-	-
Smoking history	1.655	0.729	13.759	0.227	-	-	-	-
Atypical variance	1.408	0.576	3.440	0.453	-	-	-	-
Cystectomy pathology (T3-4)	1.079	0.466	2.498	0.039*	-	-	-	-
Cystectomy pathology (TCC/nonTCC)	3.802	1.226	11.764	0.021*	4.901	1.345	17.857	0.016*
Upstaging	1.862	0.813	4.267	0.042*	-	-	-	-
Down staging	1.463	0.495	4.328	0.491	-	-	-	-
CIS presence	1.754	0.742	4.148	0.201	-	-	-	-
Positive surgical margin	1.494	0.587	3.803	0.403	-	-	-	-
Positive lymph node	2.787	1.212	6.407	0.016*	2.671	1.147	6.220	0.001*
Lymph vascular invasion	2.727	1.067	6.971	0.036*	-	-	-	-
Preoperative hydronephrosis	2.109	0.889	5.006	0.031*	-	-	-	-
Neo-adjuvant chemotherapy	2.258	0.511	3.002	0.123	-	-	-	-
Adjuvant chemotherapy	1.500	0.614	3.664	0.374	-	-	-	-
eGFR <74.10	4.102	1.865	13.888	0.001*	3.264	1.445	9.603	0.017*
ACCI >5.5	2.630	1.131	6.116	0.025*	-	-	-	-
ECOG >2	2.555	1.685	3.531	0.029*	-	-	-	-
ASA >2	2.810	0.796	4.118	0.007*	2.789	1.572	4.512	0.024*
POSPOM >25.5	2.370	0.998	5.627	0.041*	-	-	-	-
Framingham score >14.5	5.973	2.612	16.825	<0.001*	5.973	2.612	16.825	<0.001*
RFI >5.5	2.329	0.915	5.928	0.007*	-	-	-	-
NLR >2.13	2.407	0.609	3.252	0.004*	-	-	-	-
PLR >110.36	2.631	1.425	9.253	0.007*	-	-	-	-
MLR >0.26	4.287	1.666	11.029	0.003*	-	-	-	-
Clavien-Dindo (>2)	4.592	2.005	10.516	<0.001*	5.005	1.547	16.192	0.007*

BMI: Body mass index, TCC: Transitional cell carcinoma, CIS: Carcinoma *in situ*, eGFR: Estimated glomerular filtration rate, ACCI: Age-adjusted Charlson Comorbidity index, ECOG: Eastern Cooperative Oncology Group, POSPOM: Preoperative Score to Predict Postoperative Mortality, RFI: Rockwood frailty index, NLR: Neutrophile/lymphocyte rate, PLR: Platelet/lymphocyte rate, MLR: Monocyte/lymphocyte rate, MPV: Average platelet volume, HR: Hazard ratio, CI: Confidence interval
*p<0.05 shows the statistically significant difference, Cox regression analysis

univariate analysis, preoperative eGFR <74.10 values reduce the first 90-day mortality by 2.70 times. We are in the thought that the decrease to be observed in the basal eGFR values within any longer term will have a negative impact both in view of the renal function and the cardiovascular risks as supported by such findings.

Recently, there observed an increase in the number of studies examining the effects of the serum hemogram parameters and inflammatory determinants on the oncologic results as far as the cancers of genitourinary system are concerned (25). During tumor proliferation, it is considered that there observed an increase in the rate of neutrophile due to the effects of the inflammatory cytokines primarily the interleukin -6 and the granulocyte colony stimulating factors (26). Decrease in the lymphocytes as a consequence of the reactions against the inflammatory cases and increase in the tumor related macrophages derived from the monocyte in circulation have been envisaged. The tumor related macrophages expedite the tumor progression (26). As per these assumptions, we may conclude that NLR and MLR may increase for the individuals with surplus of tumor progression.

The high NLR (≥2.7) levels measured prior to the radical cystectomy are found to be in the relation with both the progressed pathological tumor stages and the decreased CSS and OS (27). Another study showed that the high NLR (>4.33), preoperative hydronephrosis and preoperative tumor stages are in relation with upstaging of T3 stage of the disease after the cystectomy (28). In different studies, low lymphocyte/monocyte ratio (<2.44) and high PLR (> 111) values have been reported to predict decreased CSS and OS after cystectomy (29). Despite all these facts, according to Schulz et al. (30), the low PLR (≤28) values are in relation with the progressed

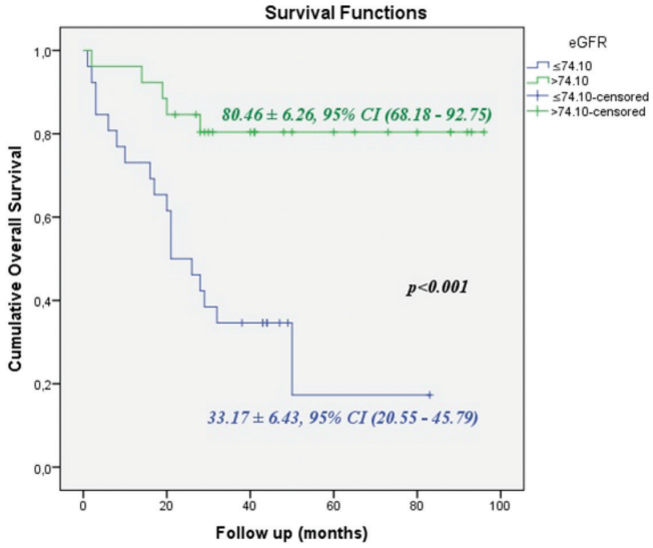

Figure 3. Graphics for Kaplan-Meier analysis showing the estimated durations of overall survival based on the eGFR values

CI: Confidence interval, eGFR: predictive glomerular filtration rate

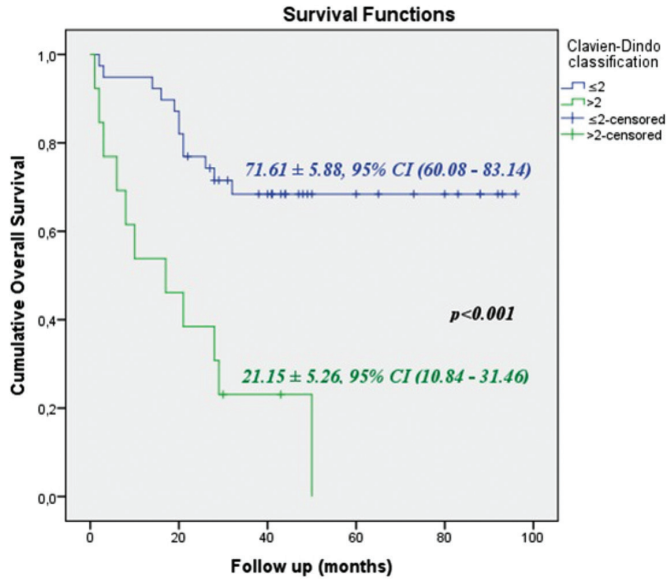

Figure 5. Graphics for Kaplan-Meier analysis showing the estimated durations of overall survival based on the Clavien-Dindo classification

CI: Confidence interval

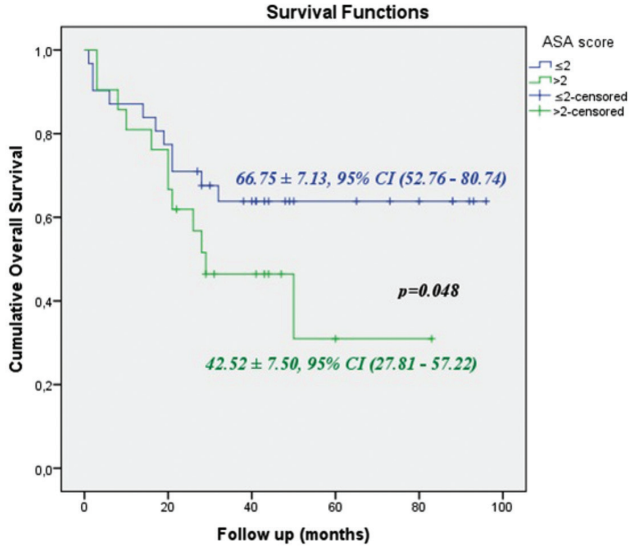

Figure 4. Graphics for Kaplan-Meier analysis showing the estimated durations of overall survival based on the ASA scores

CI: Confidence interval, ASA: American Society of Anesthesiologists

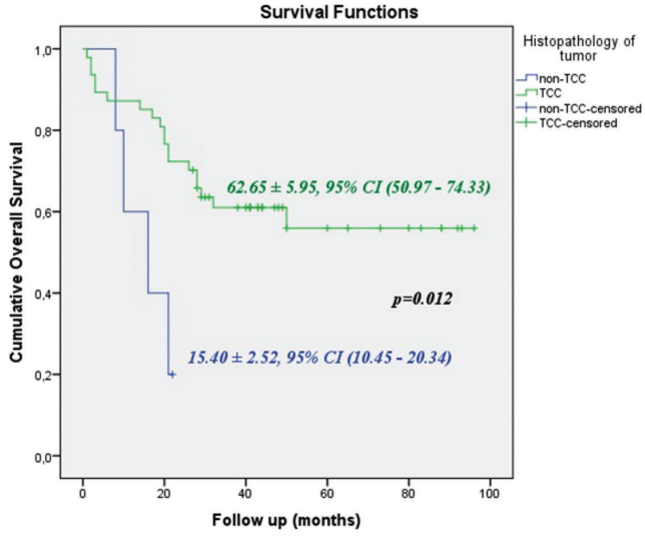

Figure 6. Graphics for Kaplan - Meier analysis showing the estimated durations of overall survival based on the tumor histology

CI: Confidence interval, TCC: Transitional cell carcinoma

tumor stages and decreased survival. Yoshida et al. (26) associated low perioperative LMR with shorter CSS and OS, suggesting that predictive power is better than NLR. Based on our findings, although the high NLR (>2.13), PLR (>110.36) and MLR (>0.26) levels predict the first 90 days mortality , PFS and OS significantly according to univariate analysis, high MLR increases the first 90-day mortality by 2.35 times according to multivariate analysis.

Study Limitations

The patients whose data were accessible were included in the study without a statistically significant sample size and randomization due to the restricted number of the patients. Therefore, the major restrictive elements of our study are the retrorespective design of the study limited number of patients involved, short follow-up period and follow-up results belong to a single center without non-randomization. The patents underwent operation by the same surgeon and the same techniques to reduce the effects of the distinctive surgical experience on the outcomes attained. However, over the 4-years period of the study, the same primary surgeon executed cystectomy operation at an annual average rate of 16.25. If we consider that an annual number of 20-25 operations are executed at the high-volume centers, the low volume of cases in

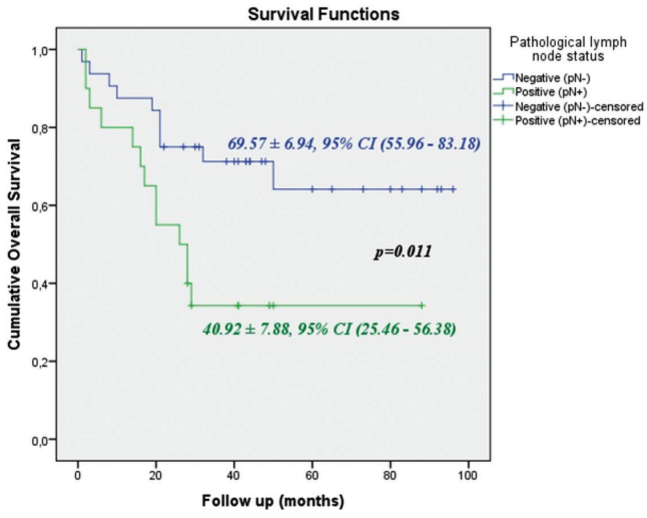

Figure 7. Graphics for Kaplan-Meier analysis showing the estimated durations of overall survival based on the status of the pathologic lymph node

our study may be deemed to be another restrictive factor which may have an impact on the results. In addition, since neoadjuvant or adjuvant chemotherapy was not applied in all cases of muscle invasion bladder cancer, we are in the thought that the heterogeneous tumor characteristics observed on the patients involved in our study might have caused a restrictive effect on the results of the survival. Nevertheless, the patients on whom no extended lymph node dissection was carried out, we have made every effort to make an assessment about the standardized group of patients as part of the surgical method applied.

Conclusions

Many of the studies evaluating the survival after cystectomy in the literature, suggest that ASA and ECOG scores predict the 90 days perioperative mortality in a substantive manner while ACCI predicts five-year OS more significantly. We have found out that the age of the patients has no sole effect on the oncologic results and that Framingham score and eGFR are much more precious and easily applicable parameters for the prediction of the PFS and OS and the Framingham score and MLR are for the prediction of the first 90 days mortality. Although Clavien-Dindo classification which categorizes the complications within the preoperative period, is one of the parameters that can not be applicable preoperatively, we are in the thought that it is particular importance in view of the postoperative follow up and treatment management due to the fact that is substantially predicts the first 90 days mortality, PFS and OS.

Nevertheless, in order to generalize our findings, we believe that long-term, prospective, multicentre, validated clinical studies are required, which include different risk classifications that predict perioperative - postoperative morbidity and mortality.

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Ethics

Ethics Committee Approval: Due to the fact that this study is a retrospective, ethical committee approval was not obtained.

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Original Article

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The Relationship Between the Risk of Prostate Cancer and Second to Fourth Digit Ratio

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Abstract

Objective: The second to fourth digit ratio is inversely related to prenatal androgen exposure, which may be a risk factor for several androgen-dependent diseases. One of these diseases is prostate cancer (PCa). Genes that play a role in the development of the fingers also play a role in the etiology of PCa. In this study, we aimed to evaluate whether there is a relationship between digit ratio and PCa.

Materials and Methods: The files of 45 patients diagnosed with PCa between 2016-2019 were reviewed retrospectively. Patients were called and invited to the hospital for digit measurement. Age-matched, 45 patients who were admitted to the outpatient clinic due to renal stones or renal cysts were included as a control group. Finger lengths were measured by the distance from the proximal crease to the tip, two times by a single observer, using a digital caliper, and the averages were recorded. Second to fourth digit ratios were calculated separately for right and left hand, and the groups were compared for variables.

Results: The mean age of patients with PCa was 62.9±7.2 years, and the mean age of control group was 64.3±7.3 years. The mean PSA level was 8.27±3.3 ng/mL and 1.39±0.63 ng/dL in study and control group, respectively. The mean digit ratios for right and left hand were 0.96±0.03, 0,99±0.03 ($p<0.001$) and 0.95±0.03, 0.98±0.03 ($p=0.003$) for study and control groups, respectively.

Conclusion: Men with PCa have a lower second to fourth digit ratio than healthy individuals. Therefore, the second to fourth digit ratio, which is indicative of prenatal androgen exposure, can be used as a marker of PCa risk.

Keywords: Androgens, digit ratio, prostate cancer

Introduction

Prostate cancer (PCa) is the most common malignancy in men (1). Although the etiology is not known, age, family history, ethnicity, and androgen exposure are known to pose a risk for the development of PCa (2). On the other hand, there are several markers indicating prenatal androgen exposure. One of these is the 2nd to 4th digit ratio (2D:4D). Low 2D:4D ratio indicates high prenatal androgenic exposure (3). Intrauterine hormones have a direct effect on the differentiation of fingers. There are studies showing a significant difference between female and male finger ratios (4,5). Furthermore, studies have shown that men and women with congenital adrenal hyperplasia have a shorter digit ratio than controls (6,7). Some of the genes that determine the ratio of fingers also play a role in carcinogenesis (8). In this context, the 2D:4D finger ratio has been associated with cancers such as gastric (8) and breast cancer (9), especially PCa (10,11). Therefore, if the 2D:4D finger ratio is associated with the activation of these genes, it may act as a marker in carcinogenic events. Some studies have reported that a low 2D:4D ratio, in other words, high prenatal androgenic exposure, is associated with an increased risk of PCa (10,11), and some have further reported that it is associated with the severity of PCa (12). The relationship between PCa and the 2D:4D digit ratio is mainly due to the simultaneous activation of genes such as *androgen receptor (AR)* genes and *Homeobox (HOX)*, involved in finger ratio and PCa development (10). Also, early hormonal exposure plays a role in the etiology of many cancers (13). Among these, PCa is also important because it is hormone-dependent (14). The natural course of PCa is challenging to predict. Some have an asymptomatic course, while others may be aggressive. Better classification of patients will help us in terms of disease management. The researchers suggest that the 2D:4D finger ratio can be used as

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a marker in diseases associated with early androgenic exposure (15).

Therefore, this study aimed to investigate whether there is a relationship between 2D:4D digit ratio and PCa.

Materials and Methods

This case-control study was approved by Fatih Sultan Mehmet Training and Research Hospital Ethics Committee (decision no: FSM EAH-KAEK 2019/95), and each patient included in the study signed informed consent form. Patients who admitted to our urology outpatient clinic between 2016 and 2019 and had a diagnosis of PCa were included in the study. The cases were called and invited to the hospital for digit measurements. Patients with metastatic PCa, hormonal disorders, history of fractures on the fingers, or who underwent hormonal therapy were excluded from the study. Age-matched patients who were admitted to the outpatient clinic due to renal stones or renal cysts and had a PSA level ≤2.5 ng/mL were included as a control group. There were 45 patients in each group. Finger lengths were measured by the distance from the proximal crease to the tip two times by a single observer using a digital caliper as in the study of Kumar et al. (16), and the averages were recorded. To calculate the 2D:4D ratio, the length of the 2nd finger was divided by the length of the 4th finger.

Statistical Analysis

IBM SPSS 22 program was used for statistical analysis. When evaluating the study data, the normality of the parameters was evaluated with the Shapiro-Wilk test. Descriptive statistics were used to describe demographic and anthropometric characteristics of the patients. The mean ± SD and median were determined for variables with normal and abnormal distribution, respectively. Studen's t-test and Mann-Whitney U test were used for the comparison of parameters with the normal and abnormal distribution. Significance was evaluated at $p<0.05$.

Results

The study was conducted with a total of 90 patients aged between 44 and 78 years. The mean age of 45 patients with PCa was 62.9±7.2 years, and the mean age of 45 age-matched control patients was 64.3±7.3 years Table 1 shows the comparison of demographic characteristics and 2D:4D ratio among Pca and control groups. There was no statistically significant difference in terms of age and prostate volume. There was no correlation between prostate volumes and digit ratios (r=-.082, p=0.44 for right 2D:4D and r=-.010, p=0.34 for left 2D:4D). The patients with PCa had significantly higher PSA levels than controls. Men with PCa had significantly lower right (R2D:4D) and left (L2D:4D) hand digit ratio than controls ($p<0.001$ and $p=0.003$), respectively.

Discussion

Evaluating the prenatal hormonal environment can be achieved by invasive procedures such as amniotic fluid sampling or fetal blood collection. Therefore, indicators of prenatal hormonal exposure, such as the 2D:4D finger ratio, can be useful in terms of diseases that may be encountered later in life. The 2D:4D finger ratio has attracted interest in the scientific world in terms of its prenatal hormonal activity and its ability to shed light on the future effects of this condition (17). Recently, the relationship between finger ratio and PCa has been investigated. Studies have shown that finger ratio may be an estimator of the presence of PCa (10,11,18). In contrast, the Melbourne Collaborative Cohort Study found no significant relationship between the risk of PCa and 2D:4D digit ratio (19). However, in patients who were diagnosed with PCa before the age of 60, a slight inverse relationship was observed between the risk of PCa and 2D:4D digit ratio in this study. Therefore, they concluded that the finger ratio might be a potential marker, especially in this age group.

The co-activation of *AR* and *HOX* genes in the development of finger and PCa has shown that the 2D:4D finger ratio is a marker linking these two conditions (10). *HOX* genes regulate the basic aspects of morphogenesis, embryogenesis, and cell differentiation and have been shown to be deregulated in a wide variety of malignancies (20,21). *AR* genes are involved in finger development, and finger four has more intense *AR* activity than finger two. Therefore, activation of the *AR* genes leads to the growth of the fourth finger, which plays a fundamental role in determining the 2D:4D finger ratio (22). It is also known that androgens affect the pathogenesis of PCa (23). Moreover, polymorphisms in the AR gene can lead to resistance to hormone therapy in PCa (24). In our study, the 2D:4D ratio was found to be significantly lower in men with PCA than in men without PCA. This finding was consistent with other studies (3,10,11,19). In our study, we evaluated the finger ratios of both hands together, and the finger ratio of both hands was statistically low in the patients with PCa.

Table 1. Comparison of demographic characteristics and 2D:4D ratio among prostate cancer and control groups

	PCa (n=45)		Control (n=45)		p
	Mean ± SD	Median (range)	Mean ± SD	Median (range)	
Age (years)[1]	62.9±7.2	65 (45-75)	64.3±7.3	65 (44-78)	0.37
PSA (ng/dL)[1]	8.27±3.3	8.2 (1.5-17)	1.39±0.63	1.34 (0.4-2.5)	<0.001*
PV (gr)[2]	45±12.46	44 (20-90)	40.7±19.18	43 (13-72)	0.55
Left 2D:4:D (mm)[2]	0.95±0.03	0.95 (0.89-1.03)	0.98±0.03	0.97 (0.90-1.05)	0.003
Right 2D:4D (mm)[2]	0.96±0.03	0.97 (0.89-1.05)	0.99±0.03	0.98 (0.92-1.07)	<0.001*

PCa: Prostate cancer, SD: Standard deviation, PSA: Prostate specific antigen, PV: Prostate volume, 2D:4D: Second to fourth digit ratio, n: Number of the patients
[1]Student's t-test [2]Mann-Whitney U-test * p<0.05

In contrast to our study, many studies have looked at only the 2D:4D ratio of the right hand (10,11,12,23), considering that the 2D:4D ratio of the right hand shows prenatal androgenic exposure better than the left hand (25). However, other studies examining the relationship between the 2D:4D ratio and cancer found significant relationships with the left hand (8,9,26). Therefore, the importance of the ratio of fingers in both hands was emphasized in these studies. As expected, patients with PCa had higher PSA values than patients without PCa. However, its effect on the digit ratio is unknown. Prostate volumes and finger ratios were not correlated. This finding may be related to the similarity of the prostate volumes of the two groups.

In our study, we could not evaluate the relationship between PCa aggressiveness and 2D:4D finger ratio due to the absence of patients with Gleason scores as high as Gleason 9,10, and the majority of patients had a Gleason score of 6. Already, there are not many studies evaluating PCa aggressiveness and 2D:4D ratio in the literature, and the results are contradictory. Waters et al. (17) found no association between Gleason score and 2D:4D digit ratio, whereas Oh et al. (27) found that individuals with a Gleason score of 9 and above had a smaller 2D:4D digit ratio. This inconsistency can be attributed to the unpredictability of natural PCa history.

Study Limitations

Firstly, testosterone levels were not predicted to make an additional contribution because the 2D:4D finger ratio was considered to be stable in adulthood. So, testosterone levels of the individuals in our study were not evaluated. Secondly, individuals were not questioned about their work or job. The work of individuals in daily life may affect the development of hands and fingers. However, it was impossible to evaluate.

Conclusions

Our study supports the hypothesis that low 2D:4D finger ratio may be a predictor of the presence of PCa. It can be concluded that increased exposure to testosterone in utero may increase the risk of PCa in later life. Further studies are needed to make the 2D:4D ratio a predictive marker for screening developing PCa risk.

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Ethics

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Concept: A.V., Design: A.V., Data Collection or Processing: T.T., Analysis or Interpretation: T.T., Literature Search: A.V., T.T., Writing: T.T.

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Original Article

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Preoperative and Postoperative Gleason Score Correlation of Patients Who Underwent Radical Prostatectomy

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Abstract

Objective: We aimed to report the consistency between transrectal needle biopsy (TRNB) Gleason scores (GSs) and prostatectomy specimen GSs based on upgrading and downgrading rates.

Materials and Methods: Data of patients who underwent open, laparoscopic or robot-assisted radical prostatectomy with the diagnosis of prostate cancer between 2006 and 2018 were retrospectively reviewed.

Results: Two hundred and fifty two patients were included in the study. The mean age of the patients was 61.9±6.1 years. The mean serum prostate-specific antigen (PSA) TRNB was 9±5.3 ng/dL. The distribution of TRNB GSs was as follows: G6 (3+3)=178, G7 (3+4)=21, G7 (4+3)=48, G8 (4+4)=1, G9 (4+5)=9. According to the final pathology result after radical prostatectomy, GSs were as follows: G6 (3+3)=141, G7 (3+4)=25, G7 (4+3)=74, G8 (4+4)=3, G9 (4+5)=8. Prostate cancer was limited to prostate in 220 patients and extracapsular spread was observed in 32 patients. There was seminal vesicle invasion in 24 patients and perineural invasion in 49 patients. When TRNB GSs and prostatectomy specimen GSs were compared, 57 (22.6%) patients were upgraded and nine (3.6%) patients had downgrading. The preoperative PSA of the patients undergoing upgrading were significantly higher than those without upgrading, 10.7+6.2 ng/dL versus 8.5+4.9 ng/dL, p=0.018. The age and body mass index of the upgrading and non-upgraded patients were similar, p=0.598 and p=0.133, respectively.

Conclusion: Upgrading in the final pathology assessment after radical prostatectomy is still an important problem for clinicians today. It may be beneficial to develop biopsy sampling techniques for accurate grading of the disease and to use radiological imaging for this purpose.

Keywords: Prostate cancer, prostate specific antigen, pathology, upgrade, downgrade

Introduction

Prostate cancer remains the most common form of cancer in men in the United States in 2018. It is also the second most common cause of cancer-related death (1). In the diagnosis of prostate cancer, digital rectal examination, serum prostate-specific antigen (PSA), and transrectal or transperineal ultrasound-guided prostate biopsy are used (2). Gleason scoring system plays a vital role in the management of prostate cancer. Gleason scoring is expressed as the sum of the primary and highest/worst grade score in samples from different anatomical regions. Conflicts between prostate biopsy and radical prostatectomy specimens remain a critical problem in clinical practice. Especially after the 2005 International Society of Urologic Pathology (ISUP) consensus, some researchers reported that the Gleason Score (GS) consistency of transrectal needle biopsy (TRNB) and biopsy and 'prostatectomy specimen pathology' increased increased. Studies conducted between 2005 and 2014 showed that the upgrading rate ranged from 22% to 47%, and the downgrading rate ranged from 5% to 21% (3).

In this study, we aimed to report the consistency between TRNB GSs and prostatectomy specimen GSs the upgrading and downgrading rates.

Materials and Methods

After the approval of our study with the decision of the local ethics committee of our hospital (2019-271), the data of patients who underwent open, laparoscopic or robot-

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assisted radical prostatectomy with the diagnosis of prostate cancer between 2006-2018 were retrospectively reviewed. The parameters analyzed included demographic data, preoperative and postoperative PSA values, TRNB and prostatectomy specimen results. All male patients aged between 40 and 75 were included in the study. Patients with malignancy other than prostate adenocarcinoma, and patients who received radiotherapy, hormonotherapy, or chemotherapy before prostatectomy were excluded from the study.

Transrectal ultrasound-guided prostate biopsy was performed by urologists experienced in the transrectal biopsy. A biopsy was taken from 12 prostate cores.

Statistical Analysis

In the statistical analysis of the data, IBM SPSS (Statistical Package for Social Sciences) was used. Continuous variables were given as mean ± standard deviation, while categorical variables were given as numbers and percentages. The normality of the data was evaluated with the Kolmogorov-Smirnov test. Student's t-test and Mann-Whitney U test were used to compare the continuous variables of the two groups, and the chi-square test was used to evaluate the categorical data. $P<0.05$ was considered statistically significant.

Results

In total, 252 patients were included in the study. The mean age of the patients was 61.9±6.1 years. The mean PSA before TRNB was 9±5.3 ng/dL. The mean body mass index (BMI) of the patients was 27±1.4 kg/m^2. The distribution of TRNB GSs was as follows: G6 (3+3)=178, G7 (3+4)=21, G7 (4+3)=48, G8 (4+4)=1, G9 (4+5)=9. According to the final pathology result after radical prostatectomy, GSs were as follows: G6 (3+3)=141, G7 (3+4)=25, G7 (4+3)=74, G8 (4+4)=3, G9 (4+5)=8 (Table 1). While prostate cancer was limited to prostate in 220 patients, extracapsular extension was observed in 32 patients. There was invasion in seminal vesicles in 24 patients and perineural invasion in 49 patients. Comparing TRNB GS and final pathology yerine prostatectomy specimen GS, 57 patients (22.6%) had upgrading and nine patients (3.6%) had downgrading. Preoperative PSA of the patients with upgrading were significantly higher than those without upgrading (10.7+6.2 ng/dL vs 8.5+4.9 ng/dL, p=0.018). The age and BMI of the patients with and without upgrading were similar (p=0.598 and p=0.133, respectively) (Table 2).

Discussion

Prostate needle biopsy is the gold-standard method in the diagnosis of prostate cancer and is one of the most common procedures in daily urology practice. It is reported that at least 800,000 prostate biopsies are performed annually in the United States (2).

The correct determination of the GS is vital for the treatment and prognostic management of the disease. In the consensus meeting held by ISUP 2005, Gleason scoring was updated to ensure that biopsy evaluations are more reliable (4).

In a study conducted by Corcoran et al. (5) in 1629 prostate cancer patients, GSs were compared in TRNB and prostatectomy pathologies, and upgrading was observed in radical prostatectomy Gleason score in 466 patients (28.6%). In multivariate analysis, GS upgrading was evaluated as a marker for biochemical recurrence after radical prostatectomy. In our current study, upgrading was observed similarly with a rate of 22.6%.

In their study, which included 286 patients undergoing robot-assisted radical prostatectomy, Henderickx et al. (6) divided patients into risk groups and reported 58.7% upgrading in the low-risk group, 30.2% upgrading in the middle-risk group, and 25% upgrading in the high-risk group. The authors emphasized that the GS was estimated lower in the pre-operative period. In a study conducted by D'Elia et al. (2) with 300 patients, the most common TRNB pathology was reported to be G6 (3+3) with 64%, while upgrading was observed in approximately 39.7% of patients. As a result of multivariate analysis, it was found that only PSA less than 4 ng/mL predicted upstaging. In our study, G6 (3+3) was the most common prostatectomy pathology, with a rate of 56%. However, in our current study, PSA of patients with upgrading were significantly higher than those without upgrading.

Table 1. Demographic and clinical features of the patients

Variable	Value
Age (year)	61.9±6.1
BMI (kg/m^2)	27±1.4
Preoperative PSA	9±5.3
TRNB Gleason score	
3+3	178 (70.6%)
3+4	21 (8.3%)
4+3	48 (19%)
4+4	1 (0.4%)
4+5	4 (1.6%)
Prostatectomy Specimen Gleason score	
3+3	141 (56%)
3+4	25 (9.9%)
4+3	74 (29.4%)
4+4	3 (1.2%)
4+5	8 (3.2%)
5+5	1 (0.4%)

BMI: Body mass index, PSA: Prostate specific antigen, TRNB: Transrectal needle biopsy

Table 2. Comparison of the patients according to changing pathological grade

Variables	Pathological upgraded group (n=57)	Pathological non-upgraded group (n=186)	p
Age (year)	62.2±6.2	61.7±6.1	0.598
BMI (kg/m^2)	26.7±1.5	27.1±1.3	0.133
Preoperative PSA	10.7±6.2	8.5±4.9	0.018

BMI: Body mass index, PSA: Prostate specific antigen

In a study by de Cobelli et al. (7) in which 311 patients who were appropriate for active surveillance and who underwent radical prostatectomy, the BMI was found to be significantly associated with upgrading, upstaging, and seminal vesicle invasion.

When the data of 10,273 patients with prostatectomy and low-risk prostate cancer recorded in the the Surveillance, Epidemiology, and Ends Results database were evaluated, it was observed that 44% of the patients had upgrading and 9.7% of them had upstaging after radical prostatectomy. In this study, the age, PSA, and positive biopsy core percentage were associated with upgrading and upstaging (8). Similarly, in our current study, PSA of patients who had upgrading were found to be significantly higher than those without upgrading. However, there was no difference in age.

In another study conducted by Maurice et al. (9), the rate of upgrading on GS 6 after radical prostatectomy was 43.3% in the disease localized to the prostate, while the rates of upgrading and upstaging of African Americans were higher than other races. Our current study was conducted in the Turkish population, and the rate of upgrading (22.6%) was significantly lower than the study mentioned.

Park et al. (10) evaluated whether patients with Gleason 7 (3+4) prostate cancer in prostate biopsy could be candidates for active surveillance. In this study, the overall upgrading rate was found to be 31.8%. While the pre-operative PSA were significantly higher in patients with upgrading, the optimal threshold PSA for predicting upgrading was 4.73 ng/mL (85.7% sensitivity, 57.8% specificity).

Some methods have been proposed to predict pathological upgrading after prostate biopsy and subsequent radical prostatectomy. Some of these are PSA density (11) and exome genotyping (12). In a study by Oh et al. (12), Rs33999879 single nucleotide polymorphism was shown to be associated with GS pathological upgrading (12). Since our current study is a retrospective study, these data could not be shared. However, they can be useful to guide future studies.

Conclusions

Upgrading in final pathology evaluation after radical prostatectomy is still an essential problem for clinicians today. It may be beneficial to develop biopsy sampling techniques for the correct grading of the disease and to use radiological imaging for this.

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Ethics

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Authorship Contributions

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

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Original Article

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Relationship Between AMACR Staining Density of Radical Prostatectomy Specimen and Biochemical Recurrence in Patients with Pathological Stage T2a-b

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Abstract

Objective: This study aimed to evaluate the relationship between Alpha-methylacyl-CoA racemase (AMACR) staining intensity of pathologic specimens and Prostate Spesific Antigen (PSA) recurrence of patients with an organ-limited disease who underwent radical prostatectomy for localized prostate cancer.

Materials and Methods: The data of 46 patients who underwent radical retropubic prostatectomy and who had prostate-limited disease without capsule invasion in the pathological evaluation were included in the study. AMACR expression was assessed by immunohistochemical staining. Expression levels were classified as negative (score=0), weak (score=1), moderate (score=2) and strong (score=3) staining. Patients with a PSA value of ≥0.2 ng/mL at postoperative follow-up were considered to have a biochemical recurrence. Patients were divided into two groups, according to biochemical recurrence. Groups were compared in terms of AMACR staining intensities of radical prostatectomy specimens.

Results: Twenty-one patients developed PSA recurrence in a mean follow-up period of 32±8 months. The remaining 25 patients were recurrence-free. The mean recurrence time was 24±5 months. According to AMACR staining scores, the biochemical recurrence rates of the patients were 33.3%, 40.7%, and 61.5% for score 1, score 2, and score 3, respectively. Although higher rates of PSA recurrence were observed in patients with more intense AMACR staining, the difference between rates was not statistically significant (p=0.38).

Conclusion: PSA recurrence rate increases with increasing AMAC-CR staining intensity. Further studies are needed to obtain statistically significant results.

Keywords: AMACR, PSA, prostate cancer

Introduction

Alpha-methylacyl-CoA racemase (AMACR) is a protein enzyme that provides beta-oxidation of branched fatty acids. The enzyme localized in mitochondria and peroxisomes is also known as P504S. Peroxisomal oxidation is a potential source of oxidative damage to the cell and causes the accumulation of carcinogenic hydrogen peroxide.

Several studies have shown increased AMACR-mRNA transcription in prostate cancer tissues (1,2). Transcript levels of the enzyme showed an average 3.75-fold increase in prostate cancer tissue when compared to BPH. AMACR was highlighted as one of the few genes explaining pathway dysregulation for prostate cancer in a gene meta-analysis (3). Pathology studies with immunohistochemical staining techniques and biochemical studies have reported similar results (4). Increased transcription of the AMACR gene and increased activity of the enzyme in cancer cells compared to benign prostate tissues suggest that the molecule can be used as a biomarker for prostate cancer. AMACR protein expression levels were first shown to be significantly associated with prostate cancer progression, and the reduced AMACR expression level was associated with

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increased biochemical recurrence and cancer-related death (5). Patients with high Gleason scores and low AMACR expression had an 18-fold higher risk of prostate cancer death.

This study aimed to evaluate the relationship between AMACR staining intensity of pathologic specimens and Prostate Spesific Antigen (PSA) recurrence of patients who underwent radical prostatectomy for the low and intermediate-risk organ-confined disease.

Materials and Methods

The data of 320 patients who underwent radical retropubic prostatectomy for localized prostate cancer in our clinic were evaluated retrospectively. The following exclusion criteria were taken into consideration;

1- Pathological stage T2c and above

2- Positive lymph node metastasis

3- Preoperative PSA >20 ng/mL

4- Biopsy Gleason Score >7 (ISUP grade group 4-5)

Forty-six patients with organ-confined disease in radical prostatectomy pathology were included in the study (pathological stage T2a and T2b). All of the patients have low and intermediate-risk prostate cancer according to the D'Amico risk classification (Gleason score 6 or 7, PSA <20 ng/mL) (6). Patients with a PSA value of ≥0.2 ng/mL at postoperative follow-up were considered to have a biochemical recurrence. Patients were divided into two groups, according to biochemical recurrence.

All hematoxylin eosin-stained sections of radical prostatectomy specimens were examined. The best samples for the tumor and the most suitable preparations for immunohistochemical examination were selected. Then the appropriate sites for immunostaining were marked. Re-sections were taken from paraffin blocks to precisely sample the marked areas. Deparaffinization and clarification were applied to the sections before immunohistochemical staining. Immunohistochemical staining was performed using Primary Antibody AMACR/P504S (Polyclonal Rabbit Antibody, P504S, Catalog Number: CP 200 AK, BK, CK) and UltraTek Anti-Rabbit (UltraTek HRP Anti-Rabbit (DAB) Staining System, Logan, Utah, USA)

We formed four groups according to staining intensity (Figure 1) (Table 1) (7). After staining, it was seen that the preparations contained areas showing different staining intensity. In order to prevent the preparations from having more than one staining score, the area with the highest staining intensity was scored for the relevant preparation. Furthermore, since all of the evaluated preparations containing areas with negative staining scores simultaneously included one of the other staining scores, no preparation received negative staining scores.

Statistical Analysis

The chi-square and Fisher's exact tests were used for the difference between the categorical variables. The Mann-Whitney U and Kruskal-Wallis tests were used for the difference between the means. For more than two groups, the ANOVA test was used. The data were analyzed with the Statistical Package for the Social Sciences v. 17 (SPSS Inc., Illinois, USA). A p value under 0.05 was considered statistically significant.

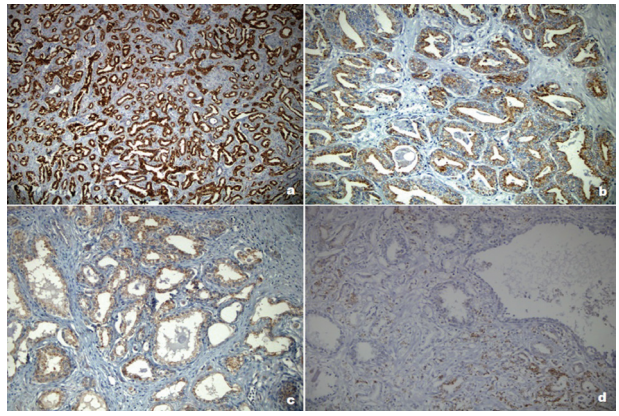

Figure 1. (a) Diffuse, strong cytoplasmic staining (AMACR X 100) in tumor tissue forming 2 abortive gland formation. (b) Disseminated, moderate cytoplasmic staining of tumor tissue 3 forming the abortive gland formation (AMACR X 200). (c) Weak cytoplasmic staining of 4 tumor tissue forming the abortive gland formation (AMACR X 200). (d) Negative staining of 5 tumor tissue forming abortive gland formation and weak cytoplasmic staining in the right 6 lower part (AMACR X 100).

Table 1. Staining classification of samples

Score	AMACR staining
0	Negative staining
1	Weak cytoplasmic staining
2	Disseminated, moderate cytoplasmic staining
3	Diffuse, strong cytoplasmic staining

AMACR: Alpha-methylacyl-CoA racemase

Results

The mean age of 46 patients was 65.23±6.36 years. The mean preoperative serum PSA level was 8.96±6.78 ng/mL, the mean number of positive biopsy quadrants was 2.60±1.74, the mean tumor percentage was 13.04±15.10, and the prostate volume was 49.89±19.94 cc. The mean follow-up period was 32±8 (3-61) months. The mean recurrence time was 24±5 (3-59) in patients with PSA recurrence.

Twenty-one patients with PSA recurrence and 25 patients without recurrence were compared for preoperative and pathological data. The two groups were similar in terms of age, preoperative serum PSA levels, biopsy Gleason scores, positive number of biopsy quadrants, percentile of tumors, and prostate volume (p=0.3, p=0.8, p=0.32, p=0.98, p=0.47, p=0.4 respectively, Table 2).

Biochemical recurrence after radical prostatectomy was observed in 33.3% (2/6), 40.7% (11/27), and 61.5% (8/13) of patients with AMACR staining intensity score 1, 2 and 3, respectively. As the immunohistochemical staining intensity increased with AMACR, the rate of PSA recurrence increased. However, there was no statistically significant difference between the groups in terms of biochemical recurrence rates (p=0.377) (Table 3).

The relationship between Gleason score, the percentile of tumors, and AMACR immunohistochemical staining intensity were investigated in radical prostatectomy material. There was no statistically significant relationship between Gleason score

Table 2. Comparison of clinical features of patients with and without PSA recurrence			
Means of characteristic	**PSA recurrence +**	**PSA recurrence -**	**p***
Age (years)	64.23±6.51	66.08±6.23	0.31
Preoperative PSA (ng/mL)	9.26±7.33	8.68±6.43	0.84
Biopsy Gleason scores	6.16±0.37	6.33±0.48	0.32
Number of positive TRUS-Bx sample	2.65±1.93	2.56±1.60	0.98
Percantile of tumor (%)	13.43±16.92	13.10±13.75	0.47
Prostate volume (%)	59.28±22.15	47.2±17.89	0.40
PSA: Prostate Spesific Antigen, TRUS: Transrectal ultrasound *Mann-Whitney U tests			

Table 3. Relationship between AMACR staining score and PSA recurrence				
Scores	**PSA recurrence +**	**PSA recurrence -**	**p**	**Biopsy Gleason score**
1	2 (33.3%)	4 (66.7%)	-	6.17±0.41
2	11 (40.7%)	16 (59.3%)	0.38*	6.33±0.48
3	8 (61.5%)	5 (38.5%)	-	6.08±0.28
p	-	-	-	0.19[α]
AMACR: Alpha-methylacyl-CoA racemase, PSA: Prostate Spesific Antigen *Chi-square test, [α]ANOVA test				

and AMACR staining intensity (p=0.568). Tumor percentages in prostatectomy specimens of patients with AMACR staining intensity score 1, score 2, and score 3 were 14.16±13.68%, 13.37±16.60% and 11.82±13%, respectively. It was found that the percentage of tumors decreased in the specimens as staining score increased. However, the difference between the groups was not statistically significant (p=0.97).

Discussion

Rubin et al. (7) have reported no significant relationship between AMACR protein expression and pathological parameters such as radical prostatectomy Gleason score, tumor stage, tumor percentage, and surgical margin positivity. Also, AMACR expression level was not associated with recurrence of PSA following surgery at a mean follow-up of 3 years in a series of 120 patients. In our study, it was found that PSA recurrence rates increased with increasing AMACR expression levels. However, there was no statistically significant difference between the groups. AMACR protein expression was evaluated in two localized prostate cancer groups of 204 patients treated with radical prostatectomy, and 188 patients followed with watchful-waiting in another study conducted by Rubin et al. (5). The development of PSA recurrence in the surgical group and cancer-related death in the follow-up group were considered endpoints, and the AMACR staining intensity was evaluated both manually and using a computer-assisted program. In the surgery-treated group, no significant correlation was found between the AMACR expression score and PSA recurrence, as was the case in previous studies. Small differences in clinical character were observed when comparing low and high AMACR expression in computer-assisted evaluation. In contrast, those with low AMACR expression were found to develop twice as much PSA recurrence during follow-up as compared to those with high expression. The cut-off value of AMACR intensity was 1.11 SD in the surgery group and 0.18 SD in the follow-up group. PSA recurrence was found in 37.5% of the patients below this cut-off value in the surgery group. This rate was found to be 14.5% in patients above that value. Patients with lower AMACR expression have a significantly higher risk of developing PSA recurrence. Three-fold more cancer-related deaths were observed in those with AMACR expression below the cut-off value in the follow-up group. Patients with low AMACR expression and high Gleason scores are reported to have a 4-fold increased risk of PSA recurrence and an 18-fold higher risk of cancer-related death.

Intense AMACR staining was reported in untreated metastatic and hormone-resistant prostate cancer cases in a study by Luo et al. (8). The author emphasized that combined staining for p63 and AMACR facilitates the detection of cancer cells in both biopsy and surgical specimens. Studies with the triple stain antibody cocktail obtained by adding high-molecular-weight keratin to these two antibodies are also available in the literature (9). The results of studies using PCR-based detection of AMACR are similar to the results obtained by immunohistochemical staining techniques and provide data that potentiate these results (10). AMACR-mRNA transcription in malignant prostate tissue has been shown to increase several-fold. Kumar-Sinha et al. (10) also reported increased AMACR enzymatic activity in prostate cancer tissues compared to benign prostate tissue.

Molinié et al. (11) emphasize that AMACR staining efficacy may be particularly prominent in suspicious biopsy sites smaller than 1 mm. Diagnosis for atypical small acinar proliferation may become easier with AMACR (12).

In recent trials, AMACR has been the subject of studies to detect prostate cancer by molecular imaging. There are positive results in the literature that molecular imaging is possible using the transcriptional specificity of the AMACR promoter (13). Gene fusions are thought to play a critical role in the development and progression of prostate cancer. Yang et al. (13) found the SLC45A2-AMACR fusion gene in their current study (14). From

understanding the genetic basis of prostate cancer to easier diagnosis, AMACR is often included basic researches a promising protein. It was shown that patients with biopsy-proven prostate cancer had higher semen AMACR levels than the control group in a study in which semen AMACR levels were measured using the indirect sandwich ELISA chemiluminescence assay (15). Also, AMACR can be used mainly in the treatment of castration-resistant prostate cancer (16).

In our study, there was no significant relationship between AMACR protein expression and PSA recurrence. Unlike Rubin et al. (7), there were no patients with very low or very high Gleason scores in our series (Gleason 5 or 8-9). Also, in our study, no patients were showing surgical margin positivity and extracapsular extension, while patients with these characteristics were present in the mentioned study. In summary, the results of the recent study determined by the patients with both clinically and pathologically localized prostate cancer who were more challenging to predict the development of PSA recurrence. Also, Rubin's study evaluated the AMACR expression intensity both manually and using a computer-assisted program, and indicated that computer-assisted evaluation was more reliable (7).

Study Limitations

There are some limitations to this study. First of all, direct visual evaluations mentioned in the paragraph above were the main limitation of our study. We designed our study in light of the studies of Rubin et al. (5) and Barry et al. (16). High-risk patients, who may have micrometastasis that could not be detected at the time of operation, were excluded. Thus, the series was homogenized. Finally, 46 of the 92 patients with appropriate specimens for AMACR staining were included in the study. This limitation affecting the patient distribution of the groups may have been determinant in the results of the study.

Conclusions

The PSA recurrence rate increases with increasing AMACR staining intensity. However, no statistically significant relationship was found between the AMACR staining intensity of pathology specimens and postoperative biochemical recurrence (PSA recurrence) in patients undergoing radical prostatectomy for localized prostate cancer. Also, no statistically significant relationship was found between RRP Gleason score, tumor percentile, and AMACR staining intensity, which are essential prognostic parameters for prostate cancer. Further studies are needed to obtain statistically significant results.

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Ethics

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Authorship Contributions

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

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Case Report
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The Role of Adrenal Cortex-Sparing Surgery for Bilateral Masses in Three Cases

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Abstract

Pheochromocytoma are the functional adrenal lesions originating from the chromaffin cells. For the cases of pheochromocytoma observed in multiple endocrine neoplasia Type 2 and Von Hippel syndrome, the bilateral adrenal glands are involved. In classical approach, total adrenalectomy is applicable on such masses while adrenal failure is almost inevitable. Lifelong cortisol and fludrocortisones replacement are necessary for the patients with adrenal failure while the rate of morbidity and mortality has significantly increased. With the introduction of the minimal invasive surgical approach, cortex sparing adrenalectomy has been brought forward for the adrenal tumors. The primary objective of the cortex sparing surgery is to prevent the lifelong replacement and the permanent adrenal failure after adrenalectomy. Therefore, it is particularly preferred in the case of genetic pheochromocytoma with bilateral adrenal involvement. However, in the case of the selected cases, it can also be applicable for adenoma producing aldostrerone and Cushing syndrome. The adrenal tumor will be completely removed and if sufficient tissue is reserved in the manner to preserve the cortex function, no long-term recurrence and adrenal failure is to be developed. Therefore, cortex-sparing surgery may be a good alternative to total adrenalectomy for the patients with small benign functional adrenal tumors or bilateral genetic pheochromocytoma.

Keywords: Pheochromocytoma, MEN 2A, VHL syndrome, partial adrenalectomy

Introduction

Pheochromocytoma are the neuroendocrine tumors originated from chromaffin cells of the adrenal gland. Multiple endocrine neoplasm type 2 (MEN 2), Von Hippel Lindau (VHL) and Von Recklinghausen (neurofibromatosis type 1) syndromes are the genetic diseases associated with the pheochromocytoma. Pheochromocytoma observed with such syndromes frequently retain the bilateral adrenal glands. The classical approach to adrenal masses is total adrenalectomy. However, in the case of bilateral adrenal involvement, the occurrence of adrenal failure is inevitable subsequent to adrenalectomy and lifelong cortisol replacement is a must. Despite the appropriate replacement of the hormones, mortality risks increase due to Addison crisis. Partial adrenalectomy option has been brought forward to preserve the functions of the adrenal cortex as a consequence in the development of the minimal invasive surgical interventions. Different terminology is applied for non-total adrenalectomy in the manner to include "sub-total adrenalectomy", "cortex sparing adrenalectomy", "partial adrenalectomy" or "adrenal sparing adrenalectomy" in the literature (2). Laparoscopic cortex sparing surgery for bilateral adrenal tumors is a recently introduced technique and it provides advantages to the patients that no adrenal failure is developed and no hormone replacement is deemed to be necessary. The widely used indications for this particular procedure are the syndromic diseases where the bilateral adrenal glands are impacted such as MEN 2A and 2B, VHL, Neurofibromatosis (3).

In this study, we aimed to summarize the role of bilateral adrenal cortex sparing surgery which is a recently introduced technique in the light of 3 cases.

Case 1

Male patient aged 39 years who was examined for hypertension attack was diagnosed with pheochromocytoma in 2012. The dynamic magnetic resonance (MR) imaging through adrenal protocol revealed bilateral non-adenoma lesions with limited diffusion. These lesions were described as 11 mm on the right adrenal body, 15 mm on the lateral adrenal crus, and 14 mm on the left adrenal. On the other hand, thyroid ultrasonography showed nodules with a size of 10x6 mm in the right lobe and a size 9x8 mm in the left lobe. The fine needle aspiration biopsy of these thyroid nodules revealed medullar carcinoma. The patient was diagnosed as MEN2A based on these findings. No parathyroid adenoma was found. In the genetic examination

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Cys634Arg heterozygote mutation was determined and genetic consultation was suggested for the first degree relatives. Left partial adrenalectomy and right total adrenalectomy were performed and the bilateral adrenal veins were resected. The postoperative urinary catecholamines were found normal. The postoperative urinary catecholamine was found to be normal. Also, the patient underwent total thyroidectomy and bilateral neck dissection by general surgeons. The pathology reported bilateral thyroid medullar carcinoma. The patient has been followed up for 72 months without the need for cortisol and fludrocortisone replacement. Patient was normotensive while the annual catecholamine levels were found to be normal. Levothyroxine replacement was given and the follow up continues for thyroid medullar carcinoma.

Case 2

A female patient, aged 43, was diagnosed with hypertension three years ago. She was under follow up at the cardiology clinic for persistent hypertension where carvedilol benidipine, spirinolactone + hydrochlorothiazide treatments were given. Upon being understood that her brother had MEN2A diagnosis, the upper abdomen computerized tomography (CT) was performed. CT revealed that bilateral adrenal lesions on the left and right adrenal glands, dimensioned as 57x53 mm and 16x10 mm, respectively. In her medical history, it was found out that she underwent parathyroid adenoma operation with total thyroidectomy in 2006. The pathologies were inaccessible. The calcitonin levels was found to be 80.6 pg/mL which was asked for the potentiality of the medullar thyroid carcinoma. No pathologic finding was determined in cervix ultrasonography. Cys634Arg heterozygote mutation was detected in the genetic examination asked for the RET proto-oncogene. 24-hour urinary catecholamines were found high. I-123 MIBG and SPECT-CT were performed with the diagnosis of bilateral pheochromocytomas. MIBG positive lesions were detected in 60 mm diameter lesion located on the left adrenal gland and 30 mm lesion on the right adrenal gland. Upon completion of the anesthesia preparations in an appropriate manner, laparoscopic left adrenalectomy was performed in the first operation and partial adrenalectomy was carried out in the second operation. The patient who has been under control postoperatively for 4 months, has been followed up without the use of the anti-hypertensive and with no need for cortisol.

Case 3

Forty-two year old man admitted to hospital with epigastric pain. Lower abdominal MR revealed 19x17 mm , oval, hyperintense lesion at segment-2 of the liver, non-adenoma lesions dimensioned to be 97x73x62 mm on the right adrenal, 21x19 mm on the left adrenal crus, 24x23 mm cortical cysts on the right kidney (Figure 1A). As a consequence of the endocrine assessments, the patient whose 24h urinary catecholamine was responsive for pheochromocytoma, underwent partial nephrectomy and total adrenalectomy for the right side subsequent to anesthesia preparation conducted in an appropriate manner. The pathology reported clear renal cell carcinoma, while the adrenal pathology revealed hyalinization and myxoid changes in stroma and the findings not encountered in sporadic pheochromocytoma such as the capsule with vascularized thick wall and local oval shaped nucleus cell. After the first operation, the patient with high catecholamine values underwent partial adrenalectomy with preserving the left adrenal vein within 6 months subsequent to the first operation. The limits of the mass was defined through ultrasonography in laparoscopic transperitoneal approach (Figure 2). After applying indo cyanine green injection, the mass and the adrenal tissues were disentangled. The mass was excised leaving aside some sound adrenal tissue (Figure 3). The postoperative MR showed no adrenal gland on the right side but excised mass on the left adrenal and the presence of adrenal tissues (Figure 1B). The urinary catecholamine of the patient after eleven months was normal and the patient has been followed up with no need for cortisol.

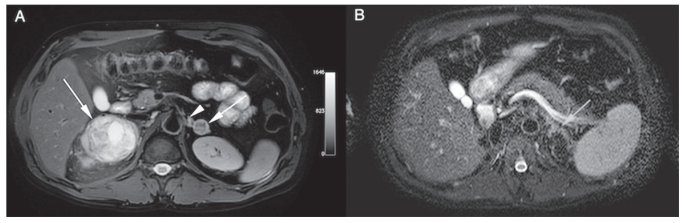

Figure 1A. Magnetic resonance image of the postoperative bilateral adrenal mass. **B.** Postoperative magnetic resonance image

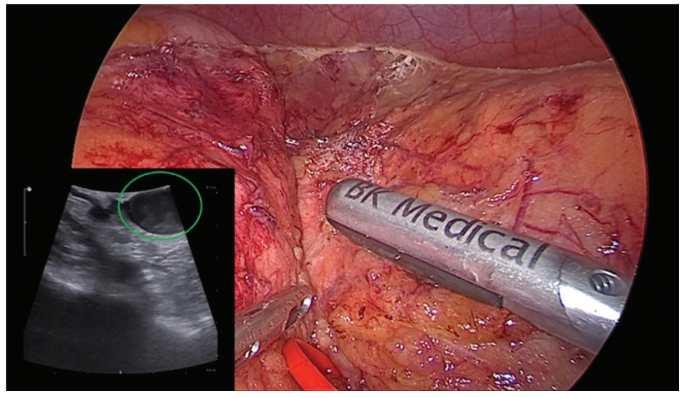

Figure 2. Determination of the borders of the mass through intraoperative ultrasonography during partial adrenalectomy for the left adrenal

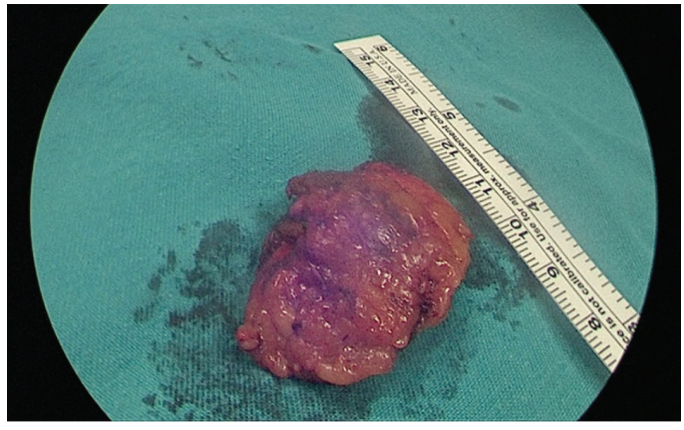

Figure 3. Specimen taken subsequent to partial adrenalectomy for the left adrenal

Discussion

Laparoscopic transperitoneal adrenalectomy was defined by Gagner et al. in (4). It is the golden standard procedure for adrenalectomy due to its high rate of achievement and low morbidity advantages. Optically increased tumor imaging, decreased pain and recovery time, short hospitalization time and improved cosmetic results are the advantages of laparoscopic adrenalectomy. On the contrary, laparoscopic technique disposes the tactile sensing used traditionally by the surgeon for the purpose of distinguishing the boundaries of the mass and defining the vascular structures. For the syndromic diseases with bilateral adrenal gland involvement, in case bilateral total adrenalectomy is applicable through classical approach, development of adrenal failure is inevitable. The probability of the additional surgeries is higher for such syndromes due to the components other than the pheochromocytoma and the protection of the endogenous corticosteroid sources is of particular importance. Therefore, partial adrenalectomy is the appropriate option for these patients. Although the indications of the cortex sparing surgery have not yet been clearly defined, the widely accepted indication is the bilateral pheochromocytoma due to the hereditary diseases. Cortex sparing or partial adrenalectomy may be applicable through open surgery, transperitoneal laparoscopic or retroperitoneal methods (5). The points which should must be taken into consideration in cortex sparing adrenalectomy are full excision of the adrenal mass and leaving off the tissue sufficient to preserve the cortex functionality. It has been reported in the contents of the study by Casinetti et al. (6) that although almost all of the patients who underwent bilateral adrenalectomy were in need of cortisol replacement, 57% of the patients who underwent cortex sparing surgery did not require any cortisol. The primary question about the cortex sparing surgery for bilateral pheochromocytoma is the risk of recurrence due to the fact that the resection of the medullar tissues cannot always be verified in a definite manner. The risk of recurrence for hereditary bilateral pheochromocytoma is higher than sporadic pheochromocytoma. One of the studies evidenced that the rate of recurrence for the patients with hereditary pheochromocytoma is 20% and the rate of patients who require steroid replacement is 8% (7). A study by Kaye et al. (8) revealed that when 22 series which include 417 patients are examined, 76% of the applicable procedure is laparoscopic, only 3% of the patients showed recurrent lesions by the end of the 56 months follow up period and 5.3% of the patients required steroid in the long term. When the study related to the data concerning 563 patients who underwent partial adrenalectomy upon being diagnosed with pheochromocytoma based on MEN 2 syndrome, 3% of the adrenal glands on which cortex sparing adrenalectomy was applied showed recurrence, while 2% of the glands with total adrenalectomy showed recurrence. The difference was not significant. It has been found out that the average recurrence period subsequent to cortex sparing surgery is 9.5 years. In the previous studies, the rate of recurrence subsequent to cortex sparing surgery was 21%, while the rates of recurrence after laparoscopic adrenalectomy are less than 5% (6). In a prospective study concerning 6 patients with bilateral adrenal involvement, retroperitoneal cortex sparing surgery was applied. After a follow up period of 26±6 months, none of the patients have developed any recurrence and 5 of the patients (83%) required any cortisol (9). Laparoscopic cortex sparing adrenalectomy was applicable in 3 of our cases and none of the cases developed recurrent pheochromocytoma.

One of the syndromes for which cortex sparing surgery may be applicable is the VHL syndrome. VHL syndrome is autosomal dominant hereditary disease and encountered at a rate of 1:36.000. Out of the widely encountered tumors accompanying to the VHL disease are the central nervous system hemangioblastoma, clear cell renal carcinoma, pancreas neuroendocrine tumor, tympanum endolymphatic sac tumors and pancreas cysts (10). The rate of bilateral adrenal involvement for the VHL patients varies between 40% and 80%. Even though there may be clinically unilateral involvement by the time of diagnosis in MEN 2 or VHL syndromes, unilateral cortex-sparing surgery is recommended since the risk of involvement of the other adrenal gland is too high (11).

The other group of disease for which cortex sparing surgery is recommended is the Conn syndrome. The study examining the prospective results of the total and partial adrenalectomy on 212 patients suffering Conn syndrome with unilateral adenoma evidence that the serum aldosterone results of all of the patients are normalized subsequent to unilateral partial or total adrenalectomy and no substantial difference has been observed between the two approaches in view of the number of patients which should have antihypertensive treatment (12). Unilateral cortex sparing surgery is the preferred method for Conn syndrome based on the fact that no adrenal failure develops in the case of occurrence of any subsequent influential disease. It is also due to the benignity of the aldosterone secreting adenoma, anatomical responsiveness for cortex sparing surgery and similar rate of treatment wise achievement of both cortex sparing surgery and total adrenalectomy.

Partial adrenalectomy may also be applicable for Cushing syndrome. The study conducted by He et al. (13), 87 patients who underwent partial adrenalectomy showed a treatment success at a rate of 97.8%. During partial adrenalectomy for the patients with Cushing syndrome, the surrounding adipose tissue should be removed for the clear detection of the adenoma limits, distinction of the normal tissues in an absolute manner and resection of adenoma to give way to a minimum 5 mm normal tissue particles (14). However, partial adrenalectomy may technically be difficult for the patients with Cushing syndrome due to the excessive retroperitoneal and the adipose tissues in the vicinity of the adrenal gland. Intraoperative ultrasonography may apply in cases where it is difficult to distinguish the boundaries of the normal tissue with the adrenal mass.

It is considered that adrenal vein should be preserved in the course of the adrenal cortex sparing surgery theoretically, while it is not a requisite to preserve the adrenal vein for the purpose of the sufficient postoperative cortical functioning. The other problem is that the minimum amount of adrenal tissue necessary for normal physiology is still not known. Brauckhoff et al. (15) have reviewed 10 patients who underwent subtotal adrenalectomy where less than one third of the adrenal gland was preserved with the transection of the main adrenal vein.

To verify the adrenal functioning during postoperative period, they have made adrenocorticotropic hormone test and they have concluded that venous drainage through the main vein is not critical for adrenocortical functions and that an estimated quantity of one third of the adrenal tissue is sufficient for adrenal functioning. The anatomic study to document the adrenal blood feeding regarding the laparoscopic partial adrenalectomy showed the numerous small veins around the adrenal gland and it is suggested that no aggressive adrenal gland mobilization should be made in order not to destruct the venous small veins (16). Meanwhile, if not adjacent to the tumor, it is recommended to keep the main venous drainage intact. In addition, the collagen tissues remaining around the adrenal tissue should be kept safe to prevent likely torsion and preserve the arterial feeding. After the cortex sparing surgery, minimum 1/3 of the unimpaired cortex tissue should be preserved for the continuance of the usual cortical functions. We have also executed partial adrenalectomy in 2 of our cases including a patient who is under follow-up for 72 months, with no preservation of the adrenal vein. and no pathology has been observed in the functions of the adrenal gland.

For the purpose of successful laparoscopic adrenalectomy, the proper definition of the anatomy is an important step. Right adrenal vein is short and connected to the inferior vena cava vein directly, while left adrenal vein is longer and discharges to the renal vein. The detection of the adrenal vein in a swift and careful manner is particularly important for the resection of the pheochromocytoma due to the hemodynamic stress observed in tumor manipulation. The surgeries carried out under the guidance of the fluorescence may provide precious data in view of the dissection and progresses of the critical vascular structures. The intensity of the fluorescent signals make the lesions and vein more often within the robusting organs in the adjacent tissues such as adrenal gland, visible. Indio cyanine green (ICG) is a non-toxic paint approved by FDA which spread away the close infrared (600-900 mm) fluorescent signals in imaging. The optimal dose which should be used has been defined while the maximum recommended dose is 2 mg/kg for the adults with normal liver function tests (17). Even if the diluted ICG used during the laparoscopic process supported by fluorescent is applied repeatedly, it is far below the recommended dosage. Therefore, whenever ICG dose is required, it may be repeated safely during the process. Pheochromocytoma, malign adrenal tumors and adrenal cortical neoplasia are hypo fluorescent. Although imaging through ICG is not superior to the conventional robotic imaging for such types of adrenal masses in view of the boundaries of the masses, it is much more superior for the hyperfluorescent masses (18). The fact that the failure to image some of the tumors such as pheochromocytoma, adrenal cortical neoplasia/carcinoma through fluorescent is deemed to be the a throwback. In addition, it may provide additional efficiency for adrenal sparing surgeries in view of imaging the usual borders of the tissues and the hypo fluorescent mass.

As a consequence, the most important points which should be taken into consideration in partial adrenalectomy are the full resection of the adrenal masses and additionally, leaving aside tissues sufficient to preserve the functioning of the cortex. In particular it should be considered as the method which should be preferred in the first priority due to less morbidity in the syndromic cases with adrenal gland involvement and no necessity for long term replacement.

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Video Article

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Youtube linki: https://www.youtube.com/watch?v=o44yyHAg3AA&feature=youtu.be

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The Key Steps in Robotic Radical Prostatectomy

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Robot-assisted laparoscopic radical prostatectomy (RARP) has become the standard of care in the surgical management of clinically localized prostate cancer. Technical refinements with robotic technology such as bladder neck preservation and vesicourethral reconstruction offer improved functional recovery, especially in the urinary domain and increased oncological efficiency by decreasing rates of positive surgical margins. Since the initial description in 2001, several novel approaches in operative techniques were proposed in order to improve oncological and functional outcomes. This video presents the surgical key-steps of two different techniques of RARP.

RARP-Posterior Approach

The onset of the posterior approach consisted of the release and vascular control of vasa deferentia (VDs) and seminal vesicles (SVs) along with the dissection of the prostate away from the rectum at the plane of Denonvillier's fascia. After dropping of the urinary bladder, the space of Retzius was accessed and the endopelvic fascia was incised. The lateral prostatic fascia was released from the levator ani muscle fibers and the prostate was mobilized on both sides. The dorsal vascular complex (DVC) was then ligated using a CT-1 needle and 0 polyglactin suture with a slip-knot, without a periurethral suspension-stitch. Once the bladder neck was identified and transected, the retrotrigonal fibromuscular layer was sectioned to gain access to the VDs and SVs. After Hem-o-Lok™ clipping of the lateral pedicle vessels, a high anterior release of lateral pelvic fascia was performed anteromedially on each side, allowing the layer of tissue containing the neurovascular structures to be dissected free. A posterior reconstruction of the musculofascial layer was utilized by a Monocryl Rocco-stitch. Finally, the urethrovesical anastomosis was performed according to Van Velthoven's method using two sets of 3-0 V-LOC™, beginning at 6 o'clock, with one clockwise and another counterclockwise continuous suture until 12 o'clock.

RARP-Retzius-Sparing Approach

Following a 5-cm horizontal incision of the peritoneum overlying the pouch of Douglas the VDs were identified and transected. The anterior and posterior surfaces of the SVs were progressively dissected and the tips of the SVs were released while avoiding extensive dissection into the posterolateral neurovascular structures. The avascular plane of Denonvilliers'fascia that separates the prostate from the anterior rectal wall was cut to enter the interfascial plane of dissection. The planes between the prostatic and DV fasciae in the posterior and the posterolateral aspect of the prostate gland were developed to maximize nerve preservation, through both intra- and inter-fascial dissection. After a triangular space has been developed at the base of the prostate gland, arteries that coursed from the NVB toward the gland were dissected, clipped, and divided. The subsequent inter- and intra-fascial release of the NVB away from the prostate was guided by the whitish surface of the prostatic capsule along the curve of the lateral surface of the midprostate toward the apex. With retraction of the peritoneum covering the bladder upward, the trigone of the bladder was progressively detached from the base of the prostate gland. Consequently, the bladder neck was transected at the posterior aspect. The subsequent dissection of the ventral prostatic surface completely spared the pubovesical complex comprising the detrusor apron with the associated pubovesical ligaments and the DVC. The urethra was then circumferentially dissected and sharply transected. A running urethrovesical anastomosis was finally performed

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with two sets of 3-0 V-lock™ running sutures, beginning at 12 o'clock, with one clockwise and another counterclockwise until 6 o'clock.

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