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

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

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

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

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

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

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

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

All submitted manuscripts are committed to rigorous peer review.

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

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

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

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

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

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

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

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

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

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-Scientific Responsibility:

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

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

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

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

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

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.

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A. Original Research Articles

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

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

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

-Introduction

- Materials and Methods

- Results

- Discussion

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

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

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

B. Case Reports

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

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

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

-Introduction

-Case Presentation

-Discussion

-References

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

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C. Review Article

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

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

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-Introduction

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

-Conclusions

-References

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

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

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

D. Literature Review

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

E. Editorial Commentary

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

F. Letters to the Editor

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

G. Surgery Videos on Urooncology (Video-urooncology)

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

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

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

Video-urooncology submission should include:

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2) Title Page

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

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

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

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Manuscripts should be prepared following sequence according to article type:

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

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The title page should include the following:

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-Running title

-Authors' names and institutions

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

C. Main Text (without authors' credentials)

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

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

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

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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.

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

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

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Risk of Neoplastic Squall Downstream Cytokine Storm of COVID-19 in Male Patients

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Introduction

Scientific information about the molecular mechanisms of Severe Acute Respiratory syndrome coronavirus-2 (SARS-CoV-2) viral infection reveals crossing paths with prostate carcinogenesis through induction of recurrent TMPRSS-ERG gene fusion in an inflammatory microenvironment. Therefore, possibility of a subsequent increased risk of prostate cancer after this viral pandemic requires proper attention with further research.

A novel betacoronavirus identified as SARS-CoV-2 is the cause of a current global public health crisis. The resulting disease was termed coronavirus disease-2019 (COVID-19) with a clinical presentation ranging over a wide spectrum (1). A subgroup of patients develop severe and potentially lethal disease associated with an immune profile characterised by high levels of proinflammatory cytokines suggesting a cytokine storm (1,2). Recent studies identified the molecular pathways of this viral infection in which SARS-CoV-2 enters host cells after binding viral spike (S) surface envelope proteins to cellular angiotensin-converting enzyme 2 (ACE2) receptors and proteolytic S protein priming by TMPRSS2, which is a transmembrane serine protease (3). Therefore, modulation of TMPRSS2 expression as well as cytokine receptor blockade have been suggested as promising potential treatment strategies against COVID-19 (1,4). Yet the pivotal role of ACE2 and TMPRSS2 in COVID-19 may rather have more ominious implications for men.

Role of TMPRSS2 and Inflammation in Prostate Cancer

TMPRSS2 is an androgen responsive, highly expressed gene in prostatic tissue and strongly associated with prostatic carcinogenesis via fusion with oncogene ETS family transcription factors, mainly ERG (5). Recently, a significant role of inflammation leading to recurrent TMPRSS2-ERG gene fusions has been demonstrated via induction of DNA breaks in an inflammatory environment (6). In addition to previous studies indicating an etiologic link between inflammation and prostate carcinogenesis, a recent population based prospective cohort study provided further evidence supporting the role of inflammation in prostate carcinogenesis and progression (7,8). The Prostate Cancer Study throughout life (PROCA-life), demonstrated an increased risk of prostate cancer with a much higher risk of metastatic disease in men with high systemic inflammatory scores (8).

Possible Mutual Mechanisms

Both ACE2 and TMPRSS2 which are the key molecules for pathogenicity facilitating SARS-CoV-2 viral entry in to the host cells are highly expressed in urogenital organs, especially in prostate (see Related links) and render them susceptible to damage by this virus as well as accompanying inflammation (5,9). Thus potential inherent tropism of SARS-CoV-2 for prostate and associated local and/or systemic inflammation with high levels of cytokines in this disease provide an extremely convenient microenvironment for carcinogenesis through induction of recurrent TMPRSS2-ERG gene fusions. Although significant injury in renal and testicular tissue was reported, information concerning histopathological findings of prostate tissue associated with SARS-CoV-2 infection is still missing (9). Also, incidence of lower urinary tract symptoms which may be associated with severe prostatic inflammation is currently not clear. This may in part related to clinical presentation of the disease where predominant symptoms are pulmonary in origin and often life threatening in these patients which probably sideline and obscure any symptoms related to lower urinary tract. Asymptomatic prostatic inflammation is also a possibility which is in fact the case in many patients (10).

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Conclusions

Available scientific evidence raises a significant concern about possibility of increased risk of prostate cancer development by recruiting the same key molecules responsible for carcinogenesis as well as SARS-CoV-2 viral entry in to host cells triggering immune response and subsequent inflammatory cascade with downstream severe inflammatory microenvironment at target organs. Therefore, the medical community should tailor the follow-up of recovering male patients accordingly until this hypothesis is refuted properly by further research.

Authorship Contributions

Authors contributed equally to this work.

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Related Links

The Human Protein Atlas portal (ACE): https://www.proteinatlas.org/ENSG00000159640-ACE

The Human Protein Atlas portal (TMPRSS2): https://www.proteinatlas.org/ENSG00000184012-TMPRSS2

Review

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Management of Patients with Urological Cancers in Turkey during the COVID-19 Pandemic: Recommendations of Uro-oncology Association

Serdar Çelik[1], İlker Tınay[2], Fehmi Narter[3], Saadettin Eskiçorapçı[4], Süleyman Ataus[5], Levent Türkeri[6], Sümer Baltacı[7]

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Abstract

Coronavirus disease-19 (COVID-19) has been declared as a pandemic by the World Health Organization. The number of cases has increased over time in correlation with the increasing number of testing worldwide. In order to use the available resources for COVID-19 treatment, urological practice has been limited only to emergency procedures and certain uro-oncological surgeries. In this report, we aim to share our recommendations for the daily uro-oncology practice in light of local circumstances in Turkey.

Keywords: COVID-19 pandemic, recommendations, urologic cancers, urologic oncology

Introduction

The human spread of a novel coronavirus, that is, Severe Acute Respiratory syndrome coronavirus 2, was first reported in Wuhan in December 2019 (1,2). The disease was named coronavirus disease-19 (COVID-19), which is basically the short for "COVID-19" (2).

COVID-19 was declared as a pandemic by the World Health Organization on March 11, 2020, which is the same date on which the first confirmed case in Turkey was announced by the Ministry of Health (2). As in other countries, the number of cases has increased over time in correlation with the increasing number of testing in Turkey as well, and as of April 18, 2020, there were 82,329 confirmed cases in Turkey, ranking eighth after China worldwide.

Like in many countries, the urological practice in Turkey has also been limited only to emergency procedures and major uro-oncological surgeries in order to use the available resources for COVID-19 treatments. Although many sources have recently published the general recommendations for the daily practice in urological oncology, a potential concern is if these recommendations would be applicable to every patient from the different geographical regions of the world (3). While the duration of preventive measures, such as lockdowns or social isolations, remains unpredictable, it is of utmost importance that national organizations share their recommendations for daily practice based on national resources, sociocultural circumstances, and restrictive administrative regulations. In this report, we aim to share our recommendations for the daily uro-oncology practice in light of local circumstances in Turkey.

Urothelial Carcinoma (Bladder and Upper Urinary Tract)

a) Patient presented with hematuria and bladder mass

Cystoscopy and transurethral resection (TUR) can be performed as an outpatient procedure, and if the current conditions of the

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institution are appropriate, we do not recommend postponing this procedure. The current guidelines recommend a single intravesical instillation of chemotherapy in early postoperative period; however, owing to the potential complications of these intravesical instillations and the limited benefit, it is reasonable not to perform early postoperative instillations during COVID-19 pandemic (4,5).

b) Second TUR in patients with pT1 or high-grade urothelial carcinoma

Residual disease can be found in 51%-58% of the patients, of which, 8%-11% are restaged to muscle-invasive disease after a second TUR (6,7). To achieve better oncological outcomes, namely recurrence-free and progression-free survivals, the optimal duration of the second TUR is between two and six weeks after the initial resection (8). A second resection can be performed as an outpatient procedure, and if the current conditions of the institution are appropriate, we do not recommend postponing this procedure and perform it no longer than six weeks after the initial TUR. If there is a sufficient amount of muscle tissue in the specimen confirmed by pathological evaluation and the surgeon is confident of complete resection of all visible tumors, avoiding a re-TUR is an option during this period.

c) Intravesical BCG in patients with carcinoma in situ, pT1, or high-grade urothelial carcinoma

Intravesical Bacillus Calmette-Guérin (BCG) instillations can be performed as an outpatient procedure, and if the current conditions of the institution are appropriate, we do not recommend postponing this procedure since the risk of progression is high. Although, these instillations might cause serious complications, the potential benefits outweigh these risks.

However, intravesical treatment in low to moderate risk non-muscle invasive bladder cancer (NMIBC) can be postponed during this pandemic.

d) Follow-up of non-muscle invasive urothelial carcinoma of the bladder

Patients with low and intermediate-risk tumors: Postponing follow-up cystoscopies in these patients for up to six months is reasonable during the COVID-19 pandemic.

Patients with high-risk tumors: Postponing follow-up cystoscopies in these patients might be reasonable during the COVID-19 pandemic. However, follow-up with urine cytology and imaging of the urinary tract might be offered as an alternative follow-up approach during this period. Nevertheless, we do not recommend postponing the first follow-up cystoscopy at the third month after the initial diagnosis and intravesical induction BCG treatment.

e) Muscle invasive urothelial carcinoma of the bladder

If the current conditions of the institution are appropriate, we recommend performing radical cystectomy in patients with muscle invasive disease. Delaying radical surgery for more than three months is associated with upstaging and lymph node-positive disease, although there are conflicting reports on the overall survival with respect to the timing of radical cystectomy (within 90 days vs more than 90 days after the diagnosis) (9,10,11,12,13). Also, cystectomy for BCG non-responsive high-risk NMIBC should not be delayed.

Generally, higher volumes of hospital and surgeon are associated with lower levels of peroperative and postoperative complications and better oncological results. Referring patients with muscle-invasive disease to high-volume centers might be reasonable during COVID-19 pandemic.

f) Upper urinary tract urothelial carcinoma

Diagnostic ureterorenoscopy and tumor sampling: Can be performed as an outpatient procedure, and if the current conditions of the institution are appropriate, we do not recommend postponing this procedure. However, with regard to the use of a single intravesical instillation of chemotherapy in early postoperative period, due to the potential complications of these intravesical instillations, it seems reasonable not to perform the early postoperative instillations during COVID-19 pandemic.

Radical nephroureterectomy: If the current conditions of the institution are appropriate, we recommend performing radical surgery in patients with high-risk non-metastatic disease. Delaying radical surgery for more than 90 days is associated with worse disease-specific and progression-free survival (14). The current guidelines recommend a single intravesical instillation of chemotherapy in postoperative period; however, due to the potential complications of these intravesical instillations, it seems reasonable not to perform the early postoperative instillations during COVID-19 pandemic.

Prostate Cancer

a) Screening

It seems reasonable not to perform the routine screening with prostate specific antigen (PSA) and/or with digital rectal examination (DRE) during COVID-19 pandemic (15).

b) Prostate biopsy

If the current conditions of the institution are appropriate, we recommend performing prostate biopsy under local anesthesia in a selected group of patients who are admitted with high PSA levels and/or DRE findings compatible with locally advanced high-risk tumors. In all other clinical scenarios, it seems reasonable not to perform prostate biopsy during COVID-19 pandemic (15).

c) Treatment of local and locally advanced prostate cancer

Postponing follow-up visits, imaging modalities for staging, and treatment alternatives (surgery, radiotherapy, etc) in these patients for up to six months seems reasonable during COVID-19 pandemic (16,17). Even in patients with asymptomatic unfavorable intermediate, high, and very high-risk disease, delaying the surgery for up to six months is not associated with deleterious results. However, we do recommend starting androgen deprivation therapy (ADT) during this waiting period.

d) Treatment of metastatic disease

We recommend starting an ADT during COVID-19 pandemic in patients recently diagnosed with metastatic disease. It seems reasonable not to start with docetaxel chemotherapy during COVID-19 pandemic (18). However, if the current conditions of the institution are appropriate, we recommend offering orchiectomy with local anesthesia. The treatment of 150 mg bicalutamide daily may be an alternative for hormonal therapy.

Patients who are undergoing an ADT might benefit from telemedicine, where they can share their PSA and testosterone results with the physician and decide together whether to pause or to continue with their treatment. Three or six monthly forms of luteinising hormone-releasing hormone agonist should be preferred in order to decrease patients' exposure to medical facilities. Moreover, as a second-line treatment alternatives, we recommend using enzalutamide, abiraterone, or apalutamide instead of docetaxel chemotherapy during COVID-19 pandemic.

Kidney and Adrenal Tumors

a) Management of clinical stage T1 and T2 kidney tumors

A three-month treatment delay in clinical stage T1 and T2 kidney tumors has no negative effect on survival (16). Therefore, it seems reasonable not to perform partial or radical nephrectomy during COVID-19 pandemic. However, in selective cases with cT1b and cT2 tumors and if the current conditions of the institution are appropriate, surgical approach might be offered as the treatment modality (17).

b) Management of clinical stage T3 and T4 kidney tumors

If the current conditions of the institution are appropriate, we recommend performing radical surgery in patients with clinical stage T3 and T4 kidney tumors. Postponing the treatment in these stages can decrease the survival rates and increase the surgery-related morbidities due to a possible risk of aggressive and progressive tumors in these stages (16,17).

c) Tumor biopsy in kidney tumors

No recommendation on performing tumor biopsy prior to deciding on its postponement has been provided in the guidelines. However, it can be recommended to discuss with the patient on the diagnostic value of the tumor biopsy and the status of the center for this procedure and to determine the necessity of tumor biopsy in this regard. In metastatic patients, biopsy can be planned for tissue diagnosing before planning of systemic treatment.

d) The case of kidney tumor-induced hemorrhage

In case of tumor-related bleeding, an emergency radical nephrectomy can be performed according to the hemodynamic status of the patient, regardless of the tumor stage and metastasis status (18). However, primary efforts for embolization by an interventional radiologist seem reasonable during COVID-19 pandemic.

e) Cytoreductive nephrectomy in patients with metastatic disease

The guidelines recommend delaying surgery in such patients with neoadjuvant therapy and minimizing the risk of patient's contact, especially those who will be undergoing a surgery (19). Moreover, in the current situation, in metastatic kidney tumors, a direct systemic treatment can be started instead of cytoreductive nephrectomy.

f) Follow-up of patients on systemic therapy

Oral (vascular endothelial growth factor-targeted therapy) treatment options might be preferred instead of intravenous therapy (checkpoint inhibitors). In addition, the use of prophylactic antibiotic and growth factor in patients under systemic therapy can reduce the potential morbidity by minimizing the risks of neutropenia and infection (19).

g) Adrenal tumors

If the current conditions of the institution are appropriate, we recommend performing adrenalectomy in patients who have >6 cm adrenal mass or unfavorable radiological findings for adrenocortical carcinoma (17). In other adrenal tumors, it seems reasonable not to perform partial or radical adrenalectomy and to offer follow-up together with endocrinology clinic during COVID-19 pandemic.

Testicular Cancer

a) Patient with a "suspected" testicular mass

Radical orchiectomy can be performed as an outpatient procedure and patients can usually be discharged within 4 hours after the surgery with oral pain medication. We recommend performing orchiectomy if the present conditions of the institution are convenient to perform surgeries (20).

b) Stage I seminoma

We recommend using the risk-adapted approach. Patients without any risk factors (ie tumor size >4 cm or stromal rete testis invasion) should be managed with surveillance. Additionally, while patients with only one risk factor can also be managed with surveillance according to the SWENOTECA trial results (21), patients with two risk factors should, however, be offered an adjuvant treatment. Considering the possible immunosuppressive effects of the chemotherapy agents, adjuvant radiotherapy to the retroperitoneal area using the irradiation dose of 20 Gy can be offered as a reliable alternative (22).

c) Stage I non-seminoma

We recommend using the risk-adapted approach. While patients without any risk factors (ie lymphovascular invasion) should be managed with surveillance, patients with lymphovascular invasion can be offered an adjuvant treatment with one course of bleomycin, etoposide and cisplatin (23). The potential pulmonary toxicity of bleomycin might be a limitation in the current circumstances.

d) Metastatic germ cell tumors

The potential pulmonary toxicity of bleomycin might be a limitation in the current circumstances. For such patients with poor lung function, Cisplatin - Etoposide - Ifosfamide (PEI) protocol can be offered. In addition, the use of prophylactic growth factor should be offered in all patients with germ cell tumors receiving chemotherapy.

e) Patient with post-chemotherapy residual retroperitoneal mass

Considering the acceptable postoperative length of stay (3 to 6 days), we recommend performing retroperitoneal surgery if the present conditions of the institution are convenient to perform surgeries (24).

Conclusion

This report reflects the temporary recommendations for uro-oncological practice in Turkey during the first three months of the COVID-19 pandemic. It is of utmost importance that national organizations share their recommendations for daily practice based on national resources, sociocultural circumstances, and restrictive administrative regulations in order to interact with other societies during pandemic.

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Review

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The Current Strategies for Neoadjuvant Chemotherapy in Muscle Invasive Bladder Cancer: The Place of Immunotherapy in Future

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Abstract

Muscle invasion is present in approximately thirty percent of bladder cancers. Radical cystectomy and bilateral pelvic lymph node dissection following neoadjuvant chemotherapy is the recommended treatment for muscle invasive bladder cancer. Local and distant relapses are seen in a significant proportion of patients with surgery alone. Micrometastases at the time of diagnosis that cannot be detected by imaging may be responsible for these relapses. The aim of neoadjuvant and adjuvant therapies is to eliminate these micrometastases. Several randomized trials have shown that platinum-based combination neoadjuvant chemotherapy can improve survival outcomes, compared with locoregional treatment alone. Although the proportion of patients receiving treatment has increased compared to previous years, it is still low. Immunotherapies in neoadjuvant treatment are promising in the appropriate patient group. In this article, we aimed to review current neoadjuvant treatment strategies in muscle invasive bladder cancer in the literature.

Keywords: Bladder cancer, chemotherapy, neoadjuvant therapy

Introduction

Although the gold standard treatment in bladder cancer is surgical, the rate of cure varies between 50-65% by surgery alone (1). It is seen that systemic treatment applications are of great importance considering the low chance of obtaining a cure and low survival rates in patients treated with surgery alone in case of the tumor invades the muscle layer. Urothelial (transitional cell) carcinoma accounts for about ninety percent of bladder cancers in Europe and North America. In other parts of the world, non-urothelial bladder cancers are more common. Although neoadjuvant cisplatin-based chemotherapies provide a survival benefit compared to local treatments alone, only twenty percent of patients receive neoadjuvant chemotherapy before radical cystectomy (2,3,4,5). The reasons such as physicians not believing in the benefit of the treatment, fear of the side effects of the treatment, not guiding the patients for chemotherapy due to the concerns of delay in curative treatment, and impaired renal function and poor performance prevent patients from receiving treatment.

All patients should be clinically staged prior to treatment in bladder cancer. It is necessary to start treatment as soon as possible after the diagnosis and staging. In an observational study, it was shown that delay of 8 weeks or more in neoadjuvant therapy was associated with the increase in stage in 2,200 patients (6).

The survival benefit of cisplatin-based chemotherapies before surgery has been demonstrated in the meta-analyses of 11 randomized studies (7). Compared with local therapy alone, neoadjuvant cisplatin-based treatments improve 5-year survival from 45% to 50%, while improve disease-free survival by 9%. However, there are no randomized studies comparing neoadjuvant chemotherapy regimens. A clear difference between regimens was not shown in retrospective studies (8,9). In the largest one of those retrospective studies, the data of 935 patients with node negative (N0) muscle invasive bladder cancer (T2-T4a), from 19 centers from North America and Europe were analyzed. In that study, 64% of patients received cisplatin gemcitabine, 20% methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) and 15% other regimens. There was no difference between the chemotherapy regimens in terms of pathological complete response rates (9).

In the intergroup-0080 trial, surgery alone was compared with neoadjuvant classical MVAC regimen (every 3 days for 28 days) followed by surgery in 307 patients with T2-4N0M0 disease. In the study with a median follow-up time of 8.7 years, median survival in the neoadjuvant therapy arm was 77 months,

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whereas it was 46 months in the surgery alone arm (p=0.06). While the 5-year overall survival benefit in the study was 5%, it was seen that this benefit was more pronounced in T3-4 tumors with 20%. In this study, the 5-year survival rate of patients with complete pathological response (pT0) was 85%. In the study, the pathological complete response (15% versus 38%, p<0.001) was found better in the arm receiving neoadjuvant chemotherapy compared to surgery alone. In summary, in that study, patients who received neoadjuvant therapy had a higher pathological complete response rate, and this was associated with increased survival (10).

The dose-dense MVAC treatment used in conjunction with the granulocyte colony stimulating factor every two weeks showed superiority in survival compared to classical MVAC treatment in locally advanced and metastatic disease (11,12). After these studies, single arm, two-phase 2 studies were conducted to investigate the neoadjuvant use of dose-dense MVAC (filgrastim every 14 days, 3 or 4 cycles depending on toxicity). In the first study, the pathological full response rate was 26% (43% of the patients were clinically node positive patients in this study), whereas in the other study, the pathological full response rate was 38% (in this study, 7% of the patients were clinically node positive patients) (13,14). The dose-dense MVAC treatment regimen is considered an alternative treatment regimen, especially in patients who have short duration until surgery and are clinically N0 patients.

Compared with MVAC treatment, gemcitabine cisplatin (GC) treatment in metastatic patients showed similar efficacy and less toxicity (15). There are no randomized studies in neoadjuvant use of this regimen. In a meta-analysis conducted in 2016, the data of 13 retrospective studies were analyzed. Although this meta-analysis showed similar response rates between GC/carboplatin treatment and MVAC treatment, survival results were found inferior in gemcitabine-platinum arm. In the analysis made by excluding carboplatin data, GC treatment was found inferior (16).

The effectiveness of neoadjuvant cisplatin, methotrexate, vinblastin therapy (methotrexate, vinblastin, cisplatin, leukoverine, 3 cycles every 28 days) was compared with local treatment in 976 high-grade patients in a phase 3 trial. In this study, 6% absolute survival benefit was shown at the end of 10 years of follow-up (36% vs 30%) (17).

In the Nordic Cystectomy 1 trial, 311 patients were enrolled in the T1-4N0M0 phase; one group underwent a combination regimen with neoadjuvant cisplatin (cisplatin and adriamycin) followed by radiotherapy and surgery, and the other group underwent surgery after radiotherapy without neoadjuvant therapy (18). While the 5-year overall survival benefit in the study was shown in T1-2 tumors, a 15% difference was found in favor of neaoadjuvant therapy in patients with T3-4 stage (p=0.03). The same study group performed Nordic cystectomy 2 trial and examined 317 patients by dividing them into neoadjuvant therapy (cisplatin and methotrexate) and surgery alone arm (19). There was no difference between the two arms in terms of survival. When Nordic 1 and 2 trials were analyzed together, it was observed that 5-year survival increased from 48% to 56% with neoadjuvant therapy (p=0.049).

In one of the studies conducted to investigate the effect of response obtained with neoadjuvant therapy on survival, the results of 449 patients with T2-4NxM0 tumor who were included in prospective Nordic cystectomy trials and had a pathological complete response with neoadjuvant therapy were retrospectively analyzed. The difference in 5 year survival between the group with and without pathological complete response was shown (57.1% versus 88.2%) (p=0.001) (20). As a result of the study, it was demonstrated that a significant advantage in 5-year survival in patients with complete pathological response with neoadjuvant therapy was gained.

Treatment in Patients with Kidney Failure

Urinary system obstruction should be investigated primarily in patients with bladder cancer presenting with kidney failure. If there is obstruction and if the kidney functions are normalized by placing a stent in the ureter or percutaneous nephrostomy, a standard dose of cisplatin can be given. If kidney failure is not caused by obstruction and if stent placement or nephrostomy does not improve kidney failure, carboplatin can be used instead of cisplatin (21). Data show that carboplatin is less effective than cisplatin in urothelial cancers (22,23,24,25). However, there are no randomized studies comparing cisplatin and carboplatin as neoadjuvant therapy.

Neoadjuvant Immunotherapy

With the demonstration of the effectiveness of immunotherapies in metastatic urothelial cancers, the use of immunotherapies in neoadjuvant therapy has also been investigated. In two different phase 2 studies, the place of atezolizumab and pembrolizumab in neoadjuvant therapy was investigated. In the PURE-01 study, the effectiveness of neoadjuvant pembrolizumab therapy was evaluated in 50 patients with muscle invasive bladder cancer. In this study, pathological complete response as the primary outcome was 42% and reduction in stage was 54%. In subgroup analysis, benefit was seen in patients with pdl1 ≥10% or with high tumor mutation. In the second study, the effectiveness of atezolizumab in neoadjuvant therapy was evaluated and similar results were obtained with pemborolizumab (26,27). If these results are confirmed by randomized phase 3 studies, immunotherapy in neoadjuvant therapy may be used in the near future.

In the light of this information, neoadjuvant therapy is recommended in clinical guidelines beginning from the T2N0M0 stage or in the disease with nodal involvement (TxN1-3M0). The contribution of neoadjuvant therapy to survival does not appear to be very high, since randomized studies and studies in meta-analysis included patients in the T2 stage. While MVAC systemic therapy is preferred in healthy individuals under the age of 70, cisplatin-gemcitabine therapy is the preferred chemotherapy regimen for individuals over 70 years of age or with comorbidity. However, in practice, cisplatin-gemcitabine therapy is applied in most centers for reasons such as treatment toxicity and difficulty of administration.

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Ethics

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Original Article

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Effect of High-dose Ascorbic Acid on Prostate Cancer Cells and Angiogenesis

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Abstract

Objective: Ascorbic acid (AA), at physiological concentrations, is a well known anti-oxidant but, at higher concentrations, it can be selectively toxic to cancer cells. Controversial data have shown that administration of intravenous high-dose AA can improve therapeutic outcomes in cancer patients. These effects are thought to occur mainly due to direct cytotoxicity mediated by generation of reactive oxygen species. The anti-tumour effects of AA can also be due to inhibition of angiogenesis, however, this has been poorly studied. This study aimed to investigate the effect of AA on prostate cancer cells and angiogenesis.
Materials and Methods: Hormone resistant and naïve human prostate cancer cell lines (PC-3 and LnCaP, respectively) were treated with different concentrations of AA. Cell viability was determined by the resazurin assay. Polymer scaffolds that releases lower (0.01 g/g polymer) and higher (0.1 g/g polymer) concentrations of AA were used to evaluate the effects of AA on angiogenesis. Angiogenesis was investigated by an *in vivo* chick chorioallantoic membrane assay.
Results: AA was toxic to PC-3 and LnCaP prostate cancer cell lines in a dose-dependent manner. Confluent cultures of LnCaP was more sensitive to high-dose AA, while confluent cultures of PC-3 were resistant. There was a biphasic *in vivo* angiogenic response to AA, that is, while high-dose of AA inhibited angiogenesis, low dose AA stimulated angiogenesis. In addition, a stable form of AA (ascorbate-2 phosphate) was not angiostatic at high concentrations, suggesting that angiostatic actions of high-dose AA may be due to its direct toxicity on endothelial cells.
Conclusion: We demonstrated that AA was toxic to prostate cancer cell lines, and inhibits angiogenesis at high doses. Further *in vivo* studies are required to validate these finding before any clinical inference can be made.
Keywords: Angiogenesis, ascorbic acid, prostate cancer

Introduction

Prostate cancer (PCa) is the most common type of cancer that affects male adults. In Turkey, PCa is the most prevalent cancer in men after lung cancer, with 17,332 new cases recorded per year (1). Deaths due to PCa accounts for 1.5% of all deaths in men (2). At the time of diagnosis, 80% of men diagnosed with PCa have organ confined disease which is can be treated by surgery and/or radiotherapy. However, some patients may subsequently develop systemic disease with distal organ involvement. Metastatic PCa responds sensitively to androgen deprivation therapy initially, but resistance to the hormone develops few years later, resulting in a castration resistant PCa which requires systemic chemotherapy. Docetaxel based chemotherapy improves overall survival in patients with metastatic castration resistant PCa, and is therefore the standard first-line treatment for these patients (3). However, there are limited options for patients whose PCa develops into disease progression after the docetaxel treatment. In this regard, better treatments modalities that can increase patient survival or quality of life are currently being investigated.

Ascorbic acid (AA), either alone or as a supplementary agent, has been put forward as a treatment option for patients with advanced PCa. AA is one of the essential vitamins in humans, and it is best known for its role in regulating the biosynthesis of collagen. Anti-tumour effects of high-dose AA was first reported in the 1970s (4). Unfortunately, subsequent clinical trials failed to demonstrate any therapeutic benefit of AA in patients with advanced cancers (5,6). These controversial findings are thought to be due to the differences in pharmacokinetics of AA when administered orally or intravenously (7). Recent evidence from clinical studies suggests a potential synergistic effect of high-dose intravenous AA and other chemotherapeutic agents (8). For treatment of PCa, AA was demonstrated to effectively

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inhibit cell division and DNA synthesis *in vitro* (9,10), and also decrease tumour growth in animal models (11). Available clinical data revealed that high-dose intravenous AA can safely be administered in PCa patients (7), with some clinical benefits (12). However, recent evidence does not support the usage of high-dose intravenous AA in patients with PCa (13). Therefore, the role of high-dose AA in treatment of patients with advanced PCa is still controversial.

Another contributing factor on this controversy has to do with the less investigated anti-tumour aspect of AA, that is, its effect on angiogenesis. All tumours require a blood supply to grow *in vivo*. Hypothetically, the therapeutic effects of AA treatment in cancer patients could be mediated via modification of angiogenesis in the tumour. Moreover, AA plays a key role in the synthesis and post-translational modification of collagen III and IV, which are the main structural proteins that form the wall of blood vessels and the basement membrane. AA has also been previously suggested as a factor involved in angiogenesis (14,15). The effects of AA on angiogenesis is not well investigated as studies have only reported the angiostatic (16) and proangiogenic effects (17).

The aimed to investigate the anti-tumour effects of AA. We have initially examined the effect of high-dose AA on two PCa cell lines, and then investigated the angiogenic effect of different doses of AA *in vivo*.

Materials and Methods

Culturing of PCa Cell Lines

This is an experimental study using human cell lines. Two human PCa cell lines were used to investigate the toxic effects of AA. The PC-3 cell line represented the hormone resistant PCa, while LnCaP represented the hormone naïve PCa. We obtained this cell lines as a generous donation from doctor Adam Glen [who initially purchased them from the American Type Culture Collection (Manassas, VA)]. Both cell lines were cultured in T75 flasks and maintained in RPMI-1640 medium supplemented with fetal calf serum (10% v/v), L-glutamine (2 µM), Penicillin (100 U/mL), Streptomycin (100 ug/mL) and Fungizone (0.625 ug/mL), all from Sigma-Aldrich.

Cultures of PC-3 and LnCaP were plated at a concentration of 50,000 cells per well in a 12-well plate. Proliferating cultures were treated with AA at 24 hours, while confluent cultures were treated with AA at 72 hours. Solutions of AA were prepared in distilled water with concentrations of 0, 50, 100, 250, 500 and 1,000 µM, and were freshly used. At the start of the experiments, the culture media were removed from the plates and the wells were washed three times with phosphate buffered saline (PBS). Freshly prepared solutions of AA were added into each plate and left in an incubator for 2, 4 and 6 hours. All experiments were repeated thrice.

Assessment of Toxicity

AA toxicity was assessed using a resazurin assay which essentially measures cell metabolic activity. In briefly, at 2, 4 and 6 hours, all media were removed from the culture plates and PBS was used to wash the wells. Then, 5 mL of resazurin solution (125 µl/mL resazurin in PBS) was added into each well and incubated for 45 minutes at 37 °C. Absorbance was then measured at 570 nm with a colorimetric plate reader (Bio-TEK, NorthStar Scientific Ltd, Leeds, UK). Culture wells without cells were used as blanks.

Achieving a Continuous Release of High-dose AA from Polymers

Studying the effect of AA on angiogenesis requires a continuous drug-release system that can effectively deliver high-dose AA into the cells. This was achieved by using a polymer as the drug carrier as previously described (18). In briefly, an electrospun polylactic acid (PLA) was used as the drug carrying polymer for AA. A technique of emulsion electrospinning was employed to obtain a stable solution of AA and the polymer. Drug releasing PLA materials were prepared in two different concentrations including 0.01 (low dose) and 0.1 (high-dose) grams of the drug per gram of PLA polymer. A salt formulation of AA [L-ascorbic acid 2-phosphate (A2P)] was used as a control to test the difference between the active form of AA (L-AA) and the salt form. PLA scaffolds releasing hydrocortisone were also constructed to serve as a negative control. This is hydrocortisone is a known angiostatic agent with an appreciable solubility in lipid, making it an excellent candidate for the negative control. All reagents and chemicals were obtained from Sigma-Aldrich, United Kingdom.

Studying Angiogenesis

The effect of AA on angiogenesis was studied *ex-ovo* using a chick chorioallantoic membrane (CAM) assay described previously (19). All embryo cultures were covered under a home office licence. Briefly, fertilised chicken eggs (gallus gallus domesticus) were cultured in a rotating egg incubator till day 3 of the embryonic development. The embryos were then transferred into petri dishes in order to continue the embryo culture *ex-ovo* in a humidified cell culture incubator at 38 °C. The AA releasing scaffolds were cut into 7 mm diameter circles with a laser cutter device [Epilog Laser Cutter (Clevedon, UK)]. Sterilisation of the drug releasing polymers were performed via exposure to ultraviolet light for 30 minute. At day 7 of the embryonic development, the test samples were placed on the CAM surface and cultured for 4 days.

At day 11 of embryonic development, the area of the CAM containing the test samples were photographed with a digital microscope. Afterwards, the cultures were terminated by sacrificing the chick embryos.

Digital photographs of the area of interest were taken at the end of the experiment. A total of 6-8 photographs were evaluated for each group. The digital photographs were converted to grayscale, and the contrast was enhanced using ImageJ software and NeuronJ, as described previously (20). All discernible blood vessels in the photographs were marked using the NeuronJ tracing tool. The total number of blood vessels, total length of blood vessels and mean length of blood vessels were calculated using the processed images.

Statistical Analysis

Statistical analysis was performed with SPSS version 17.0 (SPSS Inc., Chicago, Ill., USA). Differences between groups were tested

for statistical significance by Mann-Whitney U test. P values <0.05 was considered significant.

Results

Effect of AA on PC3 Cells

Supplementation of AA on proliferating cultures of PC3 cells at concentrations of 0, 50, 100, 250 and 1,000 μM resulted in a dose dependent reduction in cell viability as measured by the metabolic activity of the cells. AA concentrations >250 μM were the most effective to reduce PC3 cell viability. There were no significant differences between measurements taken at 2, 4 and 6 hours. On the other hand, the same concentrations of AA had no significant effect on cell viability of the confluent cultures of PC3 cells (Figure 1).

Effect of AA on LnCaP Cells

Supplementation of AA on both proliferating and confluent cultures of LnCaP cells at concentrations of 0, 50, 100, 250 and 1,000 μM resulted in a dose dependent reduction in cell viability as measured by the metabolic activity of the cells. AA Concentrations >250 μM were the most effective to reduce LnCaP cell viability (Figure 2).

Effect of AA on Angiogenesis

The effect of AA on angiogenesis was investigated using a PLA electrospun polymer system that ensures continuous release of AA at low (0.01 g/g PLA) and high (0.1 g/g PLA) concentration. It is important to continuously release the AA on the experimental medium since AA is immediately oxidised after being applied. In these experiments plain PLA scaffolds were used as controls and hydrocortisone releasing PLA scaffolds were used as negative control to show the reaction with a known angiostatic agent (Figure 3).

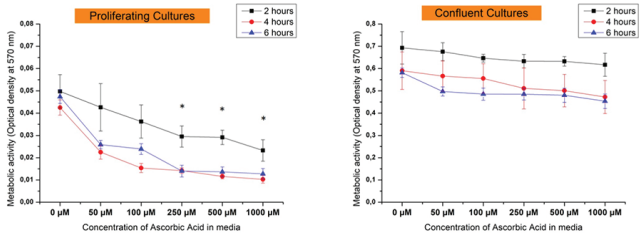


Figure 1. Assessment of different concentrations (0-1000 μM) of ascorbic acid (AA) on proliferating and confluent cultures of PC3 cells at different time points. There was a dose-dependent decrease in the metabolic activity of PC3 proliferating cells, particularly above concentrations of 250 μM. The confluent cultures of PC3 cells were resistant to the effects of high-dose AA in the cell culture medium (*p<0.05 as compared to a concentration of 0 μM)

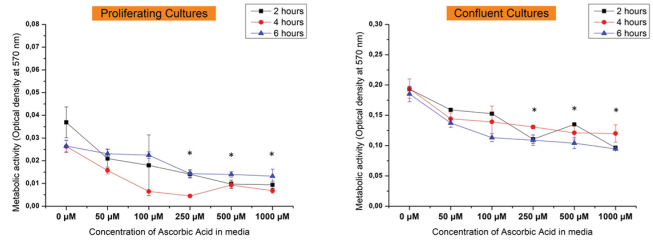


Figure 2. Assessment of different concentrations (0-1000 μM) of ascorbic acid (AA) on proliferating and confluent cultures of LnCaP cells at different time points. There was a dose-dependent decrease in the metabolic activity of both proliferating and confluent cultures of LnCaP cells, starting from a dosage of 100 μM (*p<0.05 as compared to a concentration of 0 μM)

High-dose of AA showed an angiostatic effect, with a significant decrease in total number of blood vessels (35.44±2.56 vs 85±5.66, p<0.005) and total length of blood vessels (11.14±0.61 cm vs 19.59±0.79 cm, p<0.005) when compared to control. AA caused the decrease in the total number of blood vessels and total length of blood vessels when compared to the negative control (hydrocortisone releasing scaffolds). However, these reductive effects were not statistically significant (35.44±2.56 vs 43±3.80 and 11.14±0.61 vs 13.67±0.91, respectively).

In contrast to high-dose AA, low dose AA exhibited a proangiogenic, causing a significant increase in total number blood vessels (35.44±2.56 vs 85±5.66, p<0.005) and total length of blood vessels (11.14±0.61 cm vs 19.59±0.79 cm, p<0.005) when compared to control. In addition, high and low dose of L-A2P caused an similar effect to that of low dose AA, yielding a total number of blood vessels of 100.57±6.28 and 101±4.95 at high and low dose of A2P, respectively and a total length of blood vessels of 22.43±0.77 cm and 23.8±0.77 cm at high and low dose of A2P, respectively.

The mean length of blood vessels was increased in the angiostatic samples and this can be due to the lack of newly forming blood vessels which consequently leaves a scattered larger calibre of blood vessels. These scattered larger calibre of blood vessels subsequently increased the mean vessel length. Low concentrations of AA caused a significant increase in the total number of blood vessels.

Discussion

This study confirmed the toxic effects of high-dose AA on PCa cell lines. More importantly, this is the first study to show a

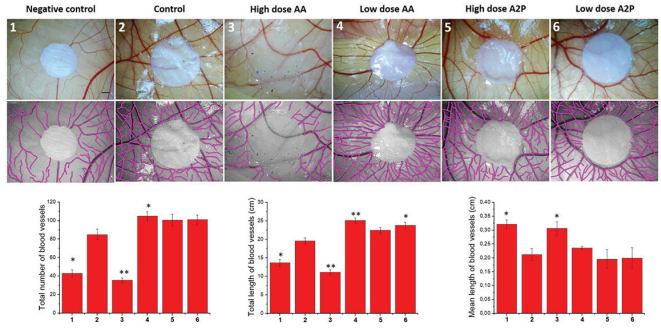


Figure 3. Demonstration of the angiogenic response to high and low doses of ascorbic acid (AA) when released from electrospun polylactic acid (PLA) scaffolds. Hydrocortisone releasing PLA scaffolds was used as negative control, whereas plain PLA scaffolds were used as controls. Additionally, the same concentrations of a more stable form of AA, L-ascorbic acid 2-phosphate (A2P) attached to the releasing scaffold was taken as another control group to check if the AA effect could be due to the acidity of the compound. High-dose AA inhibited angiogenesis, whereas low dose AA stimulated it. Both high and low doses of A2P stimulated angiogenesis, suggesting that stable forms of AA are not angiostatic (error bar represents 200 μm for all images)

biphasic *in vivo* angiogenic response to AA, where high doses inhibited new blood vessel formation and low doses stimulated it. This explains the contradictory reports on the angiogenic potential of AA in literature.

AA has been demonstrated to have different effects on cancer cell viability when used in high and low doses, thus suggesting a biphasic response. High doses of AA (1-10 mM) has been shown to reduce cell viability and mobility in PCa cells via production of excessive intracellular reactive oxygen species, triggering necrotic cell death (11). In contrast, low doses of AA are known to protect cells against oxidative stress. In the present study, the toxic effects of AA was seen at concentrations above 250 mM.

The mechanisms underlying AA toxicity is relatively well-defined. Although we have not studied the mechanisms behind the reduction of cell viability in PC-3 and LnCaP cell lines, the present study contributes to knowledge by demonstrating that confluent cell cultures of PC-3 cells were resistant to AA toxicity, whereas both proliferating and confluent cultures of LnCaP cell lines were equally sensitive to AA toxicity. Previous studies reported differences in response to treatment with high-dose AA between hormone treatment sensitive and resistant PCa cells (21). This implies that different cell lines can differ in terms of responsiveness to AA toxicity. This may also differ depending on the stage of the cancer cell cycle. Therefore, our findings confirm the toxicity of high-dose AA on PCa cell lines. Also, we suggest that this response can be dependent on the cell type and the stage of the cell culture.

Study Limitations

Several studies have also reported a reduction in tumour cell mass with systemic administration of AA in animal models (22). Angiogenesis is essential for tumour growth *in vivo*, and another mechanism for anti-tumour effects of high-dose AA could be through inhibition of angiogenesis. This has not been studied in literature, presumably because of the challenges in achieving a sustained release of AA *in vivo*. The present study addressed this challenge by constructing an AA releasing polymer system that ensured constant release of AA on the surface of the blood vessels, resulting in better visualisation of the effect. Taken altogether, our findings explained why AA is regarded as an angiostatic in literature (16) whereas others reported a proangiogenic effect (17). We further suggest that the contradictory results on the angiogenic potential of AA was due to difference in experimental design and dose regimens. Additionally, we provided a direct comparison of two different forms of AA (AA and A2P) at two different concentrations. To the best of our knowledge, this is the first direct *in vivo* comparison.

In regard to the underlying mechanisms of angiostatic effects of AA, we can argue that the inhibitory effect of high-dose AA on new blood vessel formation is a directly toxic to the rapidly proliferating endothelial cells of the CAM by increasing the reactive oxygen species. This argument is supported by the lack of anti-angiogenic effect of the same dose of A2P, which is a stable form of AA that does not rapidly trigger the accumulation of free radicals.

Another limitation of the available studies on the angiogenic potential of AA is the use of conventional 2D *in vitro* methodologies. Studying angiogenesis is complex and thus requires specialised *in vivo* methodologies to allow observations of interactions between endothelial and non-endothelial cells, as well as with many enzymes, growth factors and adhesion molecules that play a role in the formation of new blood vessels. This is only possible using *in vivo* methodologies, however, such methodology requires specialised equipment and expertise, and are often expensive (eg dorsal skin fold assay). In the current study, we made use of a modified CAM assay to study angiogenesis in a reproducible and relatively easy way (19). Our findings were obtained with a robust experimental methodology.

Conclusion

Although this study provides strong pre-clinical data on the effects of AA on PCa cells and on angiogenesis, it has several limitations. Firstly, the preliminary results lack confirmatory studies with larger animal models. Therefore, further studies on appropriate animal models are needed before any conclusion is reached. Secondly, the results do not imply any clinical applications at this stage. Thirdly, we have not undertaken any molecular investigation to help elucidate the mechanisms underlying the effects of AA. We believe that the methodology described in this study would trigger further experiments that will illuminate the underlying molecular mechanisms.

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Ethics

Ethics Committee Approval: This is an experimental study using human cell lines.

Informed Consent: All embryo cultures were covered under a home office licence.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: N.M., Design: N.M., Data Collection or Processing: N.M., Analysis or Interpretation: N.M., Literature Search: N.M., Writing: N.M., S.M.

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Original Article

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Laparoscopic Adrenalectomy: Assessment of the Surgical Outcomes and Learning Curve for Large Adrenal Tumours

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Abstract

Objective: Laparoscopic adrenalectomy (LA) is the treatment of choice for benign tumours of less than 6 cm. However, there is still an ongoing debate regarding the exact cut-off value of the tumour size. The aim of this study was to determine the effect of tumour size on intraoperative and postoperative outcomes in patients undergoing LA and also to estimate the learning curve for large adrenal tumours.

Materials and Methods: The data of 102 patients who underwent LA from April 2010 to October 2018 was retrospectively analysed. The patients were allocated to 2 groups according to tumour size: <6 cm (group 1 =76) and ≥6 cm (group 2 =26). Both groups were compared in terms of age, gender, body mass index, tumour characteristics, operative data and complication rates. The patients were also allocated to four groups (A, B, C and D) according to the chronological order of their surgery in order to evaluate the learning curve.

Results: The mean age, gender, tumour laterality and BMI were similar in both groups. Tumour size (32.7 vs 79.5 mm, p=0.001), operation time (53.3 vs 72.6 minute, p=0.001), blood loss (65.8 vs 86.35 mL, p=0.042) were significantly different between groups 1 and 2, respectively. Intraoperative and postoperative complication rates were also found to be significantly higher in group 2. The first 25 cases were sufficient to complete the initial learning curve. It showed that surgical experience increased and operation time and blood loss decreased as the mean tumour size that is managed by LA increases.

Conclusion: LA is a reliable approach for the management of large adrenal tumours. However, we can conclude that the most important factor determining the safety and efficacy of LA is the surgical experience.

Keywords: Adrenalectomy, adrenal tumour, laparoscopy, learning curve

Introduction

The first laparoscopic adrenalectomy (LA) was described by Gagner et al. (1). Since then, many retrospective studies have reported that LA is beneficial for reducing estimated blood loss (EBL), postoperative pain, hospital stay and morbidity compared to open adrenalectomy (OA). Moreover, earlier return to normal activity and improved cosmetic outcomes have been reported as other significant advantages of laparoscopic surgery (2,3,4). Over time, a variety of minimally invasive methods such as transperitoneal, retroperitoneal and robot-assisted approaches have been described for the management of adrenal masses alongside the advances in technology and surgical experience. LA is considered as the gold standard treatment modality for the management of various adrenal tumours. The conventional laparoscopic surgery has a difficult learning curve, whereas robotic surgery allows surgeons to perform surgeries in an environment where there is greater mobility in the presence of 3D imaging. However, it is stated that robot-assisted adrenalectomy has similar outcomes with LA and that tumour size is the most important limiting factor for laparoscopic retroperitoneal adrenalectomy (LRA) (5).

Despite all these innovations, the indications of laparoscopic surgery for adrenal masses larger than 6 cm are still controversial. Technical difficulties regarding the laparoscopic removal of large tumours and increased likelihood of malignancy with increasing tumour mass are the two main reasons for the controversy (6). While discussions on the tumour size continued, the efficacy and safety of laparoscopic surgery for tumours ≥8 cm was reported. There is not yet an exact cut-off value for tumour size that can be treated by LA (7,8). Moreover, a recent study also stated that

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the number of cases requiring master level experience for LA was greater than 85 cases (9).

This study aimed to evaluate the effect of adrenal tumour size on intraoperative and postoperative outcomes. In addition, we investigated the learning curve by separating the patients into four groups (A, B, C and D) according to chronological order.

Materials and Methods

All the procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ondokuz Mayıs University Clinical Research Ethics Committee - approval number: 2019/78, date: 14.03.2019) and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was registered in the Clinical Trials Register (www.clinicaltrials.gov, identifier NCT03830593) and informed consent was obtained from all the participants included in the study.

Demographic, intraoperative and postoperative data of 107 patients who underwent LA from April 2010 to October 2018 were analysed, retrospectively. The inclusion criteria were as follows: all hormonally active adrenal lesions, detection of increases in size of <4 cm of adrenal tumours on serial imaging, solitary adrenal metastases without evidence of local invasion, tumours size ≥4 cm, patients between the age of 18 and 80 and American Society of Anaesthesiologists score ≤3. The patients having adrenal masses with specific suspicious signs of malignancy on imaging such as local invasion and irregular tumour margins were evaluated as ineligible for LA, excluded from this study and addressed to open surgery. Retroperitoneoscopic and laparoscopic partial adrenalectomies were also excluded from the study.

Totally 102 patients were included in the study. The patients were divided into 2 groups according to adrenal tumour size as <6 cm (group 1, n=76) and ≥6 cm (group 2, n=26). Variables such as demographics, tumour size and laterality, operation time, EBL, per-operative and postoperative complications, length of hospital stay and final pathology result were compared between the two groups. In order to evaluate the learning curve, the patients were also classified into 4 consecutive groups including group A (1-25), group B (26-50), group C (51-75) and group D (76-102) according to the chronological order of their surgery. Variables including operation time, tumour size, EBL, hospital stay, and overall complications were used to investigate the learning curve.

The clinical diagnosis was made on the basis of a detailed history, physical examination, laboratory tests and imaging methods such as computed tomography and/or magnetic resonance imaging. The size of the tumour was defined using the largest size of the adrenal mass on imaging. Detailed hormonal and endocrinological evaluations were performed in terms of pheochromocytoma, hypercortisolism (Cushing's syndrome) and hyperaldosteronism (Conn's syndrome) in all the patients who were scheduled for definitive treatment.

According to the results of the hormonal evaluation, specific preoperative treatment was given to patients with a functional mass, and hormonal replacement therapy was also applied with respect to the postoperative hormonal status of the patients, when it is necessary. Laparoscopic transperitoneal adrenalectomies (LTAs) were performed at a tertiary care centre by a board certified and experienced laparoscopic surgeon. All demographic, intraoperative and postoperative variables were recorded. Postoperative complications were also evaluated using the Clavien-Dindo classification system (10).

Surgical Technique

All the surgical interventions were performed using a standard lateral transperitoneal approach. After general anaesthesia induction, a urinary drainage catheter and nasogastric tube were placed for decompression of the bladder and stomach respectively during insufflation, respectively. Patients were positioned at 90 degrees, slightly rotated toward the supine and flank-up positon, with the operative side facing upwards. The table is flexed to open the angle between the costal margin and the iliac crest. After a pneumoperitoneum was established using a Veress needle, a 10 mm optic trocar was placed below the costal margin at the lateral edge of the rectus muscle. On the left side, 2 additional working trocars, (10 mm for the dominant hand and 5 mm for other) were placed and the 4th additional trocar was used for liver retraction on the right side.

Dissection was maintained using monopolar hook cautery or Thunderbeat (Olympus, Tokyo, Japan). For right LTA, the first step was the dissection of the right triangular ligament of the liver, thereby mobilising it off of adrenal gland. Then, the retroperitoneal region was opened along the vena cava and the adrenal vein was identified. The adrenal gland was mobilised from the surrounding tissues after controlling the adrenal vein. For left LTA, the lateral peritoneal attachment of the colon was incised and then, the lateral and retroperitoneal attachments of the spleen were divided and the spleen and tail of the pancreas were dissected from the adrenal field. After opening the Gerota's fascia, the left adrenal vein and the rest of the gland were dissected off. Resected tissue was placed in an endo-bag, and removed using the modified Gibson's incision.

Statistical Analysis

The data were analysed using Statistics Package for Social Sciences version 24 (IBM SPSS®, Armonk, NY). In the comparison of the binary groups, independent sample t (when normal distribution was provided), Mann-Whitney U test (when it did not provide normal distribution) and the chi-square test were used to examine categorical data. The analysis results were presented as the mean ± standard deviation for quantitative data and as frequency (percentage) for qualitative data. The significance level was set at $p<0.05$. For evaluation of the learning curve, One-Way ANOVA test was used to compare the numeric variables among groups A, B, C and D. When the homogeneity of variances test was performed, it detected a $p>0.05$ (the normal distribution) for variables such as operation time, hospitalisation, EBL and tumour size. Then, Bonferroni test was used as Post-hoc tests and $p<0.05$ was considered significant.

Results

There were 76 patients (23 males, 53 females) in group 1 and 26 patients (14 males, 12 females) in group 2. The mean age

was 49.7±12.2 and 49.1±12.0 (p=0.826) years old in groups 1 and 2, respectively. The mean tumour size was 32.7±12.7 mm (range, 10-56 mm) in group 1 and 79.5±21.9 mm (range, 60-170 mm) in group 2, (p=0.001). The mean operation time was 53.3±20.4 minute in group 1 and 72.6±29.0 minute in group 2, (p=0.001). The mean EBL was significantly lower in group 1 (65.8±28.6 mL; range: 20-150 mL) than in group 2 (86.35±72.2 mL; range: 30-400 mL), p=0.04. Demographic, preoperative and operative data of both groups are shown in Table 1.

All the patients were managed using the LTA approach and conversion to an open surgery was not required in any cases in both groups. In the perioperative period, there were no spleen, colon or liver injuries in both groups. However, in the intraoperative period, a total of 3 (11.5%) complications occurred in three distinct patients in group 2. One patient had a left renal vein and another had a right renal vein injury. In the patient with left renal vein injury, there was a 7 cm mass adjacent to the left renal vein and the pathology appeared as a paraganglioma. Moreover, in the patient with a right renal vein injury, there was an 8 cm mass that was reported as a myelolipoma. Both intraoperatively injured vessels were repaired laparoscopically suing the intracorporeal suture technique. The third patient had a diaphragmatic injury with opening of the pleural space on the left side, which was repaired laparoscopically without the need for conversion to open surgery.

Table 1. Demographics and operative data of patients

Variable*	Group 1 (n=76)	Group 2 (n=26)	p
Gender, n (%)			
Male/Female	23/53	14/12	0.03
Mean age (years)	49.7±12.2	49.1±12.0	0.826
Functioning tumours, n (%)	57 (75)	11 (42.3)	0.02
PCC	28 (36.8)	9 (34.6)	0.03
Conn's disease	9 (13.1)	0	
Cushing	20 (26.3)	2 (7.7)	
Non-functioning tumours, n (%)	19 (25)	15 (46.1)	
ASA score, n			
1	35	8	0.347
2	38	16	
3	3	2	
BMI, kg/m²	29.4±5.5	27.2±4.7	0.07
Tumour localisation, n			
Right side	40	10	0.212
Left side	36	16	
Tumour size, mm	32.7±12.7	79.5±21.9	0.001
Operation time, min	53.3±20.4	72.6±29.0	0.001
Blood loss, mL	65.86±28.6	86.35±72.2	0.042
Follow-up, month	38.7±23.9	26.3±27.14	0.03
Hospital stay, day	1.22±0.6	2.12±2.2	0.003

ASA: American society of anaesthesiologists, BMI: Body mass index, mm: Millimeter, min: Minute, PCC: Pheochromocytoma, SD: Standard deviation, statistically significant difference was (p<0.05), *: Variables are presented as mean ± SD or number (percent)

Regarding postoperative complications, it was determined that the complication rate was higher in group 2 (p=0.01). Overall, 4 (15.3%) patients had complications in the postoperative period in the group 2. One patient required transfusion due to reduced haemoglobin (grade 2), one patient had a chylous drainage lasting 3 days (grade 1), one patient had postoperative fever (grade 1) and the other one had a fat necrosis on the incision line (grade 2). In group 1, postoperative complications were detected in 2 (2.6%) patients. No patient needed a postoperative transfusion. Postoperative Reversible Encephalopathy syndrome developed in a patient that lasted for 3 days and improved with medical treatment (grade 2), while the other patient had a fat necrosis on the incision line (grade 2). Complications are shown in Table 2.

Pathological evaluation showed that 72 (94.7%) patients were benign and 4 (5.3%) were malignant in group 1, while 19 (73.1%) patients were benign and 7 (26.9%) were malignant in group 2. The final pathology results are shown in Table 3. Upon evaluation of the final pathology results in terms of positive surgical margin in patients who had a malignant disease, no positive surgical margin was detected in both groups. Moreover, in group 2, only 3 patients were shown to have primary adrenocortical carcinoma (ACC) on the final pathological examination and they were followed-up for 35, 26 and 18 months, respectively. Local and distant recurrences or metastasis were not detected during the follow-up.

When the results of the groups (A, B, C and D) allocated by chronological order for the definition of the learning curve were evaluated, there was a statistically significant decrease in the operation time, increase in the tumour size as well as a decrease in the EBL after the completion of the learning curve. However, there was no statistically significant difference in the length of hospital stay and overall complications between the groups. The details of the learning curve are shown in Table 4.

Discussion

LA is the gold standard method for the surgical management of benign adrenal masses <6 cm in size (11). Laparoscopic

Table 2. Overall complications

	Group 1 (n=76)	Group 2 (n=26)
Intraoperative complications		
Renal vein injury	-	2
Diaphragmatic injury	-	1
Total %	0	11.5% p=0.01
Postoperative complications*		
Blood transfusion (grade 2)	-	1
PRES (grade 2)	1	-
Chylous drainage (grade 1)	-	1
Fever (grade 1)	-	1
Fat necrosis (grade 2)	1	1
Total %	2.6%	15.3% p=0.01

*According to the Clavien-Dindo classification system, PRES: Postoperative Reversible Encephalopathy syndrome

surgery has significant advantages including the decrease in postoperative pain and analgesic requirement, earlier resumption of oral intake, shorter hospital stay, earlier return to normal life and better cosmetic outcomes compared with OA (12). Despite the innovations in minimally invasive treatment methods such as laparoscopic, robot-assisted, and single-incision procedures, the widely accepted view is that OA is recommended for patients who have a clinical suspicion of ACC. It was reported that the incidence of ACC for tumour sizes <4 cm, 4-6 cm and >6 cm is 2%, 6% and 25%, respectively. However, tumour size alone is not a decision-making criterion for malignancy. It has been shown that 13.5% of adrenal masses smaller than 5 cm might reveal an ACC (13). In addition, large necrosis areas, irregular borders and the presence of local invasion on radiological evaluation may suggest malignancy (14,15). It has been strongly emphasised that complete resection of ACCs with a negative surgical margin is the strongest predictor of mortality and it has been suggested the necessary care should be taken in selecting patients (16).

Table 3. Final pathological outcomes

	Group 1 (n=76)		Group 2 (n=26)	
	Frequency (n)	Percent (%)	Frequency (n)	Percent (%)
Adenoma	50	65.7	2	7.7
PCC	14	18.4	9	34.6
ACC	-	-	3	11.5
Solid metastasis	3	3.9	3	11.5
Mesenchymal tumour	1	1.3	-	-
Lymphoma	-	-	1	3.8
Other benign lesions*	8	10.5	8	30.7
Total	76	100	26	100
Overall final pathology p<0.05				
Benign	72		19	
Malign	4		7	

ACC: Adrenocortical carcinoma, PCC: Pheochromocytoma, *: Cyst, ganglioneuroma, schwannoma, myelolipoma, solid metastasis: renal cell carcinoma, colon cancer, breast cancer and lung cancer metastasis

In this study, ACC was detected in 3 (11.5%) of 26 patients in group 2. In all of these patients, the masses were completely removed without damaging the tumour capsule. Also, it is shown in the final pathology report that we obtained a negative surgical margin. No recurrence was detected on follow-up in patients with ACC. Furthermore, no ACC was detected in any patient in group 1 according to the final pathology reports.

Debates on this topic such as operation indications and limitations, advantages and disadvantages of the recent approaches and comparison of safety and effectiveness of minimally invasive techniques are still ongoing. Although many experienced surgeons have reported that laparoscopic treatment of adrenal masses of up to 12-15 cm is available, no generally accepted cut-off value in terms of tumour size has been described (17,18,19). Consequently, we performed LA for all patients without a local invasion on radiological imaging and these patients did not require additional open surgery.

It has been reported that LRA decreases operation time, hospital stay and postoperative analgesic requirement compared with LA (20). Morbidity and mortality rates are have also been reported similarly in those techniques (21). However, the most important limiting factor for LRA is mass size. Wang et al. (22) reported that >7 cm large masses leads to increased operative time and more blood loss. It has been shown that LRA and LA were similar in terms of perioperative and postoperative complications and conversion to an open surgery (23). Besides, Castillo et al. (24) reported that adrenal tumour that were larger than 8 cm increased the duration of surgery, blood loss and hospital stay, but did not affect perioperative morbidity. In the present study, it was determined that as the tumour size increased, the operation time and the length of hospital stay also increased. Additionally, EBL was found to be higher in group 2 when the 2 groups were compared (p=0.042). Technically, a transperitoneal lateral laparoscopic approach has been implemented to all of our patients with adrenal tumours who were included in this study. This is because we believe that this technique will allow the surgeon to create a more comfortable working space and will also enable the laparoscopic repair of vascular injuries without the need to convert to an open surgery.

Table 4. The learning curve for laparoscopic adrenalectomy

Variables*	Group A (1-25)	Group B (26-50)	Group C (51-75)	Group D (76-102)	p
Operation time (min)	71.52±27.0	56.4±17.7	54.8±25.8	50.96±21.79	0.01
Tumour size (mm)	35.48±20.37	41.8±22.28	45.20±24.34	55.22±31.21	0.04
Groups by tumour size					
<6 cm	21 (84)	20 (80)	19 (76)	16 (59.3)	0.04
≥6 cm	4 (16)	5 (20)	6 (24)	11 (40.7)	
Blood loss (mL)	107.8±65.63	68.2±18.9	66.6±33.5	43.89±16.0	0.001
Hospitalisation (day)	1.24±1.0	1.24±1.05	1.72±2.2	1.59±1.0	0.467
Overall complication					
No	23	24	24	23	0.629
Minor (grade I-II)α	2	1	1	3	
Major (grade III-V)α	0	0	0	1	

α: Clavien-Dindo classification of surgical complications (grade I-V), *: Variables are presented as mean ± SD or number (percent), SD: Standard deviation, mm: Millimeter, cm: Centimeter

A surgeon who performed ≥4 adrenalectomies per year was defined as a high-volume surgeon by Lindeman et al. (25). We found that mortality and complications were inversely proportional to the number of annual cases of the surgeon. Moreover, low surgeon volume was found to be an independent indicator of complications. The most significant advantage of LA is that it has lower morbidity and mortality rates compared to the open technique. In the laparoscopic technique, the overall complication rates are stated as less than 10% and the rate of conversion to an open surgery was 3.5%. Furthermore, laparoscopic surgery might need to be converted to an open surgery due to complications such as vascular or visceral injuries. In this study, the overall complication rate was 8.8% (9 of 102 patients). Intraoperative complications were more common in group 2 and were detected in 3 (11.5%) patients; 2 of 3 had renal vein injury and the other had a diaphragm injury.

According to the literature, the first 30 cases were evaluated as part of the learning curve (11,26). In the present study, in contrast to the previous literature, patients were divided into 4 distinct groups as A, B, C and D according to chronological order and then the learning curve was evaluated. In this study, 25 patients were included in the first 3 groups (A, B, C) and 27 patients in the last group (D). It was found that the reduction in the mean operating time, tumour size and blood loss was statistically significant ($p<0.05$). However, hospital stay and overall complication rates were similar among the groups over time ($p>0.05$). We can conclude that the completion of the learning curve requires approximately 25 cases, while laparoscopic treatment of large adrenal masses requires more than 75 cases of experience to achieve a significant decrease in the operation time and blood loss. Moreover, increased tumour size may pose a risk for intraoperative and postoperative complications.

The final pathology reports were evaluated between group 1 and group 2. As tumour size increases, ACC was likely to be detected, if solitary adrenal metastasis is excluded in patients with tumour size >6 cm. In the final pathological exam, only 2.94% (3 of 102) of patients had revealed ACC. Furthermore, the ratio of functional and benign masses increases in cases with an adrenal mass size less than 6 cm. It was reported that resection of isolated metachronous adrenal metastasis of many kinds of primary cancers with the laparoscopic technique may help to achieve a negative surgical margin and may improve the overall survival (27). As a general practice, our primary surgical principle is to identify surrounding tissues before the tumour is dissected. For this reason, adjacent structures including renal vein, the upper pole of the kidney and the vena cava or aorta are first identified and then tumour dissection is completed. Furthermore, specific attention to oncological principles during surgery resulted in achieving a negative surgical margin in all the patients whose final pathology results were revealed as malignancy in both groups.

Study Limitations

There are some limitations to the present study. The retrospective nature and the difference in the number of patients between groups are the main limitations. However, it may be difficult to design a prospective study in patients who underwent LA. On the other hand, all the surgeries were performed by a single surgeon and calculating the learning curve in terms of evaluation of the surgical experience over time in the entire cohort may reduce this limitation.

Conclusion

LA is a reliable and an effective approach for the management of large adrenal tumours (>6 cm). However, in order to improve surgical outcomes and reduce complications in patients with large adrenal tumours, it is necessary to have competent experience in LA.

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Ethics

Ethics Committee Approval: All the procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ondokuz Mayıs University Clinical Research Ethics Committee - approval number: 2019/78, date: 14.03.2019) and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all the participants included in the study.

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Authorship Contributions

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

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Original Article

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Renal Angiomyolipoma: A Clinicopathological Study of Seven Cases and Review of the Literature

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Abstract

Objective: Renal angiomyolipomas (AMLs) are mesenchymal kidney tumours that have triphasic histology. This study aimed to present the clinical, pathological and immunohistochemical features of seven AML cases along with a review of the relevant literature.

Materials and Methods: Seven cases of pathologically diagnosed AML were included in the study. The presence of fat tissues, smooth muscle cells, blood vessels and epithelioid components were determined for all cases. Tumour necrosis, haemorrhage, mitosis, lymphovascular and perineural invasion were also recorded. Immune markers [human melanoma black-45 (HMB45), Melan-A, smooth muscle actin (SMA), cytokeratin], previously applied to the tissue sections, were re-evaluated as positive and negative staining.

Results: All cases were classic AML types. Five patients had flank pain and two had haematuria. The tumour was located in the left kidney in two cases and in the right kidney in five cases. The mean size of the AMLs was 7.36±4.23 cm. Tumours were separated from the normal kidney parenchyma with good margins and composed of mature fatty tissues, blood vessels and fusiform spindle smooth muscle cells in varying proportions. Immunohistochemically, all cases were positive with HMB-45, Melan-A and SMA. No case was positive for cytokeratin staining.

Conclusion: Correct histological diagnosis of renal AML subtypes is crucial. Incorrect diagnosis of classic renal AML may lead to inadequate postoperative management. Clinicians should be aware of the malignant potential of epithelioid AML and the need for long-term follow-up.

Keywords: Clinicopathological features, immunohistochemistry, renal angiomyolipoma

Introduction

Renal angiomyolipoma (AML) was first defined in 1951 by Morgan et al. (1). They are mesenchymal kidney tumours containing smooth muscle cells, dysmorphic blood vessels, and adipocytes (triphasic histology). AMLs are usually benign tumours, but at risk of spontaneous bleeding. Generally, AMLs are asymptomatic and found incidentally by routine imaging techniques and rarely become symptomatic (2,3,4).

AMLs are rare kidney tumours and constitute 2%-6.4% of all renal tumours (2). The prevalence of renal AML in the general population ranges from 0.3% to 3%, and female individuals are four times at risk than their male counterparts (5).

The World Health Organization (WHO) identified two types of renal AML: classic AML (CAML) and epithelioid AML (EAML). CAML is a benign tumour and consists of the three components mentioned in the first paragraph. However, EAML has a predominant epithelioid component and potentially malignant behaviour (6). EAML cases were found to present the characteristics of malignancy, such as tumour venous extension, distant metastasis and local recurrence. Therefore, it is important to distinguish EAML from CAML (7).

Approximately 80% of renal AMLs are sporadic and have no association with any Genetic syndrome. However, some AMLs can be seen with tuberous sclerosis complex (TSC) or pulmonary lymphangioleiomyomatosis. Moreover, 10%-20% of renal AMLs are thought to be associated with TSC. In addition, 80%-90% of patients with TSC have AML (8).

The most common group of patients with sporadic renal AMLs are middle-aged women. Generally, sporadic AMLs do not

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cause any symptoms and are detected incidentally during renal imaging. In addition, slow-growing sporadic AML usually does not lead to deterioration of renal function. Some AMLs can grow over time and have increased risk of bleeding in lesions greater than 4 cm (9). Moreover, these tumours can be found outside the kidney, mainly in the retroperitoneal area and in the liver (10). This study aimed to present the clinical, pathological and immunohistochemical features of seven AML cases along with a review of the relevant literature.

Materials and Methods

In this study, 343 patients who underwent radical or partial nephrectomy from 2010 to 2018 at a university hospital were screened retrospectively, and seven patients with pathologically diagnosed AML were included. Clinical information of the patients (age, gender, hospital admission complaints, radiology of tumours, type of surgery) was obtained from medical records.

The study was approved by the University for the non-interventional Clinical Research Ethics Board (approval number: 05, date: 07.03.2019).

Classification of AMLs

AMLs were classified as CAML and EAML according to the 2016 WHO Classification of Tumors of the Urinary System and Male Genital Organs. CAMLs were diagnosed when the tumour is composed of a variable proportion of adipose tissue, smooth muscle cells and abnormal thick-walled blood cells. When the tumour shows proliferation of predominantly epithelioid cells, the diagnosis was EAML (11).

Pathological Parameters and Immunohistochemistry

The size, localization and focality of the tumours were obtained from the pathology reports. The largest tumour diameter was determined from the macroscopic examination. Presence of fat tissues, smooth muscles, blood vessels and epithelioid components were determined for all cases. In addition, tumour necrosis, haemorrhage, mitosis, extrarenal metastasis and lymphovascular and perineural invasion were recorded. Immune markers [human melanoma black-45 (HMB-45), Melan-A, smooth muscle actin (SMA), cytokeratin], previously applied to tissue sections, were re-evaluated as positive and negative.

Statistical Analysis

The present study has been conducted with 7 patients. The data of the patients were expressed as mean + standard deviation and percentage.

Results

A total of seven CAML cases were analysed in this study. Their clinicopathological features are listed in Table 1. Of the seven patients, five were women (71.4%) and two were men (28.6%), and the female/male ratio was 5/2. The mean patient age was 59±16.7 years, which ranged from 44 to 90 years.

Clinical Features

Five patients (71.4%) had flank pain and two (28.6%) had haematuria. According to the medical records, none of the patients had TSC. Radiologically, four patients (57.1%) had a solid + fatty mass lesion in the renal parenchyma. By radiological examination, one patient (14.3%) had solid tumour, and the tumours of two patients (28.6%) could not be assessed. The patients were subjected to different procedures. Five patients (71.4%) underwent radical nephrectomy, and two patients (28.6%) underwent partial nephrectomy.

Pathological and Immunohistochemical Features

The tumour was located in the left kidney in two cases (28….6 %) and in the right kidney in five cases (71.4%). One patient (14.3%) had multifocal tumour, while other patients had unifocal tumours.

In gross pathology, the mean size of the AMLs was 7.36±4.23 cm (range, 3.5-16 cm). The tumours have marked borders, and the cross sections of the tumours varied from yellow to dark brown according to the percentage of the components they contained. In haematoxylin-eosin staining, tumours were separated from the normal kidney parenchyma with good margins and consisted of mature fatty tissues, blood vessels and fusiform spindle smooth muscle cells (classical triphasic histology) (Figures 1, 2). Blood vessel walls were thick, and some were hyalinised. The mitotic activity was 0-1/10HPF in all tumours. No tumour necrosis, haemorrhage, extrarenal metastasis and lymphovascular and perineural invasion were detected. Immunohistochemically, all cases (100%) were positive with HMB-45 (focal but strong),

Table 1. Clinicopathological features of the cases

Case no	Age	Gender	Symptoms	Radiology	Surgical procedure	Tumour location	Focality	Tumour size (cm)	Diagnosis
1	72	F	Flank pain	Solid mass	Partial nephrectomy	Right	Unifocal	4	CAML
2	44	F	Flank pain	Solid + fatty mass	Radical nephrectomy	Left	Unifocal	5	CAML
3	58	F	Flank pain	NRR	Radical nephrectomy	Left	Unifocal	7	CAML
4	56	F	Haematuria	Solid + fatty mass	Radical nephrectomy	Left	Multifocal	16	CAML
5	90	F	Haematuria	NRR	Radical nephrectomy	Left	Unifocal	3.5	CAML
6	48	M	Flank pain	Solid + fatty mass	Partial nephrectomy	Right	Unifocal	8	CAML
7	45	M	Flank pain	Solid + fatty mass	Radical nephrectomy	Left	Unifocal	8	CAML
Mean	59							7.36	
SD	16.7							4.23	

M: Male, F: Female, NRR: No radiological reports, CAML: Classic type angiomyolipoma, SD: Standard deviation

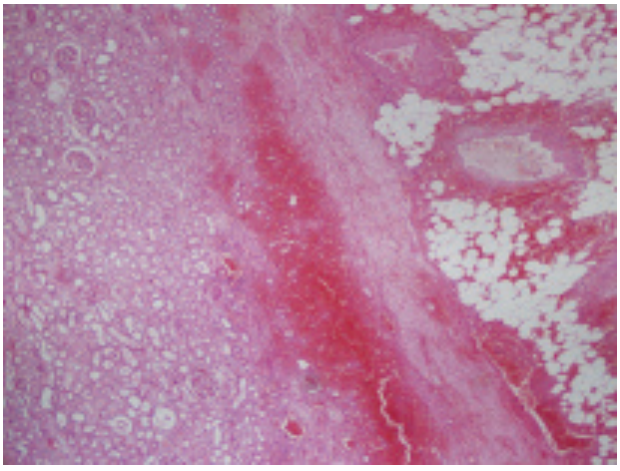


Figure 1. The tumour is separated from the normal kidney parenchyma with good margins (H + E ×40)

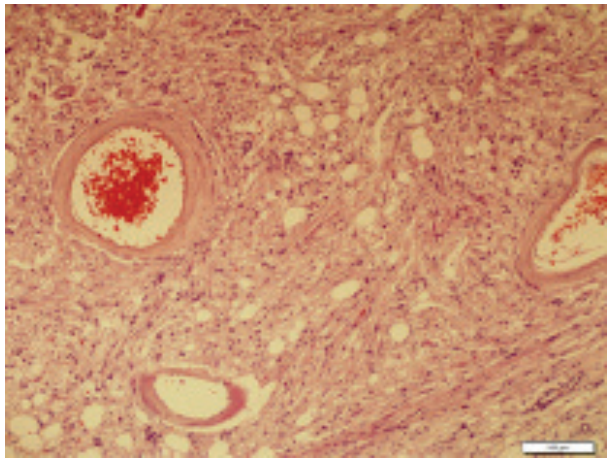


Figure 2. Classic triphasic histology. The tumour is composed of a mixture of mature fat, thick-walled blood vessels, and smooth muscle cells (H + E ×100)

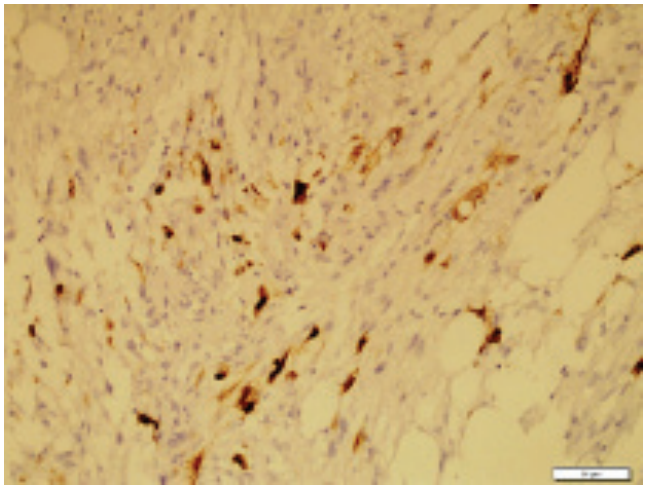


Figure 3. Human melanoma black-45 (HMB-45) expression in tumour cells (HMB-45, ×200)

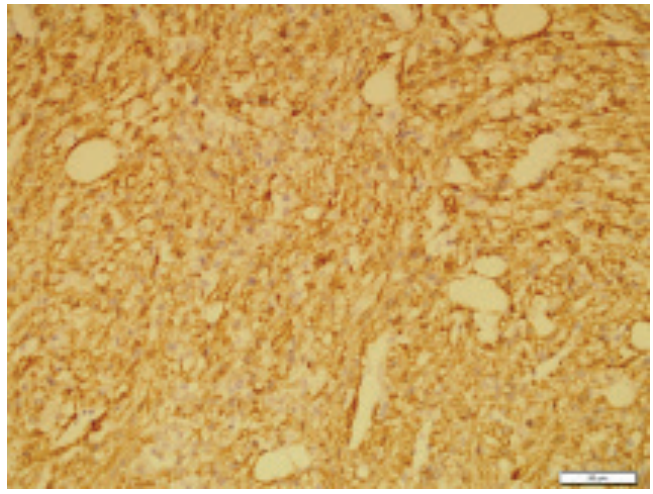


Figure 4. The spindled smooth muscle cells are positive for smooth muscle actin (SMA) (SMA, ×200)

Melan-A and SMA (Figures 3,4). No case was positive for cytokeratin staining.

Discussion

A previous study examined >60,000 patients by abdominal ultrasonography (USG) and reported an AML prevalence of 0.44% (n=270/61,389). In the present study, the occurrence rate of AML was higher in women (0.60%) than in men (0.28%). In addition, 57% of the patients had right kidney and 43% had left kidney involvement (12). Another study examined 1,948 patients by abdominal computed tomography (CT) and reported an AML prevalence of 2.2%, with a mean tumour size of 5 mm (13). Compared with studies performing USG, the high incidence of AML in CT examinations was the result of a more advanced imaging technique of CT and detection of smaller tumours.

In our study, most of the patients (5 of 7 patients) were female, with mean age of 59±16.7 years, which ranged from 44 to 90 years. The tumours were located in the right kidneys in five patients and in the left kidneys in two patients. All cases were unifocal except for one case, which was multifocal. The tumour diameters ranged from 3.5 to 16 cm, with mean diameter of 7.36±4.23 cm. The tumours had good margins, and the cross sections of the tumours varied from yellow to dark brown according to the percentage of the components they contained.

The most serious complications of AML are retroperitoneal haemorrhage (Wunderlich syndrome), haematuria and renal dysfunction. Wunderlich syndrome occurs classically during pregnancy, and haemorrhagic shock may be observed in 20% of the patients (8). Especially, large tumours (>4 cm) may cause complications such as bleeding into the retroperitoneal region or the renal collecting system, even if they are benign (14). AMLs also have the potential to invade local structures. Pregnancy and hormonal treatment are known to increase tumour growth (9). In our study, five patients had flank pain and two had haematuria.

On USG, AML classically present as hyperechoic lesions with posterior acoustic shadowing (8). CT is the most commonly used imaging technique in AML diagnosis, and renal AML diagnosis is established using CT, showing negative fat density (between -10 and -100 Hounsfield units) with an accuracy rate of 86% (4). As the fat content decreases in AML, diagnosis becomes more difficult with CT and USG. Magnetic resonance imaging (MRI) can be used in these cases. A study reported that half of AML cases had poor fat content, thus causing difficulty in differentiating AML from other renal lesions by imaging methods (15). In both T1 and T2 weighted sequences, hyperintense appearance due to fat content and hypointense appearance in fat-suppressed T1 images are helpful in differentiating AMLs from other lesions (16). If the AML cannot be diagnosed with imaging techniques, imaging assisted percutaneous needle biopsy may be recommended as an alternative to surgical exploration. The risk of bleeding after biopsy of AMLs with low fat is not higher than the risk of bleeding of other renal tumours when an appropriate needle is used for biopsy (17).

In the differential diagnosis of AML, renal cell carcinoma (RCC), oncocytoma and metastasis of any other primary tumours are present. Fat-predominant and muscle-predominant AMLs may mimic liposarcoma and leiomyosarcoma, respectively, which are the most common types of retroperitoneal sarcomas. These lesions can be usually distinguished by their own radiological findings. For example, in T2 weighted MRI, smooth muscles are observed as hypointense signal in AML while hyperintense in RCC (18).

TSC is a multisystemic hamartomatous disease with autosomal dominant inheritance, affecting both adults and children. It is usually caused by a decreased or absent expression of TSC1 (hamartin) or TSC2 (tuberin) genes. The lack of hamartin-tuberin complex results in the development of tumours in a number of organs, including AML in the kidneys. Affected individuals have a high risk of developing various skin lesions, including facial angiofibromas, hypopigmented macules, shagreen patches and ungual fibromas. Bilateral and multifocal renal AMLs, consisting of abnormal vessels, immature smooth muscle cells, and fat cells, are one of the benign tumours of the kidney and develop in approximately 55%-75% of patients with TSC aged <10 years. In addition, RCCs may develop in various histological types in some patients with TSC. Although lifelong risk is similar to that in the general population (2%-3%), the age of onset of renal tumour is younger in patients with TSC (mean age, 36 years) (9). Although the majority of AMLs occur sporadically, this tumour occurs in 80%-90% of patients with TSC. TSC is caused by germline mutations of TSC1 on 9q34 and TSC2 on 16p13. Kidney AMLs related with TSC are frequently multifocal and bilateral. Mutations of TSC2 can also be seen in sporadic AML. AML is also associated with lymphangioleiomyomatosis (9). Although only 10%-20% of AML cases are associated with TSC, all patients should be investigated in terms of non-diagnosed or subclinical TSC. When compared with renal AML associated with TSC, sporadic renal AML usually occurs at an older age, usually single involvement, causes rare spontaneous haemorrhage and symptoms, and shows a slower growth course (19). TSC was not observed in any of our cases.

Because most of the AMLs are small and benign, the first option recommended in the current approach and in the European Association of Urology guidelines is active surveillance (9). However, the first choice in the indications of treatment is selective artery embolisation, and the surgical option should be only the final option. In any case, nephron protective surgery should be preferred (7).

In our study, all patients were followed up for a while, and the surgical method was then selected. Only two patients had partial nephrectomy. In the remaining five cases, radical nephrectomy was performed. According to their histological appearance, AMLs are classified as classic and epithelioid types. The classical type is observed more frequently (20). The major characteristic feature of CAMLs are abnormal thick vessel walls, which prevent the proper development of internal elastic lamina, smooth muscle-like cells and adipose tissue. These three components can be observed in different ratios, and some components may not be seen at all CAMLs. CAML is found primarily in the kidney, as well as in the spleen, liver, uterus and fallopian tubes (21). EAML is a monotypic type of AML that can mimic RCC and is clinically benign or malignant (aggressive and metastatic). It is distinguished from CAML by the presence of epithelioid component with abundant eosinophilic and granular cytoplasm. EAML may show malignant transformation, and it can manifest itself as local recurrence or distant metastasis. There is also a need for adjuvant therapy after surgery (22). However, there is no consensus on the epithelioid component ratio of the tumour for the diagnosis of EAML (10,20).

Aydin et al. (20) reported clinical and histopathological features of AML in 194 patients. EAML was found in 15% of the patients, nuclear atypia in 7%, and abnormal histological findings were also observed in 3.6%. The mean epithelioid component ratio was 51% in these patients. The presence of epithelioid component was higher in patients with TSC (27%) than in those with sporadic AML (7%). Local recurrence or distant metastasis was not observed in the study, which gave a mean follow-up of 5.1 years.

Four microscopic features are recommended in the EAML definition, which are as follows: presence of atypical epithelioid cells at ≥70%, ≥2 mitosis in the area of 10× magnification, atypical mitosis and necrosis. The presence of three or all of these features has a high predictive value for malignancy. With this model, 78% of the patients with malignant EAML and 100% of benign lesions can be distinguished (23).

There is no consensus as to the percentage of epithelioid cells required for diagnosing EAML, with some authors suggesting that only ≥5% of the cells must exhibit epithelioid histology, while others demanding at least 20% or even 80% (2,23,24). EAML was first described by Mai et al. (25) in 1996. In 2004, the WHO stated that EAML is a mesenchymal tumour with a potential for malignancy. Renal EAML is examined in two groups as pure sporadic EAML and TSC-associated EAML. EAML was found to have higher rate of association with TSC than with CAML (26).

Typically, AMLs are unencapsulated and well-circumscribed masses. The colour of the cut surface varies depending on the existing fatty content in the lesion. Fat-poor tumours appear

to be tan white to pink, while fat-rich ones are predominantly yellow. As the name implies, AMLs consist of three components: thick-walled vessels, smooth muscles and fat tissues. For the diagnosis of fat-poor lesions, the fat ratio of the tumour should be less than 25%. In some cases, hyalinisation, cystic change or calcifications have also been reported. Epithelioid cells may be found in very few cases. The presence of more than 70% atypical epithelioid cells, ≥2 mitoses per 10 high power fields, atypical mitotic figures and necrosis are associated with increased risk of malign behaviour (9).

Study Limitations

In our study, all cases were of CAML type. AML tumours were well separated from the normal kidney parenchyma. Thus, the structure was suitable for classical triphasic histology: it contained mature fatty tissues, blood vessels and fusiform spindle smooth muscle cells. Mitotic activity, tumour necrosis, haemorrhage, extrarenal metastasis, lymphovascular and perineural invasion were not seen.

In addition to the epithelioid histology in EAML, epithelioid cells must have enlarged vesicular nuclei with prominent nucleoli. When the epithelioid component predominates and nuclear atypia is extensive, these tumours may be erroneously diagnosed as RCC or sarcoma. For this reason, it may be necessary to perform immunohistochemical studies to confirm the diagnosis of EAML (7). Moreover, in suspected cases, the renal tissue taken for biopsy can be analysed by specific immunohistochemical techniques. The smooth muscle component in AMLs is positively stained with mesenchymal markers such as vimentin and actin (8).

The smooth muscle morphology seen in AML is similar to sarcomatous RCC or leiomyosarcoma, making it difficult to interpret the biopsy. The development of smooth muscle-specific dyes and HMB-45 increased the reliability of percutaneous biopsy. HMB-45 immunoreactivity is a feature of perivascular epithelioid cell tumours; in fact, all AMLs are stained positive with HMB-45. RCCs are not stained with HMB-45. However, a small proportion of AMLs, especially epithelioid types, cannot be stained with HMB-45 (8). The cells often express smooth muscle markers as well, particularly SMA and, less commonly, desmin. However, the fat-poor tumours are typically negative for Melan-A. Staining for S-100 protein is usually negative. The majority of EAML cases demonstrate membranous and cytoplasmic staining of E-cadherin, whereas CAML cases demonstrate cytoplasmic staining alone. Moreover, in diagnostically challenging cases, staining for CD68 (PG-M1) and anti-melanoma antibody (PNL2) may be helpful in distinguishing renal EAML from other renal tumours. Some AML samples can be stained positive for CD-177 (27,28,29,30).

In our study, all cases (100%) were positive with HMB-45, Melan-A and SMA. No case was positive for S100 and cytokeratin staining.

Conclusion

Renal AMLs are mesenchymal kidney tumours and have triphasic histology. The most common group of patients with renal AMLs are middle-aged women. Generally, AMLs are asymptomatic and rarely become symptomatic. AMLs are unencapsulated and well-circumscribed masses. The colour of the cut surface varies depending on the existing fatty content in the lesion. As the name implies, AMLs consist of three components: thick-walled vessels, smooth muscles and fat tissues. HMB-45 immunoreactivity is a feature of perivascular epithelioid cell tumours; in fact, all AMLs are stained positive with HMB-45. The cells often express smooth muscle markers as well, particularly SMA and, less commonly, desmin.

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Original Article

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Evaluating the Effects of Different Ischaemia Techniques on Functional Outcomes of Laparoscopic Partial Nephrectomy

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Abstract

Objective: This study aimed to investigate the influence of different ischaemia techniques on short-term and one year renal function following laparoscopic partial nephrectomy (LPN).

Materials and Methods: Data of 359 patients who underwent LPN between November 2009 and April 2018 were reviewed, retrospectively. A total of 287 patients were included in the study. Patients were divided into 4 groups according to type of ischaemia as follows: group A (n=33) was warm ischaemia time (WIT) >20 minute, group B (n=202) was WIT ≤20 minute, group C (n=16) was selective arterial clamping and group D (n=36) was off-clamp. Demographic data, preoperative and postoperative outcomes were compared. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Change in eGFR according to group and time was evaluated using two-way analysis of variance. P values <0.05 were adopted as significant.

Results: The mean tumour size was 46, 34, 36 and 25 mm (p=0.001), and operation time was 123, 92, 100 and 79 minute (p=0.001) for groups A, B, C and D, respectively. There was no need for open surgery in any of the patients. Blood loss, intraoperative and postoperative complication rates were found to be non-significantly different (p>0.05) between groups. Only 4 patients in group B had positive surgical margin. The percentage of relative eGFR (% of ΔeGFR) decline 1 year after LPN was significantly (p=0.001) higher in the ischaemic groups (A and B: 9.3% and 7.5%) compared to the zero-ischaemia groups (C and D: 5% and 3.7%).

Conclusion: This study revealed that after LPN, cumulative renal function decreases to a certain extent regardless of the technique. However, it was found that cumulative renal functions are better preserved when ischaemia time is reduced to ≤20 min or eliminated.

Keywords: Ischaemia, laparoscopy, partial nephrectomy, selective ischaemia, zero-ischaemia

Introduction

Partial nephrectomy (PN) is the gold standard treatment modality for patients with kidney confined renal tumours (if technically feasible) since it ensures similar oncological outcomes and better renal function (RF) preservation compared to radical nephrectomy. Nephron sparing surgery (NSS) preserves RF, decreases the risk of cardiovascular mortality due to chronic renal failure and provides a crucial survival advantage (1).

Postoperative RF status is associated with quality (age, gender, baseline RF and comorbidities), quantity (the amount of healthy kidney tissue preserved) of the renal parenchyma, as well as ischaemia time of one of the essential modifiable risk factors affecting preserved renal parenchyma and postoperative RF (2). The hypothesis of 'every minute counts' under ischaemia by Thompson et al. (3) led to the advancement in various PN techniques that helped to minimise or eliminate the warm ischaemia time (WIT), although their cut-off limit is still unclear. These techniques include early unclamping, selective arterial clamping and off-clamping. The contribution of laparoscopic and robot-assisted surgeries to this rapid development in the era of minimally invasive NSS cannot be underestimated. Although each technique has its own advantages and disadvantages, open, laparoscopic and robot-assisted approaches produce similar functional and oncologic outcomes (4).

In this article, we aimed to evaluate the effect of different laparoscopic partial nephrectomy (LPN) techniques including global ischaemia, selective-clamp and off-clamp on functional and oncological outcomes.

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Materials and Methods

The study has been approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (OMU KAEK 14.02.2019/151), and conducted in conformity with the Declaration of Helsinki in 1995. Written informed consent were obtained from all patients included in the study.

Medical records of 351 (out of 359) patients with the complete data who underwent LPN from November 2009 to April 2018 and followed-up at a tertiary care university hospital, department of urology were analysed, retrospectively. Prospectively stored patients' data were retrieved from the hospital's database. All LPNs were performed by the same surgeon.

Patients with solitary kidney (n=10), horseshoe kidney (n=4), pelvic ectopic kidney (n=2), graft kidney (n=2), multiple renal tumours in a single kidney (n=3), bilateral renal tumours (n=8, 16 procedures) and patients <18 years of age (n=3) were excluded in this study. In addition, patients who without a one year follow-up (n=32) were also excluded from this study. A total of 287 patients with contralateral functioning kidney were included in this study. Patients were grouped into 4 according to the type of ischaemia as follows: group A (n=33) was WIT >20 minute, group B (n=202) was WIT ≤20 minute, group C (n=16) was selective-clamp and group D (n=36) was off-clamp.

Demographic characteristics of patients such as age, gender, body mass index (BMI); and systemic diseases such as Diabetes Mellitus, hypertension and coronary artery disease were recorded. Medical data of patients including tumours size, lateralisation of the tumour, surgical technique, operation time (OT), estimated blood loss (EBL), WIT, preoperative and postoperative haemoglobin values, as well as preoperative and postoperative (1st day, 1st month, 6th month and 1st year) serum creatinine levels at were also recorded. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (5). Clinical diagnosis was done by radiological imaging techniques. Magnetic resonance imaging and/or triphasic contrast-enhanced computed tomography was used to analyse the tumour anatomy. Tumour complexity was evaluated by radius of the tumour size, exophytic, nearness to collecting system, anterior, location (RENAL) nephrometry score (6). The final decision on how to perform LPN was based on renal vascular anatomy, RENAL Nephrometry score (RNS), tumour characteristics, vascular anatomy of the kidney, as well as the surgeon's preference or discretion. Intraoperative and postoperative complications, length of hospital stay, final pathology outcomes and surgical margin status were recorded. Furthermore, postoperative complications were graded according to the modified Clavien-Dindo classification system (I-V) (7).

Surgical Techniques

Although the patient position and trocar configuration differed according to the transperitoneal (8) and retroperitoneal approach (9), both techniques were applied as previously described in the literature. The renal artery, renal vein and ureter were dissected and then isolated with vascular silicon tapes. The kidney was released from the surrounding tissues as much as possible, and care was taken to ensure the preservation of perirenal fat tissue on the tumour. Laparoscopic ultrasound was used to detect the tumour mass and thus the surgical margin. Monopolar hook was used to score the surgical margin. The renal tumours were completely excised using cold scissors, with a thin negative margin. The tumour bed was sutured in two layers supported with hem-o-lock clips. A great effort was made to secure the remnant renal parenchyma, and prevent bleeding during tumour bed control. The specimen was extracted in an endo-bag, and a drain was placed in the surgical field.

Global ischaemia technique: The main renal artery and vein were dissected and isolated, and then controlled using laparoscopic bulldog clamps, separately.

Selective-clamp technique: The main renal and segmental renal arteries and also the renal vein was dissected and isolated. Afterwards, the segmental artery was controlled with a bulldog clamp. The indocyanine green (ICG) with near-infrared fluorescence imaging was implemented to specify resection margins of the tumour after control of the segmental artery (10).

Off-clamp technique: The main renal artery and vein were dissected and isolated, however, neither hilar nor segmental vessels were clamped in any of the cases. All LPN procedures were performed with WIT of zero (11).

Statistical Analysis

Data was analysed using Statistics Package for Social Sciences version 24 (IBM SPSS®, Armonk, NY). Test for normal distribution was done by the Shapiro-Wilk test. One-Way analysis of variance and independent samples t-test were used for the comparison of normally distributed data. Post-hoc multiple comparisons was done using Tukey HSD test. Generalised linear models were used to determine whether temporal changes of eGFR and ΔeGFR values were influence by the groups. Categorical data were analysed using chi-square test. Analysis results were presented as mean ± standard deviation for quantitative data, and presented as frequency (percentage) for categorical data. P value <0.05 was adopted as significant.

Results

A total of 287 (79.9%) patients who underwent LPN were included in the study. The demographic data and clinical tumour characteristics of the patients in each group (A-D) are summarised in Table 1. The age distribution, gender, BMI, American Society of Anesthesiologists score, tumour laterality and tumour localisation were non-significantly (p>0.05) different between the groups. However, the mean tumour size and RNS were statistically different between the groups.

Intraoperative variables, perioperative and postoperative complications are shown in Table 2. While the mean OT in group A was statistically different when compared to groups B and D, it was non-significantly different when compared to group C (p=0.074). In terms of WIT, a statistically significant difference was found between group A and B, and between group B and C (p=0.001), while WIT was non-significantly different between group B and C (p=0.923). Since WIT in group D was zero, no statistical comparison was made with respect to other groups. Although the mean EBL was highest in group D, it did not differ when compared to the other groups.

Table 1. Demographics and clinical tumour features of groups according to the kind of ischaemia technique					
Variable*	**A (n=33)**	**B (n=202)**	**C (n=16)**	**D (n=36)**	**p**
Age, years	52.82±10.6	54.77±12.1	56.56±11.9	57.61±13.9	0.391
Gender					
Male	20 (60.6)	119 (58.9)	9 (56.3)	19 (52.8)	0.901
Female	13 (39.4)	83 (41.1)	7(43.8)	17 (47.2)	
BMI (kg/m^2)	27.18±3.1	27.47±3.5	26.20±2.7	26.75±3.0	0.378
DM					
Yes	9 (27.3)	34 (16.8)	8 (50)	6 (16.7)	0.009
No	24 (72.7)	168 (83.2)	8 (50)	30 (83.3)	
HT					
Yes	9 (27.3)	91 (45)	11(68.8)	15 (41.7)	0.048
No	24 (72.7)	111(55)	5 (31.3)	21 (58.3)	
CAD					
Yes	3 (9.1)	31 (15.3)	3 (18.8)	6 (16.7)	0.758
No	30 (90.9)	171 (84.7)	13 (81.3)	30 (83.3)	
ASA score					
1	12 (36.4)	72 (35.6)	3 (18.8)	11 (30.6)	0.501
2	19 (57.6)	102 (50.5)	10 (62.5)	22 (61.1)	
3	2 (6.1)	28 (13.9)	3 (18.8)	3 (8.3)	
Side					
Right	19 (57.6)	97 (48)	8 (50)	16 (44.4)	0.718
Left	14 (42.4)	105 (52)	8 (50)	20 (55.6)	
Localisation					
Central	13 (39.4)	80 (39.6)	7 (43.8)	12 (33.3)	0.880
Polar	20 (60.6)	122 (60.4)	9 (56.3)	24 (66.7)	
Tumour size, mm	46.12±24.6^a	34.21±13.4^b	36.19±16.7^{abc}	25.67±12.79^c	0.001
RNS	7.85±1.9^a	6.64±1.6b	6.44±1.8^{bc}	5.50±1.1^c	0.001
RNS group					
Low (4-6)	8 (24.2)	105 (52)	9 (56.3)	29 (80.6)	0.001
Intermediate (7-9)	19 (57.6)	84 (41.6)	6 (37.5)	7 (19.4)	
High (10-12)	6 (18.2)	13 (6.4)	1(6.3)	-	

A: WIT >20 min, B: WIT ≤20 min, C: Selective- clamp, D: Off-clamp, ASA: American society of anesthesiologists, BMI: Body mass index, CAD: Coronary artery disease, DM: Diabetes Mellitus, HT: Hypertension, RNS: RENAL Nephrometry score, WIT: Warm ischaemia time, *: Continuous data are expressed as mean ± standard deviation and categorical data as number (%), ^{a,b,c}: Different lowercase letters show a significant difference between groups by One-Way ANOVA followed by Bonferroni Post-hoc test ($p<0.05$), mm: Millimeter, kg: Kilogram

Table 2. Intraoperative and postoperative outcomes					
Variable**	A (n=33)	B (n=202)	C (n=16)	D (n=36)	p
Operation time, min	123.76±35.1^a	92.72±30.5^b	100.3±18.5^{ab}	79.72±30.6^b	0.001
WIT, min	23.82±2.6	12.94±3.8	13.31±4.1	0	-
Blood loss, mL	136.36±76.3	140±83.8	118.13±54.8	165.9±87.3	0.570
PSM	0	4 (2)	0	0	-
Intraoperative complications rate	2 (6.1)	4 (2)	2 (12.5)	0	0.085
Postoperative complication rate	6 (18.2%)	18 (8.9%)	1 (6.3%)	3 (8.3%)	0.443
Relative eGFR change (%)*	9.3^a	7.5^a	5^b	3.7^b	0.001

A: WIT >20 min, B: WIT ≤20 min, C: Selective-clamp, D: Off-clamp, ^{a,b,c}: Different lowercase letters show a significant difference between groups by One-Way ANOVA followed by Bonferroni Post-hoc test ($p<0.05$), PSM: Positive surgical margin, *1 year after LPN, **: Continuous data are expressed as mean ± standard deviation and categorical data as number (%), min: Minute, WIT: Warm ischaemia time, eGFR: Estimated glomerular filtration rate

The main effect of groups on eGFR was statistically significant (p<0.001). The main effect of time on eGFR was also statistically significant, and in the preoperative period, eGFR was higher than others, except in the first year (p<0.001). Nevertheless, group and time interaction was not statistically significant (p=0.960). The group, time, and group-time effect on eGFR are summarised in Table 3.

When the change in eGFR (ΔeGFR) between the groups over time was evaluated, the main effects of the groups were statistically significant (p<0.001). Although there was no statistical difference between groups D and C, these two groups were significantly different from the other groups. There was no statistical difference between group A and group B. The time effect was also statistically significant (p<0.001). There was no difference between the postoperative first-day ΔeGFR and the first-month ΔeGFR. Similarly, ΔeGFR values in the sixth month was non-significantly different (p>0.05) from ΔeGFR in the first year. However, other time comparisons were statistically significant. Group-time interaction was not statistically significant (p=0.960). The group, time and group-time effect on ΔeGFR are summarised in Table 4.

Discussion

The present study revealed that zero-ischaemia groups (C and D: 8.71 vs. 5.49 mL/minute/1.73 m^2) have an advantage in terms of eGFR decline (ΔeGFR) compared to the global ischaemia groups (A and B: 10.38 vs 8.98 mL/minute/1.73 m^2, p<0.001) at one year after LPN. The percentage of relative eGFR decline 1 year after LPN was statistically different in the zero-ischaemia groups (C and D: 5% and 3.7%) compared to the global ischaemia groups (A and B: 9.3% and 7.5%, p=0.001).

Baseline RF and volume of preserved renal parenchyma are the significant determiners of functional recovery following PN. Besides, prolonged WIT negatively also affects postoperative RFal recovery (12). It is difficult to detect the effect of PN on total RF in patients with contralateral healthy kidney because of the compensatory role played by the unaffected kidney. Renal scintigraphy, also known as renal scans, in combination with eGFR gives the most accurate results in assessing the RF of affected kidney after PN (13). However, preoperative and postoperative evaluation of patients who underwent PN by scintigraphy is a difficult, and is a non-cost effective approach in clinical practice. Therefore, total eGFR has been widely employed as a surrogate measure of RF. Furthermore, the necessity of evaluation by scintigraphy may be questioned in patients with uncomplicated renal mass, normal contralateral kidney, or whose WIT is below recommended time levels. Additionally, it would be more accurate if the amount of preserved renal parenchyma following PN was calculated alongside the tumour size and WIT. However, there is no adequate technical infrastructure to precisely estimate the preserved renal parenchyma. This situation is therefore considered a limitation of the present study.

We routinely evaluated the RF of patients who underwent LPN using the CKD-EPI equation before and after the surgery. CKD-EPI equation, compared to the Modification of Diet in Renal disease equation, has been associated with more accurate outcomes in patients with eGFR levels >60 mL/minute (5). In this study, total eGFR values were used for the interpretation of functional evaluation. Furthermore, patients who underwent PN, and with normal contralateral kidney, are expected to have a 10% reduction in RF or maintain 90% of total RF in general. These criteria was recently used in the evaluation of surgical success in functional aspects (14).

Table 3. The comparison of estimated glomerular filtration rate according to time and groups

eGFR	A (n=33)	B (n=202)	C (n=16)	D (n=36)	Total
Baseline	101.31±28.45	104.98±28.17	108.75±23.01	98.81±26.97	104.00±27.77[a]
1st day	81.49±17.68	87.27±18.28	97.61±15.31	90.39±21.85	87.57±18.75[b]
1st month	84.08±18.11	90.42±19.74	99.42±15.25	93.61±23.21	90.59±19.98[b]
6th months	88.1±20	94.05±21.53	100.8±15.42	94.65±23.73	93.81±21.41[b]
1st year	90.93±22.37	96±22.15	102.31±16.26	94.62±24.45	95.60±22.2[ab]
Total	89.18±22.5[a]	94,54±22.99[b]	101.78±17.3[c]	94.41±23.98[abc]	-

A: WIT >20 min, B: WIT ≤ 20 min, C: Selective- clamp, D: Off-clamp, [a,b,c]: Different lowercase letters show a significant difference between groups and time by Two-Way ANOVA followed by Bonferroni Post-hoc test (p<0.001), eGFR: Estimated glomerular filtration rate

Table 4. The comparison of Δestimated glomerular filtration rate according to time and groups

ΔeGFR	A (n=33)	B (n=202)	C (n=16)	D (n=36)	Total
1	19.82±16.29	17.72±14.76	11.13±12.18	8.42±11.42	16.43±14.79[c]
2	17.23±15.98	14.56±12.8	9.33±10.88	5.2±6.46	13.4±12.92[bc]
3	13.21±12.24	10.94±9.73	7.94±11.1	4.16±5.8	10.18±10.01[ab]
4	10.38±10.49	8.98±9.32	6.44±8.36	4.19±5.62	8.4±9.17[a]
Total	15.16±14.28[a]	13.05±12.31[a]	8.71±10.61[b]	5.49±7.82[b]	-

ΔeGFR is expressed as mean ± standard deviation, [a,b,c]: Different lowercase letters show a significant difference between groups and time by Two-Way ANOVA followed by Bonferroni Post-hoc test (p<0.001), ΔeGFR-1: (baseline-1st day), ΔeGFR-2: (baseline-1st month), ΔeGFR-3: (baseline-6th month), ΔeGFR-4: (baseline-1st year), eGFR: Estimated glomerular filtration rate

Standard PN requires transient ischaemia to obtain a higher quality of vision, with a relatively bloodless field during tumour resection and renorrhaphy. However, it is well established that postoperative renal functional preservation is closely associated with preserved nephron volume, as well as ischaemic damage on the remaining renal parenchyma (15). A variety of experimental and clinical investigations has focused on this issue. Nevertheless, the optimal threshold for ischaemia time to preserve postoperative RF following PN is still controversial (12). Moreover, recent studies suggest that the optimal threshold of WIT does not exceed 20 minute (16,17). On the other hand, selective-clamp and off-clamp techniques have been demonstrated to minimise or eliminate ischaemia-related kidney injury. However, the indication of these techniques that refer to zero-ischaemia in patients with contralateral healthy kidney is debatable as a result of the increased risk of perioperative blood loss, and technical challenges, thus requiring a considerable PN experience (18).

Although there is an increase in the amount of EBL in studies comparing the off-clamp technique with the global ischaemic technique, it is stated that the complications are similar, while the functional results are better. However, selection bias, heterogeneity of patients and differences in surgical techniques are the major concerns that may affect the final outcomes.

Smith et al. (19) compared 116 clamped and 192 off-clamp PNs in terms of perioperative, functional and oncological outcomes. While all patients were managed by open PN in the off-clamp group, more than half of the patients underwent laparoscopic or robotic PN in the clamped group. It has found that the median tumour size (3 vs 2.8 cm, p=0.002), EBL (500 vs 200 mL, p<0.001), perioperative transfusion rate (42% vs 23%, p=0.001) and OT (226.5 vs 192 min, p=0.001) were significantly higher in the off-clamp group when compared to the clamped group. The authors also reported that eGFR decline was significantly higher in the clamped group compared to the off-clamp group (12.3% vs 9.8%, p=0.037) after 1 year of follow-up.

Kopp et al. (20) compared 164 clamped with 64 off-clamp open PNs in patients with bilateral kidney. The off-clamp group had higher EBL (300 vs 200 mL, p=0.001) and lower rate of de novo CKD (12.5 vs 24.4%, p=0.049) following PN when compared to the clamped group. However, the complication rate was non-significantly (p>0.05) different between the groups (14.2% vs 14.1%, p=0.43). In their study, the significant drawbacks was that tumour complexity (RENAL score 6.9 vs 6.4, p=0.02) was higher in the clamped group, and standard surgical technique was not employed.

Simone et al. (21) compared the functional outcomes of 472 off-clamps versus 157 on-clamp open PNs after Propensity score matching analysis. The authors found that the on-clamp group had a higher probability of developing ≥3b CKD when compared to the off-clamp group. The risk of developing CKD was 7.3 fold higher in the on-clamp group during follow-up.

Browne et al. (22) evaluated preioperative and postoperative outcomes of 43 patients who underwent LPN. They used a YAG laser or vessel sealing device for tumour resection and tumour bed ablation. The authors found that the mean tumour size was 28.2 mm, OT was 172 min and EBL was 341 mL. The relative change in eGFR was reduce by 2.8% 6 months after the surgery.

In a recent systematic review of 23 retrospective and 2 prospective cohort studies, early postoperative eGFR decline, long-term eGFR change and percentage of change were significantly lower in off-clamp patients when compared to the on-clamp cohorts (23). In our study, the amount of preoperative bleeding in the off-clamp group was non-significantly different from that of the other groups. Surgical time was also significantly shorter than in other groups compared to the off-clamp group. In terms of functional results, the decrease in GFR was minimum in the off-clamp group in both early postoperative period and during follow-up.

Selective arterial clamping is another zero-ischaemia PN method introduced for the first time by Gill et al. (24). In this technique, ischaemia is created in the region to be excised, while the remaining part of the kidney is protected from ischaemia. NIRF/ICG-guided minimally invasive PN is one of the important advancement in imaging systems. Although not widely used, it is considered as a useful technique for specifying tumour margins and preserving normal parenchyma (25). Selective-clamping is said to have similar functional outcomes with the off-clamp PN, however, it has more advantage in terms of preservation of RF when compared to the global ischaemia technique (2). The results of the present study is consistent with that of previous studies in literature where postoperative functional outcomes were similar between selective-clamp and off-clamp group, and selective-clamp better than the global ischaemic groups.

Study Limitations

The limitations of our study was due to retrospective design, single-centredness, single-surgeon experience and different distribution of patients within the groups. However, single-surgeon experience may be an advantage for the standardisation of laparoscopy technique. Since patients with contralateral healthy kidney were included in the study, we presumed that the negative effect of selection bias on final functional outcomes would decrease.

Conclusion

Reduction or elimination of ischaemia time in LPN has positive effects on the preservation of RF in the postoperative period. If global ischaemia technique is preferred, tumour resection and renorraphy should be performed in less than 20 minutes. Prospective studies are however required to validate this study.

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Ethics

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Original Article

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Experiences of Laparoscopic Partial Nephrectomy for T1a Kidney Tumours: Results of Two Hundred and Fifteen Patients

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Abstract

Objective: The best therapeutic option for renal tumours smaller than 7 cm is partial nephrectomy. The aim of this study was to compare the positive surgical margin (PSM) rates, recurrence rates and oncological outcomes between laparoscopic partial nephrectomies and open partial nephrectomies at a single tertiary referral centre.

Materials and Methods: We included patients with renal tumours treated with partial nephrectomies between January 2008 and December 2016 in the study. We retrospectively reviewed the patients' demographic data, surgical reports, clinical charts, laboratory results and histopathological reports. Binary regression analysis was used to assess the impact of the tumour diameter, laterality, polarity and localization for PSM.

Results: We included a total of 215 patients in the study. The mean preoperative and postoperative haemoglobin and creatinine levels, blood loss, time of surgery and follow-up periods was similar between the two groups. The mean ischaemic time in the open partial nephrectomy group was significantly lower than that of the laparoscopic partial nephrectomy group ($p<0.05$). Local recurrence was seen in a patient with a PSM in the laparoscopic partial nephrectomy group. However, recurrences were also seen in the negative surgical margin patients in both the open partial nephrectomy and laparoscopic partial nephrectomy groups.

Conclusion: The presence of a PSM is not associated with an increased risk of distant metastases or local recurrences. However, higher PSM rates were associated with the early learning curve for a laparoscopic procedure. Finally, an open partial nephrectomy is associated with shorter warm ischaemia time compared to laparoscopic partial nephrectomy group.

Keywords: Distant metastasis, kidney tumour, local recurrence, partial nephrectomy, surgical margin positivity

Introduction

The best therapeutic option for localized renal tumours is surgical removal amongst other therapeutic options (1). As a standard treatment option, a partial nephrectomy (PN) provides better oncological and functional results for T1 renal tumours (≤7 cm); with the advantage of healthy renal parenchyma preservation (1,2). An open PN (OPN) has been a safe technique for many years, with high cancer-free survival rates, a better quality of life results, and low local recurrence rates (3). Due to, OPN technique requires longer hospitalisation rates, the need for longer surgical incisions, higher analgesic requirements and an increased comorbidity rate, minimally invasive techniques have become more popular. Advancements in minimally invasive procedures have increased the potential for laparoscopic and robot-assisted PNs, increasing the number of nephron sparing surgeries for T1 tumours. The evolution of imaging techniques (4) have led to the diagnosis of asymtomatic renal masses (up to 27%), with an risk of residual tumours (0.1%-10.7%) (5,6). The surgical technique applied, the skill of the surgeon, and tumour characteristics, such as the location, stage, and grade determines the recurrence rate of the tumour (5,7). No matter the technique, the main goal of a successful tumour management is to remove the renal tumour completely, with lower warm ischaemia times (WITs) (8) and minimal postoperative complication rates (9).

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In this study, the positive surgical margin (PSM) rates mean ischaemic times, perioperative complication rates, and associated risk factors were compared between OPNs and laparoscopic partial nephrectomies (LPNs) in patients undergoing PNs for kidney tumours.

Materials and Methods

After obtaining Institutional Board Approval from the Clinical Research and Ethics Committee of Zonguldak Bülent Ecevit University (Zonguldak, Turkey) (approval number: 2019-94-12/06, date: 12.06.2019). We then retrospectively reviewed the data of 315 patients with kidney tumours who had undergone LPNs or OPNs, done in a high volume experienced centre between January 2008 and December 2016. We excluded patients with bilateral kidney tumours (n=16) and with a less than two year follow-up (n=14) from the study. Seventy patients with tumours higher than 7 cm, with lymph nodes or distant metastases, and with a history of PNs for benign diseases of the kidney were also excluded from the study.

Finally, the preoperative and postoperative data from 215 patients with complete data were evaluated. The demographic, surgical reports, clinical charts, laboratory results and histopathological reports were reviewed. In addition, detailed medical histories and physical examination findings were obtained in all of the cases.

Patients with T1 kidney tumours were divided into two groups according to the applied surgical technique: an OPN group (group 1, n=46) and an LPN group (group 2, n=169). We assessed the recurrence using radiological methods and additional histopathological examinations where needed. The cancer recurrences were clinically or radiologically assessed in both groups. The presence of a contralateral non-functional kidney or the presence of a tumour in an anatomically solitary kidney was accepted as imperative indications for a PN. The LPN criteria were based on the computed tomography (CT) findings, including the size, localization, and accessibility of the mass, in addition to the general health status and comorbidities of the patient.

Surgical Procedure

The LPN procedure was performed transperitoneally with the patient in a lateral decubitus position. A 12 mm optical camera port was inserted 5 cm lateral at the level of the umbilicus after the pneumoperitoneum was created using a Veress needle. The 10 mm subxiphoidal trocar and 5 mm trocar were placed approximately 2 cm medially and superior to the anterior superior iliac crest to create a triangularly shape under direct vision. For tumours on the right side, an additional 5 mm port was used to retract the liver. The colon was then mobilised medially, and the renal vascular pedicle was exposed. The main renal artery was clamped using a bulldog clamp and the tumour was resected within a safe margin, and put into an endo bag. The renal parenchyma was sutured using 2-0 monofilament poliglecaprone (Monocryl®, Ethicon) sutures in a running manner.

For the OPN, a flank incision was made in patients with lower pole kidney tumours. A subcostal approach was used for those who had upper pole or middle tumours. The renal artery was clamped and the resection of the tumour with the surrounding normal parenchyma was completed and figure eight knots were used for closing the collecting system and the renorrhaphy.

The follow-up protocol was defined as follows:

1. Complete physical examinations and serum creatinine measurements were done at the postoperative first, third and twelfth months and annually thereafter.

2. Plain chest X-rays and CT scans of the abdomen were obtained in the sixth postoperative month and annually after that.

Histopathological Investigation

All the PN specimens were evaluated by the same pathologist. Tumour grading and pathological staging were done according to the Fuhrman et al. (10) nuclear grading system and the 2016 World Health Organization classification (11). The presence of malignant cells at the surgical margin was defined as surgical margin positivity.

Statistical Analysis

The demographic variables, including age, gender and indication for surgery, laterality, diameter and location of the tumour was assessed. The mean follow-up periods, histopathological diagnoses, tumour grades and recurrence rates of the groups were compared using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). An Independent Sample t-test and chi-squared test was used to compare the variables and ratios between the two groups. A p value of less than 0.05 was considered statistically significant. Binary regression analysis was performed to assess the impact of the tumor diameter, laterality, polarity and localization for PSM.

Results

The demographic and clinical characteristics of the LPN and OPN groups, including the age, body mass index, gender, glomerular filtration rate, American Society of Anaesthesiologists score, and comorbidity, presence of surgical margin positivity, tumour location and diameter are given in Table 1. The mean preoperative and postoperative haemoglobin, blood loss, and creatinine levels and the mean surgical time and follow-up periods were similar between the groups ($p>0.05$). The mean warm ischaemia time in the OPN group was significantly lower when compared to the LPN group ($p<0.05$). Other variables, such as the recurrence rate and the clinical and histopathological findings are shown in Table 2.

One patient with a surgical margin positivity in the LPN group had local recurrence. One patient in the OPN group with negative surgical margins (NSMs) and two patients (1.2%) in the LPN group with NSMs had local recurrences within a mean follow-up period of 29.8 months. Two patients in the LPN group with NSMs (1.2%) had bone and lung distant metastases in the 19^{th} and 54^{th} months. The overall recurrence or metastasis rate was 2.8%.

Binary logistic regression analysis was performed to assess the impact of the tumor diameter, laterality, polarity and localization for PSM ($p>0.05$). The individual characteristics of the patients with recurrences or metastases following the PNs are given in Table 3. Three of the patients had recurrence in the LPN group with Fuhrman grade 3, and two had Fuhrman grade 2 tumours.

Table 1. Demographic and clinical variables between the groups

	OPN group (n=46)	LPN group (n=169)	p
Age (years), (mean ± SD[1])	54.7±12.1	55.9±11.9	0.87
BMI[2] (kg/m^2), (mean ± SD)	27.3±4.1	26.8±3.7	0.89
Gender			
Male	22	79	-
Female	24	90	
ASA[3] Score			
I	25	96	-
II	17	56	
III	4	15	
IV	0	2	
GFR[4] (mL/min x1.73 m^2)	91.3±23.2	92±22.4	0.85
Comorbidity			
Hypertension	16	37	-
Diabetes Mellitus	11	17	
Past surgery	17	62	
Symptom			
No	28	109	-
Haematuria	2	3	
Pain	13	42	
LUTS[5]	1	10	
Nonspecific	2	5	
Tumour diameter (mm)	35.3±12.9	30.1±10.8	0.15
Tumour localization			
Right kidney	27	98	-
Left kidney	19	71	
Anterior	32	120	
Posterior	14	49	
Upper pole	14	70	
Middle pole	9	53	
Lower pole	23	46	
Exophytic	41	153	
Endophytic	5	16	
Lateral rim	37	136	
Medial rim	9	33	
Surgical margin (n, %)			
Positive	3 (6.5)	13 (7.7)	0.91
Negative	43 (93.5)	153 (92.3)	0.89

ASA: American Society of Anaesthesiologists score, BMI: Body Mass index, GFR: Glomerular filtration rate, LUTS: Lower urinary tract symptoms, SD: Standard deviation, OPN: Open partial nephrectomy, LPN: Laparoscopic partial nephrectomy, n: Number

Discussion

PN has become the standard surgical method for the treatment of T1 renal tumours with similar oncological results; however, there are still debates with regards to its relationship with PSMs and local recurrences. Our results showed that the tumor diameter, laterality, polarity and localization were not associated with PSM. Kwon et al. (12) showed that local recurrence after a PN was related to the high malignant potential of the tumour and the presence of a PSM. Irrespective of the tumour complexity, a PSM was found to be associated with a higher Nephrometry score, the presence of bilateral tumours, a prior renal cell carcinoma treatment history, local recurrence and distant metastasis when compared to patients with NSMs (13). On the contrary, many institutional data have shown that the surgical margin status did not influence the tumour recurrence risk in pT1 tumours after a PN (14). In a comparative meta-analytical study analyzing the data of 45,786 patients, a larger tumour size, a pT3a stage, nuclear grade 3-4 and minimally invasive procedures, were found to be potential risk factors for a local recurrence. However, cancer-specific and overall survival rates were not increased by the use of minimally invasive procedures (15). Our results showed that local recurrence was observed only in one patient with a PSM in the LPN group, a very low number of patients with NSM showed that there was no association with surgical margin positivity and local recurrence or distant metastasis in both groups. Two of the patients in the LPN group had bone and lung metastasis respectively. One of the patients with distant metastasis had a tumour necrosis (Fuhrman grade 3) and the other had a relatively endophytic mass close to the collection system with microvascular invasion. Histopathological and morphological findings such as high tumour grade and endophytic location of the tumour, may explain the distant metastases in our patients with NSM as reported earlier.

In this study, three patients (6.5%) in the OPN group showed PSM with no local recurrence. Although only a patient in the OPN group and two patients in the LPN group had local recurrence, no difference was observed in cancer-specific or overall survival which is consistent with the literature (16). A previous cohort study of 11,587 patients, showed that the PSM rates were 4.9%, 8.7% and 8.1% for open, robotic and laparoscopic PNs respectively (17). Considering PSM ratios, our results in the OPN group were similar to those of the previously published reports, which may be attributed to the cumulative skills of the urologists in open surgery. The 7.7% PSM rate recorded for the LPN group was similar to that found in literature. However, when a detailed analysis was done, the PSM rate was the highest for the first 50 cases (10.0%), and it decreased to a rate of 8% for the second 50 cases. As previously reported, this can be explained by the need for more complex skills and a relatively long learning curve (18). Consistent with literature, the PSM ratio was only 4.3% in the last 69 patients in the LPN group (19).

Nevertheless, the primary goal should be not to leave a PSM during a PN (7). A healthy parenchymal margin of 1 cm has been suggested for optimal cancer control (20,21). Due to the likelihood of a PSM, challenging cases require close follow-ups and careful surveillance and salvage procedures should

Table 2. Clinical, operative and histopathological findings of the groups					
	OPN group (n=46)		LPN group (n=169)		
	PSM* (n=3)	NSM** (n=43)	PSM (n=13)	NSM (n=156)	p
Haemoglobin (g/dL, mean ± SD*)**					
Preoperative	12.8±2.3	13.2±1.8	13.5±1.3	13.2±1.6	0.66
Postoperative	11.6±2.3	11.8±2.3	12.4±1.6	12.0±1.1	0.65
Serum creatinine (mg/dL, mean ± SD)					
Preoperative	0.8±0.1	0.9±0.3	0.9±0.2	0.8±0.2	0.39
Postoperative	0.7±0.2	1.1±0.4	0.9±0.3	1.0±0.3	0.10
Warm ischaemia time (min, mean ± SD)	10.5±8.0	18.8±8.3	21.2±9.0	21.3±8.9	**0.02**
Surgery time (min, mean ± SD)	160.6±67.4	161.4±69.6	156.8±75.2	136.8±71.1	0.95
Non-klemp (n)	1	1	2	7	-
Surgical technique (n)					
Retroperitoneal	0	8	1	11	-
Transperitoneal	3	35	12	145	-
Blood loss (mL, mean ± SD)	125.0±35.4	137.1±127.0	138.7±43.5	139.6±52.9	0.89
Follow-up (months, mean ± SD) (minimum-maximum)	44.8±13.5 (29-62)	45.6±18.8 (25-90)	46.5±32.4 (25-147)	40.6±18.7 (25-137)	0.93
Local recurrence (n, %)	0	1 (2.2)	1	2 (1.2)	-
Distant metastasis (n, %)	-	-	-	2 (1.2)	-
Time to local recurrence (month mean ± SD)	0	29	3	29.8	-
Histology (n, %)					
Clear cell	2 (4.3)	26 (56.5)	8 (4.7)	111(65.7)	-
Papillary	1 (2.2)	10 (21.7)	3 (1.8)	24 (14.2)	
Chromophobe	0	4 (8.7)	1 (0.6)	12 (7.1)	
Other	0	3 (6.5)	1 (0.6)	9 (5.3)	
Pathological stage (n, %)					
T1a	3	35	9	131	-
T1b	0	8	4	25	
Pathological grade (Fuhrman)					
Grade 1	0	8	1	35	-
Grade 2	3	21	5	71	
Grade 3	0	14	7	50	
Presence of tumour necrosis (n, %)	0	2 (4.3)	1 (0.6)	10 (5.6)	-
Invasion to collecting system (n, %)	-	-	-	-	-
Pernephric infiltration (n, %)	-	-	-	3 (1.8)	-
Vascular invasion (n, %)	-	-	-	-	-

Clinical, operative and histopathological findings of the groups. *PSM: Positive surgical margin, **NSM: Negative surgical margin, ***SD: Standard deviation, OPN: Open partial nephrectomy, LPN: Laparoscopic partial nephrectomy, n: Number, min: Minute

Table 3. Morphological and histological characteristics of the patients with recurrence and metastasis after partial nephrectomy								
Age	Grouping	Tumour type	Fuhrman grade	Largest tumour size (mm)	Surgical margin	Time to recurrence (months)	Local recurrence	Site of metastasis
59	LPN	Clear cell	2	35	-	54	-	Bone
72	LPN	Clear cell	3	12	-	19	-	Lung
71	OPN	Papillary	3	40	-	29	Ipsilateral kidney	-
42	LPN	Papillary	3	42	-	2	Ipsilateral kidney	-
59	LPN	Papillary	3	40	-	8	Ipsilateral kidney	-
73	LPN	Clear cell	2	35	+	3	Ipsilateral kidney	-

OPN: Open partial nephrectomy, LPN: Laparoscopic partial nephrectomy

be reserved for patients with locally advanced or high-grade tumours.

Only two of our patients showed distant metastases in the LPN cases with NSM, but no metastasis was observed in the participants in the OPN group or the LPN patients with PSM. At first glance, although the absence of metastasis in PSM seemed unreasonable, as previously reported, distant metastasis was not only related to the presence of PSM, but also tumour grade, subtype, microvascular invasion, necrosis and tumoural invasion to the collecting system (22).

The WIT is an essential parameter for postoperative kidney function (23). Studies have shown that a lower WIT was associated with better kidney function postoperatively (9). When compared to an OPN, a longer WIT is expected for an LPN (24). This study's result showed that the mean WIT values were significantly less than 25 minutes, particularly in the OPN group.

Study Limitations

Oncological outcomes and PSM rates between LPNs and open partial nephrectomies at a single tertiary referral centre were compared in this study. This study had some limitations including;

1. Lack of a long-term follow-up period

2. The retrospective design of the study

3. Many studies have been done in literature about surgical margin positivity.

Conclusions

The presence of a PSM, although considered to be a risk factor for distant metastasis, was not associated with an increased risk of distant metastasis in this study. Nevertheless, the early stages of the learning curve for an LPN may be associated with higher PSM rates, and this may be a risk factor for distant metastases when combined with other histological and morphological features, such as the nuclear grade of the tumour, the presence of necrosis and endophytic localization.

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Ethics

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Authorship Contributions

Supervision: H.V., Concept Ö.Ç., Design: Ö.Ç., M.Ç.Ç., Ç.G.Ö., Data Collection or Processing: M.Ç.Ç., Ç.G.Ö., B.A.V., Analysis or Interpretation: Ö.Ç., Literature Search: M.S.B., Writing: Ö.Ç.

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Original Article

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Association of Preoperative De Ritis Ratio (Aspartate Amino Transferase/Alanine Amino Transferase) and Tumour Histology in Patients with Primary Bladder Cancer

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Abstract

Objective: De Ritis ratio, defined as the ratio of serum aspartate amino transferase (AST) and alanine amino transferase (ALT), has been demonstrated to be an independent prognostic marker in bladder cancer (BC) patients who underwent radical cystectomy. We aimed to investigate the relationship between preoperative De Ritis ratio and tumour histology prior to transurethral resection of bladder tumour (TUR-BT) in patients newly diagnosed with BC.

Materials and Methods: Data of the patients who underwent TUR-BT between May 2016 and August 2019 at two tertiary hospitals were evaluated, retrospectively. The patients were grouped as either non-muscle invasive BC (NMIBC) or muscle invasive BC (MIBC), and as grade (G) 1, 2 and 3 according to pathological and histological G, respectively. Further, patients were classified as low, intermediate or high risk according to risk group stratification. Demographic features of the patients including age and gender were recorded. Pre-treatment biochemical indices including serum levels of AST and ALT were recorded. P value <0.05 was considered significant.

Results: Mean age of patients (156) included in this study was 67.10±10.15. Exactly 104 (66.7%) patients were placed in the NMIBC group, while the remaining 52 (33.3%) patients were placed in the MIBC group. De Ritis ratio was lower in the NMIBC group than in the MIBC group (p=0.014). Also, there was a significantly difference in De Ritis ratio between G1 and G3 carcinomas (p=0.040). According to receiver operating characteristics analysis, the cut-off threshold of De Ritis ratio for clinically predicting MIBC and high-G carcinoma was 1.21 and 1.20, respectively. Based on Spearman's correlation analysis, a weak positive correlation was found between De Ritis ratio and MIBC (p=0.036), and G of tumour (p=0.009).

Conclusion: This study demonstrated that an increase in De Ritis ratio, which can be easily determined from the peripheral blood in preoperative period, may be associated with muscle invasion (T2) and high tumour G of BC.

Keywords: Amino transferases, bladder cancer, de ritis ratio, grade, stage

Introduction

Bladder cancer (BC), a common genitourinary tract cancer, is the sixth most frequently diagnosed cancer in the United States, and also the third most common type of cancer in male population of Turkey (1,2,3). Globally, it has an average standardized mortality rate of 3.2 per 100,000 men and 0.9 per 100,000 women (1). In approximately 75%-85% of newly diagnosed BC cases, tumour is infiltrated in the mucosa [stage Ta and carcinoma *in situ* (CIS)] or submucosa (stage T1) and are classified as non-muscle invasive BC (NMIBC) for therapeutic purposes (4,5). For treatment of BC, transurethral resection of the bladder tumour (TUR-BT) is performed and, thereafter, intravesical instillations are incorporated in order to prevent disease recurrence and progression to muscle invasive BC (MIBC). However, radical cystectomy (RC) is a preferred treatment strategy for localized MIBC (6,7). Moreover, some patients with high risk NMIBC may undergo RC prior to muscle invasion (8).

Amino transferase enzymes such as aspartate amino transferase (AST) and alanine amino transferase (ALT) are leaked into circulation from liver cells as indication for hepatocellular damage. De Ritis (9) put forward an hypothesis in 1957 that the ratio of these enzymes could be used to predict viral hepatitis. Successfully, the term De Ritis ratio (calculated by dividing AST by ALT) took its place in the literature. Till date, this ratio has been employed in a lot of research as biomarker for diagnosis,

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treatment and follow-up of, not only hepatic disorders, but also non-hepatic diseases (10,11,12,13,14). Today, it is popularly employed for prognosis of many cancers (15,16,17,18,19,20). In literature, elevated preoperative De Ritis ratio was regarded as an independent indicator of poor prognosis in patients who underwent RC (18,21,22).

Therefore, we aim to investigate whether De Ritis ratio can be employed to predict tumour histology and risk group prior to TUR-BT in patients newly diagnosed with BC.

Materials and Methods

After obtaining ethics committee approval of institutional review board (approval number: 2019/21, date: 05.08.2019), we conducted a cross-sectional study including patients who underwent TUR-BT for primary BC between May 2016 and August 2019 at two tertiary hospitals. Age, gender, grade and stage of tumour, risk group of tumour, and preoperatively evaluated serum AST-ALT levels were obtained from electronic database and surgery notes in the hospitals. Patients whose records were not sufficient for the evaluation, as well as those with liver metastasis, were excluded from this study. In addition, patients undergoing any form of treatment which may influence the level of amino transferase enzymes; patients with hepatic disorders such as chronic hepatitis, liver cirrhosis or other concurrent cancers, and patients with inadequate muscle tissue in the resected histopathology specimens were excluded from this study. Classification of tumour stage and tumour grade was according to the 2009 tumor node metastasis classification updated in 2017 (23) and 1973 World Health Organization (WHO) grading system (24), respectively. Where a second resection was required according to the criteria specified in European Association of Urology (EAU) Guidelines (25), we performed a second TUR-BT. We accepted findings regarding upstaging or upgrading of pathological results of second TUR-BT. Since some pathologists examined specimens of TUR-BT only according to WHO 1973 classification for reporting BC histology, we could not evaluate the results according to 2004 WHO grading system. According to the 2019 EAU Guidelines, risk group stratification was low, intermediate or high risk (25). Further, patients were grouped into two (NMIBC and MIBC) according to the pathological stage, and into three according histological grade. We further grouped patients with NMIBC into three based on the risk group stratification.

Statistical Analyses

Statistical analysis was done using IBM SPSS version 21 (IBM Corp., Armonk, NY, USA). Variables were expressed as means and standard deviations. Student's independent t-test was used to compare differences between two groups, while One-way analysis of variance followed by Tukey Post-hoc test was utilized to compare differences between three groups. Chi-square test and Fisher's Exact test were used for comparison of qualitative data. The capacity of De Ritis ratio in predicting muscle invasion and high grade of tumour was determined using receiver operating characteristics (ROC) curve analysis. Spearman's correlation analysis was used to evaluate relationship between De Ritis ratio and the groups. Also, we used a linear regression model to identify independent predictors of tumour histology. $P<0.05$ was considered significant.

Results

After the exclusion of patients (67) who did not meet inclusion criteria, a total of 156 patients with primary BC were included in the study. Of the total patients included, 104 (66.7%) patients had NMIBC, while the remaining 52 (33.3%) patients had MIBC (stage T2 tumour). Descriptive statistics and mean values for all patients are summarised in Table 1. Mean age and De Ritis ratio were significantly different between patients with NMIBC and MIBC (Table 2). Based on T stage, mean age of patients with stage Ta tumour was significantly lower than that of patients with stage T2 tumour (63.58±10.02 vs 70.50±10.03, p=0.004). Similarly, patients with stage Ta tumour had lower De Ritis ratio than patients with stage T2 tumour (1.17±0.31 vs 1.47±0.69, p=0.027). Based on the tumour grade, there were significant differences between grade 1 and grade 3 carcinomas in terms of age and De Ritis ratio (p=0.011 and p=0.040, respectively). All the parameters between the risk group of patients with NMIBC were non-significantly different (p>0.05) (Table 3). According to ROC curve, the cut-off value of preoperative De Ritis ratio for predicting MIBC was 1.21, with 56% sensitivity and 55% specificity [area under curve (AUC)=0.603, 95% confidence interval (CI) =0.503-0.702, p=0.037] (Figure 1). On the other

Table 1. Baseline characteristics of the patients

Tumor histology	n (%)	Age (year)	AST (U/L)	ALT (U/L)	AST/ALT
Stage					
Ta	46 (29.9)	63.58±10.02	19.28±4.76	17.78±7.87	1.17±0.31
T1	54 (34.6)	67.25±9.45	21.61±5.01	19.16±7.43	1.25±0.46
T2	52 (33.3)	70.50±10.03	19.78±5.53	16.02±8.66	1.47±0.69
Tis	4 (2.2)	61.50±9.98	18.50±1.73	18±4.76	1.05±0.22
Grade					
G1	49 (31.4)	63.93±11.74	19.77±5.10	19.18±8.71	1.15±0.43
G2	10 (6.4)	64.10±3.84	23.10±3.54	18.90±2.13	1.21±0.07
G3	97 (62.2)	69.02±9.29	20.17±5.24	16.79±7.90	1.38±0.57
Total	156	67.10±10.15	20.23±5.13	17.68±7.98	1.29±0.52

AST: Aspartate amino transferase, ALT: Alanine amino transferase

Table 2. Comparison of the variables between the patients with non-muscle invasive bladder cancer, and muscle invasive bladder cancer

Variables	NMIBC (n=104)	MIBC (n=52)	p
Age (year)	65.41±9.83	70.50±10.03	0.003
Gender			
Male (n=136, 87.2%)	90 (86.5%)	46 (88.5%)	0.735
Female (n=20, 12.8%)	14 (13.5%)	6 (11.5%)	
AST (U/L)	20.46±4.94	19.79±5.53	0.460
ALT (U/L)	18.51±7.53	16.02±8.66	0.082
AST/ALT	1.21±0.39	1.47±0.69	0.014

NMIBC: Non-muscle invasive bladder cancer, MIBC: Muscle invasive bladder cancer, AST: Aspartate amino transferase, ALT: Alanine amino transferase

Table 3. Comparison of data in patients with non-muscle invasive bladder cancer in terms of risk group stratification

Data	Low risk (n=19)	Intermediate risk (n=19)	High risk (n=66)	p
Age (year)	61.89±11.15	63.10±9.57	67.09±9.23	NS
Gender				
Male (n=90)	16 (84.2%)	15 (78.9%)	59 (89.4%)	NS
Female (n=14)	3 (15.8%)	4 (21.1%)	7 (10.6%)	
AST (U/L)	19.68±5.96	20.05±3.59	20.80±4.98	NS
ALT (U/L)	20±11.11	17.36±3.74	18.40±7.12	NS
AST/ALT	1.14±0.41	1.17±0.19	1.24±0.43	NS

AST: Aspartate amino transferase, ALT: Alanine amino transferase, NS: Not significant

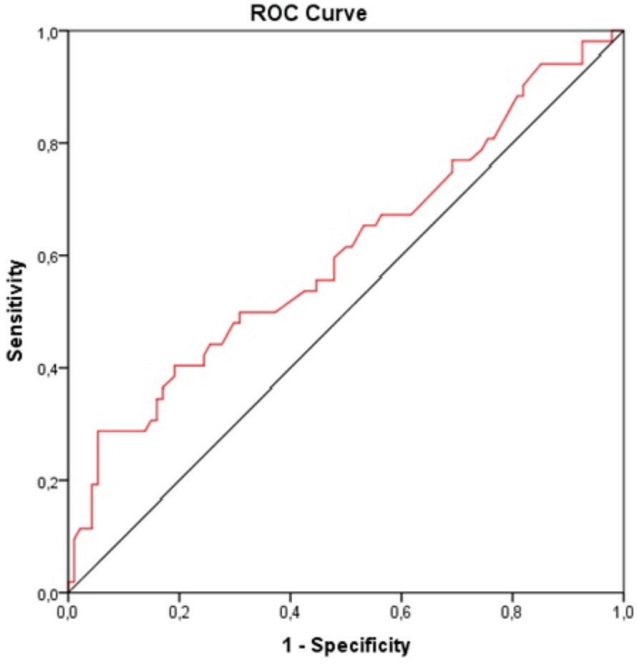


Figure 1. ROC curve for prediction of MIBC (AUC=0.603 (95% CI=0.503-0.702, p=0.037)

ROC: Receiver operating characteristics, MIBC: Muscle invasive bladder cancer, AUC: Area under curve, CI: Confidence interval

hand, for prediction of high-grade BC, ROC cut-off value was 1.20, with 58% sensitivity and 66% specificity (AUC=0.617, 95% CI=0.528-0.705, p=0.015) (Figure 2). According to Spearman correlation analysis, De Ritis ratio had a weak positive correlation with muscle invasion of BC (r=+0.236, p=0.036) and grade of tumour (r=+0.208, p=0.009). On the other hand, there was no correlation between De Ritis ratio and risk groups (p=0.471). According to regression analysis, patients' age did not influence the De Ritis ratio.

Discussion

Surgeons are poised to forecast histopathologic features of tumours prior to operation. The ability to clinically predict the invasiveness or grade of new tumours is often aid the decision on tumour management. According to European Organization for Research and Treatment of Cancer risk scores, BC patients are primarily grouped into NMIBC or MIBC, and into risk groups in order to predict 1 and 5 year recurrence and progression in terms recurrence rate, number of tumours, tumour size, T stage, grade, and simultaneous CIS presence. In this regard, patients with NMIBC are classified into low, intermediate and high risk groups for the purpose of treatment (26). Many studies have evaluated blood biomarkers and cystoscopy of tumour in view of predicting the histopathological stage and grade of BC (27,28,29). Vartolomei et al. (27) revealed in their meta-analysis that NMIBC patients with higher neutrophil-to-lymphocyte ratio, assessed prior to TUR-BT, have greater risk of disease recurrence and progression.

Tumour cells require excessive uptake of glucose (for glycolysis) in order to produce sufficient adenosine triphosphate, which

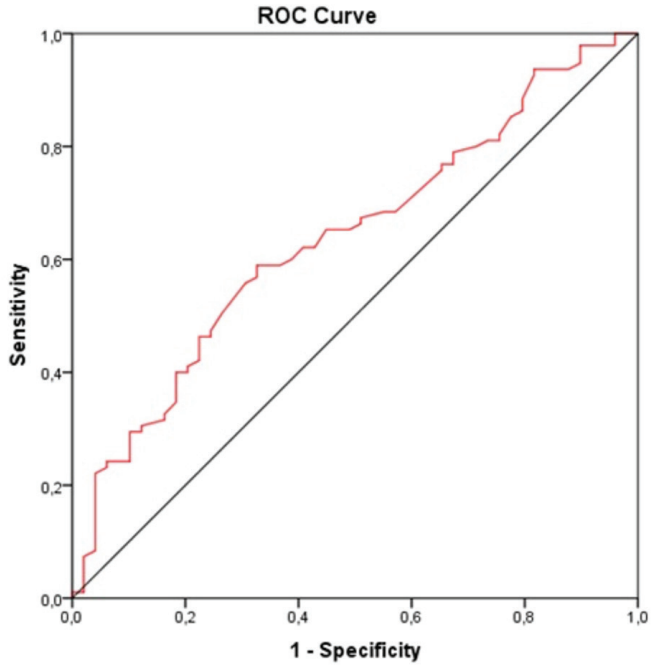


Figure 2. ROC curve for prediction of high-grade BC (AUC=0.617 (95% CI=0.528-0.705, p=0.015)

ROC: Receiver operating characteristics, AUC: Area under curve, BC: Bladder cancer, CI: Confidence interval

is referred to as the Warburg (30) effect. Increased glycolysis results in certain changes in mitochondrial activities and, in turn, alterations in activity of nicotinamide adenine dinucleotide-related enzyme and glucose transporters (31). BC is regarded as one of the glucose-reliant malignant tumours (32,33). This was also revealed by a study in which fluorescence microscopy images of BC cells show utilization of glucose (34). AST and ALT are needed as catalyst in glutamine metabolism. AST is also main component of malate-aspartate shuttle pathway (35,36). They are highly implicated in cellular metabolism and tumour proliferation. AST is a less liver-specific enzyme and increases much more in cancer compared to ALT (12,15,37). Therefore, De Ritis ratio might, not only is a predictor of glucose consumption in cancers, but also a predictor of tumour aggressiveness.

De Ritis ratio has been frequently used as a prognostic marker in many cancers (38). In uro-oncology, it was investigated in several types of cancer including BC, prostate cancer, renal cell carcinoma and urinary tract urothelial carcinoma (15,16,18,19,21,22). All the studies on BC showed an elevated preoperative De Ritis ratio, which was related to poor prognosis in patients who underwent RC (18,21,22). However, these studies focused on predicting the survival of previously diagnosed BC patients. To the best of our knowledge, our study is the first to predict tumour histology in patients newly diagnosed with BC. We found that higher preoperative De Ritis ratio was associated with higher stage and grade of BC. We observed a statistically significant correlation between high and low grade of BC, and between NMIBC and MIBC. In addition, our study revealed that De Ritis ratio was an age independent predictor of tumour histology.

A study conducted in Turkey revealed that patients with elevated De Ritis ratio (with a cut-off value of 1.3) had worse disease-specific and overall survival outcomes (18). Similar results were reported by Ha et al. (21). In our study, the cut-off value of preoperative De Ritis ratio for predicting muscle invasive and high-grade BC was 1.21 (sensitivity =56%, specificity =55%) and 1.20 (sensitivity =58%, specificity =66%), respectively. We demonstrated in our study that preoperatively evaluated AST/ALT value >1.21 was shown to be useful in predicting T2 or upstage in BC patients. Despite the low levels (Figures 1, 2), the AUC, sensitivity and specificity of De Ritis ratio in predicting both muscle invasion and high-grade BC were similar to aforementioned studies. In addition, we showed that patients with stage Ta and G1 tumour were younger than those with higher stage and grade of tumour. Age and tumour stage, along with an elevated De Ritis rate, were found to be independent prognostic factors for cancer and overall survival of patients with BC who underwent RC (18,22).

Study Limitations

In spite of the significant and new contributions of this study to literature, it has some inherit drawbacks. Firstly, this study was limited by its retrospective nature and relatively small sample size. Secondly, the type of BC was not classified. This was due to low number of patients with adenocarcinoma and squamous cell carcinoma in urinary bladder, and less than 10% of all BC patients, paralleling with literature (39). Regardless of the cancer type, we analysed the data obtained based on tumour stage and grade. Also, MIBC patients were not evaluated based on metastasis since we aimed to investigate the relationship between preoperative De Ritis ratio and primary BC and tumour histology prior to TUR-BT. If there was any distant organ metastasis of the tumour in MIBC group, it might affect the serum level of the amino transferase enzymes. Nevertheless, a prospective study including all pathological tumour stage with a long follow-up period will help to clarify this gap. Lastly, we could not evaluate the results according to WHO 2004/2016 grading system. However, the WHO 2004/2016 grading system is not superior to the WHO 1973 used in the present study (40).

Conclusion

AST and ALT are rapidly, cheaply and reproducibly measured serum biomarkers before performance of surgery. Considering the necessity for intensive and sustainable treatment for BC, we suggest that preoperatively assessed De Ritis ratio will be a helpful and useful predicting tool after diagnosis, treatment, and during follow-up of BC. However, this study needs to be validated by well-designed large-scale prospective clinical studies.

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Ethics

Ethics Committee Approval: After obtaining ethics committee approval of institutional review board (approval number: 2019/21, date: 05.08.2019), we conducted a cross-sectional study including patients who underwent TUR-BT for primary BC between May 2016 and August 2019 at two tertiary hospitals.

Informed Consent: Retrospective study.

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Authorship Contributions

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

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Original Article

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Evaluation of General Features of Patients with Testicular Cancer

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Abstract

Objective: Testicular cancers (Tca) are most common in men aged 20-34. Despite the increase in its incidence, the mortality rate from Tca decreases. In our study, it was aimed to evaluate the general characteristics, the treatments and survival of the patients who were followed up and treated with the diagnosis of Tca.

Materials and Methods: In this study, patients who were admitted to Okmeydanı Training and Research Hospital and Abant İzzet Baysal University, Medical Faculty, Medical Oncology Outpatient Clinic between January 2004 and December 2014 with the diagnosis of Tca, were evaluated retrospectively.

Results: In 324 (96.7%) of 332 patients included in the study with the diagnosis of Tca, testicular germ cell tumor (TGCT) was present. Of the patients, 150 (46.3%) had seminoma and 174 (53.7%) had non-seminoma tumors. The median age of patients with TGCT was 32 (minimum 18-maximum 81) years. Non-seminoma group was diagnosed at a younger age ($p<0.05$). The most common histology in the non-seminoma group was mixed germ cell tumor which was found in 135 patients (77.6%).

The stage in which the patients were most diagnosed was stage I (seminoma 73.3% and non-seminoma tumor 44.3%, $p<0.001$). Distant metastasis was present in 3.5% of patients with seminoma and 32.7% of patients with non-seminoma tumor ($p<0.001$). It was observed that 98% of the patients in the seminoma group and 85.6% of the patients in the non-seminoma group were in the good prognostic group ($p<0.001$). Radiotherapy, which was applied in 90 (81.8%) patients, was the most applied treatment in the group with stage I seminoma. In stage I non-seminomatous group, the most common treatment was cisplatin-based combination treatments, which was given to 58 (75.3%) patients.

The median follow-up period of patients with stage I seminoma was 60 (minimum 3-maximum 134) months, and the median follow-up period of patients with non-seminoma tumor was 69 (minimum 8-maximum 178) months. Three hundred twelve (96.3%) patients with TGCT survived and 145 (96.7%) in the seminoma group and 167 (96%) patients in the non-seminoma group survived ($p>0.05$).

Conclusion: The majority of our patients were diagnosed at an early stage and were in the good prognostic group. Most of our patients survived during our follow-up period.

Keywords: Survival, testicular cancer, testicular germ cell tumor

Introduction

Although testicular cancer (Tca) constitutes 1% of all cancers seen in men, it is the most common solid malignant tumor in men aged 20-34 (1,2). Although the incidence can vary from country to country, there has been an increase in the incidence of Tca in the last 20 years (3,4,5).

Cryptorchidism is one of the most important risk factors in its etiology. Other risk factors include family history, ethnicity, Testicular Feminization syndrome, and contralateral Tca history (1,6,7).

Of the Tca, 95% originate from the germinal tissue. Testicular germ cell tumors (TGCT) are divided into two groups as seminomatous and non-seminomatous germ cell tumors (GCT) (7).

The prognosis in Tca depends on the histological type, stage, tumor markers and metastasis of the tumor (8,9). Today, thanks to the developing surgery, radiotherapy techniques and chemotherapies, the survival rates of patients in especially good prognostic group are at 95% (1,10).

In this study, it was aimed to evaluate the demographic characteristics, histological subtypes of the tumor, the serum

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level of tumor markers, the stage at the time of diagnosis, the groups according to their prognostic features, treatment options, relapse and survival status of the patients who were diagnosed as having Tca, followed-up and treated.

Materials and Methods

For this study, approval was obtained from Abant İzzet Baysal University Faculty of Medicine Ethics Committee with the approval number: 2015/86, date: 13.08.2015. In this study, patients who were ≥18 years old, admitted to Okmeydanı Training and Research Hospital and Abant İzzet Baysal University, Faculty of Medicine, Medical Oncology Outpatient Clinic between January 2004 and December 2014 with the diagnosis of Tca, followed-up and treated, were included. Patients with missing file data were excluded from the study. Patient data in computer records and patient files were analyzed retrospectively.

The age of diagnosis, whether there was cryptorchidism, location of the tumor, histopathological diagnosis, serum level of tumor markers, stage at the time of diagnosis, risk categories, primary treatment type and date, whether there was recurrence, last control date and last status of the patients were recorded. The clinical staging of the patients was performed according to the American Joint Committee on Cancer Tca tumor node metastasis staging (11). Metastatic TGCT was classified according to the International Germ Cell Concensus Group as good, moderate and poor prognosis (12).

Statistical Analysis

The collected data were recorded and evaluated with SPSS 20.0 program. While the values showing homogenous distribution were expressed as "mean ± standard deviation"; parameters showing non-homogeneous distribution were expressed as "median (minimum-maximum)". The differences between the data of the seminoma and non-seminoma groups were evaluated using the Student t-test for numerical parameters showing homogeneous distribution, and the Mann-Whitney U test for parameters not showing homogenous distribution. The chi-square test, Fisher test was used to compare nominal data such as the location of the primary tumor, history of cryptorchidism, and the stage at the time of diagnosis, between the independent seminoma and non-seminoma groups. The correlation between the stage of the tumor and the serum level of tumor markers was evaluated by Spearman and Pearson Correlation tests. A p value <0.05 was considered statistically significant.

Results

It was determined that there were 343 patients who were admitted to the two centers with the diagnosis of Tca, treated and followed up. Eight of the patients were excluded from the study because the age at diagnosis was under 18 years and 3 patients were excluded because their file data were not available.

The remaining 332 patients with Tca were included in the study. Distribution of all patients according to histopathological subtypes is given in Table 1.

The median age of 324 patients with TGCT was 32 (minimum 18-maximum 81) years. In the seminom group, the median age was 36 (minimum 18-maximum 77) years; in the non-seminomatous group, it was 28 years (minimum 18-81). Patients in the seminoma group were most frequently diagnosed in the 30-39 age group (40%), whereas in the non-seminomatous group, they were most frequently diagnosed in the 20-29 age group (51.7%). The patients in the non-seminomatous group were diagnosed at a younger age. The distribution of age groups at the time of diagnosis between the two groups was statistically significantly different (p<0.05).

Table 1. Distribution of patients with testicular cancer by histological subtypes

	n	%
Testicular germ cell tumors	324	97.6
-Seminomatous	150	-
-Non-seminomatous	174	-
Embryonal carcinoma	28	-
Teratoma	6	-
Yolk sac tumor	3	-
Choriocarcinoma	2	-
Mixed germ cell tumor	135	-
Gender cord stromal tumor	**4**	**1.2**
-Leydig cell tumor	2	-
-Sertoli cell tumor	2	-
Other non-specific stromal tumors	**4**	**1.2**
-Diffuse large B cell lymphoma	1	-
-Leiomyosarcoma	1	-
-Liposarcoma	1	-
-Rhabdomyosarcoma	1	-
Total	**332**	**100**

Cryptorchidism was detected in 7.4% of patients with TGCT. It was present in 8% of the seminoma group and 6.9% of the non-seminomatous group. There was no statistical difference in terms of cryptorchidism between groups (p>0.05).

Of TGCT, 50% were located in the right testicle, 48.5% in the left testicle and 1.5% were in bilateral testicles. No statistical difference was found between the groups in terms of tumor location (p>0.05).

The most common histological subtype among the non-seminomatous group was mixed GCT, which was detected in 135 patients (77.6%) patients. Of 135 patients with mixed GCT histology, 111 (82.2%) contained histological component of embryonal carcinoma, 72 (53.3%) teratoma, 67 (49.6%) yolk sac tumor, 51 (37.8%) seminoma, and 8 (5.9%) choriocarcinoma. The most common combination was the embryonal carcinoma/teratoma combination seen in 26 patients (19.3%).

Of patients with TGCT, 0.3% were diagnosed as having stage 0 disease, at diagnosis, 57.7% as stage I, 17.6% as stage II, and 24.4% as stage III disease at the time of diagnosis. The stages of patients diagnosed as having seminoma and non-seminomatous tumors are given in Figure 1.

Distant metastases were present in 62 (19.1%) of 324 patients with TGCT at the time of diagnosis. The most common site of

metastasis was lung (48.4%). Multiple organ metastasis was present in 30.6% of the patients. Distant metastasis was present in 5 (3.5%) patients in the seminoma group and 57 (32.7%) in the non-seminomatous group. The difference between the two groups in terms of the presence of distant metastases at the time of diagnosis was statistically significant (p<0.001).

Distribution of patients diagnosed as having seminoma and non-seminomatous tumor by prognostic groups is given in Figure 2.

There was a positive correlation between the stage of the tumor and serum alpha feto protein and beta human chorionic gonadotropin (β-hCG) levels in patients in the non-nematomatous group (p<0.05).

When the primary treatments received by 110 patients diagnosed as having stage I seminoma were examined; radiotherapy was preferred in 90 (81.8%) of the patients, carboplatin chemotherapy in 11 (10%), and observation in 7 patients (6.4%). Two patients (1.8%) received treatment outside of the standard protocols.

The median follow-up period of patients diagnosed as having stage I seminoma was 60 (minimum 3-maximum 134) months.

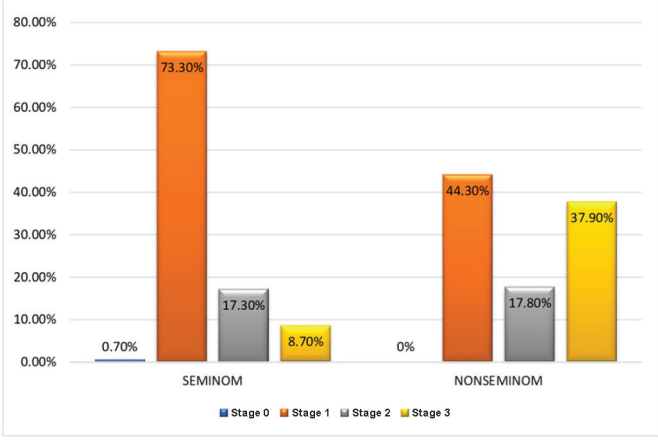


Figure 1. The disease stages at the time of diagnosis in patients with seminomas and non-seminomatous tumors

Stage 0, stage 1, stage 2, stage 3

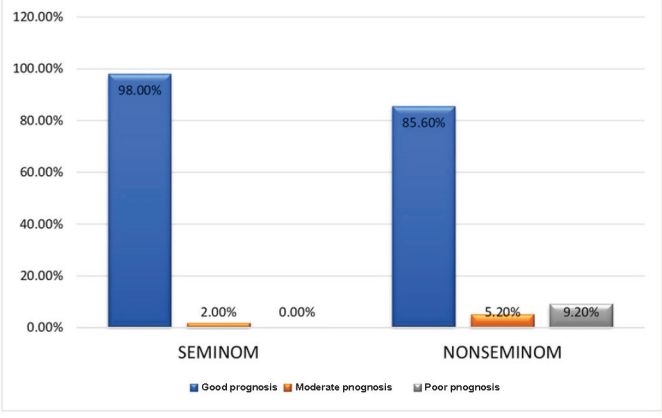


Figure 2. The distribution of patients with seminoma and non-seminomatous tumor according to prognostic groups. Good prognosis, moderate prognosis, poor prognosis

Median disease-free survival (DFS) duration was 14 (minimum 6-maximum 71) months. Disease recurrence was observed in 3 (3.3%) of 90 patients receiving radiotherapy, 2 (18.2%) of 11 patients who received carboplatin chemotherapy, and 2 (28.6%) of 7 patients in observation. The difference between preferred treatment methods in terms of recurrence was statistically significant (p<0.05).

The recurrence site was lymph nodes (regional and non-regional) in patients with stage I seminoma with recurrence after radiotherapy. The place of recurrence after treatment with carboplatin was lymph nodes (regional) and lung. Recurrence site was found to be lymph nodes (regional) in patients under observation. There was no statistically significant difference in terms of location of recurrence between three treatment options (p>0.05).

It was found that only 1 patient (0.9%) in the seminoma group died as a result of acute abdomen as a complication of adjuvant radiotherapy, and other patients were alive.

The median follow-up period of patients in stage I non-seminomatous group was 69 (minimum 8-maximum 178) months. The median time from the time of diagnosis to the relapse was 65 (minimum 3-maximum 137) months.

'Of 77 patients diagnosed as having stage I non-seminomatous tumor, observation was preferred in 11 (14.3%), 58 (75.3%) received cisplatin based chemotherapy, 4 (5.2%) preferred RPLND, and 4 (5.2%) patients did not accept treatment. Recurrence was observed in 3.4% of patients receiving chemotherapy, 18.1% of patients in observation, and 75% of patients who refused treatment. There was a statistically significant difference in terms of recurrence between treatment groups (p<0.001). It was found that only 2 (2.6%) of the patients died due to disease progression and other patients were alive.

In the follow-up; 318 (95.8%) of 332 patients diagnosed as having Tca, 312 (96.3%) of 324 patients with TGCT, 145 of 150 (96.7%) patients in the seminoma group, and 167 (96%) of 174 patients in the non-seminomatous group were found to be alive.

Discussion

TGCT is rare below the age of 15 and above the age of 60, but makes a peak at the age of 30-34 (7). In a study published in 2014 on this issue, it was found that patients were diagnosed most frequently in the second decade (13). While the median age at the time of diagnosis in seminomatoous GCT is 35-39 years, the median age is 10 years younger in the non-seminomatous GCT and it is 25-29 years (5).

Mixed GCT is the most common histological subtype in non-seminomatous GCT with a rate of 40% (14). Mixed GCT is the second most frequent tumor in the TGCT after seminoma (15). In a study conducted in Denmark, it was found that the most common component in mixed GCT was embryonal carcinoma (80%) and the most frequently observed combination was embryonal carcinoma/teratoma (16). In our study, it was concluded that the incidence of TGCT and the rate of histological subtypes were similar to the literature data.

History of cryptorchidism is one of the most important risk factors associated with the development of TGCT. In the study

of Wood and Elder. (17), it was found that the relative risk of Tca development in patients with cryptorchidism was between 2.75-8. In a study on this subject, cryptorchidism was detected in etiology in 10.7% of patients with TGCT (13). In our study, unlike these data, cryptorchidism was found lower in etiology. It was thought that this was because of our study was retrospective and cryptorchidism was not mentioned in the records of some patients.

Stage and prognosis have been shown to be directly related to early diagnosis in Tca (1,8,10). In a study conducted by Opot and Magoha (18) in Kenya, 64.1% of patients diagnosed as having Tca had advanced metastatic disease. Also, in a study conducted in Nigeria, 62.5% of patients were admitted with advanced stage metastatic disease (19). According to the data of the European Tca guideline, less than 20% of patients diagnosed as having TGCT present with a widespread metastatic disease with moderate or poor prognosis. While 90% of seminomatous GCTs have a good prognosis, 56% of non-seminomatous GCTs have a good prognosis (10). In our study, 60% of our patients with TGCT were diagnosed at an early stage. Of the patients in the seminoma group, 98% were in the good prognosis group, and 85.6% of the patients in the non-seminomatous group were in the good prognosis group. With the ease of access to health services in developed countries, high level of education and informing patients about self-examination, rate of admission with early stage disease is high. In the undeveloped countries, the vast majority of patients are admitted with metastatic disease for reasons such as difficulty in accessing health services, beliefs in traditional medicine, and low educational and socioeconomic level (13). We though that majority of patients were admitted with early stage disease and good prognostic features due to easy admission to health institutions in our country.

The first choice in the treatment of Tca is orchiectomy (10). Postoperative radiotherapy or carboplatin chemotherapy or observation are standard treatment options in patients with stage I seminoma (1,10,20). In a study comparing 1 cure carboplatin chemotherapy and adjuvant radiotherapy by Oliver et al. (20), it was shown that there was no difference between treatments in terms of relapse rate after 5 years of median follow-up, time to relapse, and survival rates. In a meta-analysis on this subject, the median DFS rate was 94.7% in patients receiving carboplatin during the 6.5-year follow-up period, and 96% in patients receiving radiotherapy. Although radiotherapy and carboplatin chemotherapy reduced the likelihood of relapse compared to the observation option, the cumulative survival rates were similar in all three treatment options (21). The most important disadvantage of the follow-up protocol in patients with stage I seminoma is the need for more intensive follow-up due to the possibility of recurrence (22,23). It was thought that the radiotherapy option might have been more preferred since the radiation oncology clinic had been actively working before the medical oncology clinic in one of our hospitals. It was thought that the reason why the observation option was less preferred was that it required more frequent follow-up, more frequent computed tomography and that patients preferred this option less because of fear of not being treated for cancer.

In non-seminomatous GCT, treatment options after orchiectomy vary according to stage, observation, chemotherapy and retroperitoneal lymph node dissection (RPLND) (1). The predominance of embryonal carcinoma component and/or the presence of lymphovascular invasion in the pathology of patients with stage I disease may change the treatment method to be followed. Active observation may be sufficient in patients without those at the time of diagnosis. However, if one of these factors is present, chemotherapy or RPLND may be considered in addition to active observation (1,10,24). In our study, it was seen that patients preferred the chemotherapy option instead of RPLND. As a result of this, it was concluded that high complication rates depending on the surgeon's experience and the surgical technique itself may have affected this preference.

According to the data of the 2019 European Tca guideline, the 5 year survival rate is 92% in patients with non-seminomatous GCT in the good prognosis group, while the 5 year survival rate in patients with seminomatous GCT is reported as 86% (10). Even in advanced disease, survival increases with advances in diagnosis and treatment. Prognosis improves, mortality decreases and survival results are satisfying due to early diagnosis, advances in treatment methods and follow-ups with frequent intervals. In recent years, 10 year survival rates are approaching to 95% with effective treatments (1,25). In the undeveloped countries where those cannot be achieved, survival rates are still very low. In the study conducted by Chalya et al. (13) in Tanzania, the survival rate was reported as 22.2%, and the survival rate in the study by Opot and Magoha (18) in Kenya was reported as 38.89%. In our study, in the median 60 month follow-up period, 95.8% of patients diagnosed as having TGCT were alive. Of patients diagnosed as having seminomatous GCT, 96.7% were alive and 96% of patients diagnosed as having non-seminomatous GCT were alive at the end of follow-up period. These survival results were very satisfactory and similar to the survival results of developed countries.

Although long survivals are achieved in patients diagnosed as having Tca, malignant neoplasms and cardiovascular disease secondary to treatment appear as important survival problems in the long term. In addition, patients may experience hearing loss, tinnitus, neurotoxicity, nephrotoxicity, pulmonary toxicity, hypogonadism, infertility, anxiety, depression, and cognitive impairment as adjuvant treatment side effects (26). In this regard, we believe that it will be appropriate to follow up the patients diagnosed as having Tca in terms of treatment complications.

Conclusion

Although the incidence of Tca has increased in recent years, there is a decrease in mortality due to early diagnosis and treatment methods. Unfortunately, admission rates with metastatic stage disease are still high and survival rates are low in some underdeveloped and developing countries. In our study, the majority of our patients were diagnosed at an early stage and were in a good prognostic group. During our follow-up period, 96.3% of our patients were alive. Radiotherapy was preferred as an adjuvant treatment among patients with stage I seminomatous GCT among the options of observation, radiotherapy and chemotherapy. Recurrence rate was low in those receiving radiotherapy. In patients diagnosed as having stage I non-seminomatous GCT, cisplatin-based combination

therapy was mostly applied. Recurrence was also very low in this treatment group. However, it has been concluded that there is a need for prospective studies that can screen the side effects of treatments more closely, clarify the choice of treatment, especially in patients with stage I TGCT, and also prevent data loss.

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Ethics

Ethics Committee Approval: Approval was obtained from Abant İzzet Baysal University Faculty of Medicine Ethics Committee with the approval number: 2015/86, date: 13.08.2015.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.E.G., Ü.Ü., Design: M.E.G., Ü.Ü., Data Collection or Processing: M.E.G., Ü.Ü., Ç.G., Analysis or Interpretation: M.E.G., Ü.Ü., Literature Search: M.E.G., Ü.Ü., Writing: M.E.G.

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Original Article

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Effect of Primary Testicular Tumor Localization on Prognosis and Survival of Non-seminomatous Testis Cancer Patients

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Abstract

Objective: Unlike left testicular vein, right testicular vein drains into inferior vena cava. Consequently, the systemic spread of testicular cancers in each side is expected to differ based on the vascular structures of the right and left testis. In this study, we investigated the effect of tumour localization on survival of non-seminomatous testicular cancer patients.

Materials and Methods: We included three hundred and twenty-one (321) non-seminomatous testicular cancer patients who were followed-up at Gülhane Training and Research Hospital between January 1981 and December 2015.

Results: The primary tumour found in the left testis in 152 (47.2%) patients, while 170 (52.8%) patients had the primary tumour in the right testis. The lungs (n=62, 42.5%) was the most common site of metastasis. During follow-up and primary treatment, 74 (23.1%) patients had recurrence, which was common in retroperitoneal lymph nodes (10.3%) and lung (5%). Median follow-up period was 88.3 (range: 1-386) months, while median survival was 337 months in all cases. Median 10 year survival rate was 74.1%, while median 20 year survival rate was 70.7%. We found that survival of patients with the primary tumour was significantly different between the left and right testis (337.6 months vs denotes not reached, p=0.001). The recurrence rate was significantly higher (84.7% vs 68.2%; p=0.002) in patients with right testicular tumour when compared to patients with left testicular tumour.

Conclusion: The survival of the patients with tumour localized in the right testis was higher than patients with tumour localized in the left testis.

Keywords: Germ cell tumours, survival, testicular cancer

Introduction

Testicular cancer, which constitutes 1% of all solid tumours, is the most common solid malignancy in men aged between 15 and 35 years (1). Germ cell tumours, which constitute 95% of testicular cancers, are classified as pure seminoma and non-seminomatous germ cell tumour. The 5 year survival rate of testicular cancer patients treated with platinum-based combination chemotherapy is 95% (2). Despite having extensive organ metastasis and/or high serum tumour markers, patients can be cured with effective combination chemotherapies (2). In spite of this remarkable cure rates, additional treatments may be required in patients with refractory and/or relapse arising from first-line treatment (3). International Germ Cell Cancer Collaborative Group divided patients into three (good, intermediate and poor) based on prognostic factor-based staging classification (4). According to a meta-analysis published in 2006, survival rates with standard treatment were significantly increased (71%) among patients with poor prognosis following the publication of the International Germ Cell Consensus Classification (5). However, some patients do not benefit significantly from the treatment despite having better Prognostic score (4). Therefore, there is an urgent need for additional prognostic factors.

Similar to other solid cancers, non-seminomatous testicular cancer also spreads through lymphatic and vascular pathways (6). When the vascular structures are evaluated, we observe that the venous drainages of both testicles are different. While the collector vein of the right testis is connecting to the inferior

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vena cava directly, the collecting vein of the left testis is initially drains into the collector vein of the left kidney, and then joins approximately 8-10 cm proximal to the inferior vena cava. Therefore, the left testis is exposed to more pressure and have relatively slower blood flow than the right testis. There is a hypothesis that the systemic spread will be higher due to the direct drainage into the heart, and due to the low pressure in the vascular structure of the right testis (7).

This study aimed to investigate the effect of tumour localization (right and left testis) on survival of non-seminomatous testicular cancer patients.

Materials and Methods

Setting and Study Population

This was a single-center retrospective study including non-seminomatous testicular cancer patients diagnosed at a medical oncology clinic of a university hospital between January 1981 and December 2015.

Information regarding demographic characteristics of patients, biochemical findings including beta-human chorionic gonadotropin, alpha-fetoprotein and lactate dehydrogenase, tumour localization and histopathology, T stage, lymph node infiltration status, distant metastasis, orchiectomy status, response to chemotherapy, response to radiotherapy (if administered), relapse and refractory status, stem cell transplantation and tumour localization, progression-free survival, and overall survival were obtained from patients' files, retrospectively. Histopathology of tumour was determined according to World Health Organization classifications (8).

The tumour stage in the patients was defined according to the American Joint Committee on Cancer and Union for International Cancer Control (9). Local ethics committee approval was obtained, and the study protocol conformed to the ethical guidelines of 1975 Declaration of Helsinki (approval number: 19/26, date: 12.02.2019).

Statistical Analyses

Descriptive statistics for continuous (quantitative) variables were presented as mean, standard deviation, minimum and maximum values. The categorical variables were presented as number (n) and proportion (%). Independent t-test and One-way analysis of variance were used for comparison. Chi-square test was used to the determine relationship between categorical variables. The adopted statistical level of significance (p) was 5%. Progression-free survival was estimated as the time from diagnosis to progression/recurrence or death. Total survival (OS) was estimated as the period from diagnosis to death. All statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 18.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

A total of three hundred and twenty-one (321) non-seminomatous testicular cancer patients aged ≥18 were included in the study. Demographic characteristics and treatment methods are summarized in Table 1. Median age of patients was 34 (range: 18-77) years. The primary tumour was located in the left testis in 152 (47.2%) patients, and in the right testis in 170 (52.8%) patients. The most common histopathology was mixed non-seminomatous germ cell tumour (39.4%), while the most rare tumour type was immature teratoma (4.7%). Exactly 146 (44.3%) cases were metastatic at the time of diagnosis, while 176 (54.7%) cases were localized. The most common site of metastasis was the lungs (n=62, 42.5%). The second most common site of metastasis was in multiple visceral organs (n=37, 25.3%). There were elevated tumour markers in 30 (9.3%) patients.

After analysis of treatments details, 6 cases (1.9%) in the suitable stage were closely followed-up. Adjuvant chemotherapy following radical orchiectomy was administered to 277 (86.3%) patients. Exactly 9 (2.8%) patients received adjuvant radiotherapy, and in three of these cases, the radiotherapy site was the pelvic region. Retroperitoneal lymph node dissection was performed in 109 cases, and only 3.7% of these cases had metastasis in the liver. Metastasectomy was performed in 41 (12.8%) patients. Although bleomycin-etopocyte-cisplatin chemotherapy (of three or four cycles) was the most preferred protocol in first-line therapy, single-agent carboplatin, etoposide-cisplatin and etoposide-ifosfamide-cisplatin protocols were other plausible options.

Exactly 74 (23.1%) patients had recurrence in the follow-up period and during primary treatment. The most common recurrence sites were retroperitoneal lymph nodes (10.3%) and lung (5%).

Median follow-up period was 88.3 months (range: 1-386), while median survival was estimated as 337 months in all cases. Median 10-year survival rate was 74.1%, while 20-year survival rate was 70.7%. Primary tumour localization, left and right testis, was significantly different in terms of survival of patients (337.6 months vs denotes not reached (NR), p=0.001). No statistically significant difference was observed between the groups based on factors affecting survival (Table 2). The recurrence rate in patients with right testicular tumour was significantly higher (84.7% vs 68.2%; p=0.002). In one case, high dose chemotherapy was needed for salvage treatment. Third-line chemotherapy was required for 83 patients. The most preferred salvage regimen was vinblastine-ifosfamide-cisplatin (17.1%). Following salvage treatment, complete response, partial response, and stable disease were observed in 24 (7.5%), 32 (10%), and 13 (2.8%), respectively. The unresponsiveness to salvage treatment was 3.4%. Autologous stem cell transplantation was performed in 40 (12.5%) patients. Overall, exactly 251 cases were healthy, while 70 (21.7%) patients died.

Lung and retroperitoneal lymph node recurrence were more common in patients with right testicular tumour (p=0.02) than in patients with left testicular tumour. The effect of tumour localization on survival was independent of metastasis, histopathology, site of metastasis, and disease stage at the time of diagnosis.

Discussion

Based on the human anatomy, it is observed that the lymphovascular structures of each organ are asymmetrical. Due

Table 1. Demographic characteristics and treatment details							
		Right		Left		Total	
		n	n%	n	n%	n	n%
Metastasis site		74	49	103	60.6	177	55.1
	brain	5	3.3	5	2.9	10	3.1
	multiple organ metastasis	22	14.6	15	8.8	37	11.5
	other	5	3.3	8	4.7	13	4
	liver	8	5.3	2	1.2	10	3.1
	bone	3	2	3	1.8	6	1.9
	pulmonary	32	21.2	30	17.6	62	19.3
	supradiaphragmatic lymph node	2	1.3	4	2.4	6	1.9
Stage	1	29	-	55	-	84	-
	2	48	-	52	-	100	-
	3	74	-	63	-	137	-
Treatment	chemotherapy	132	87.4	145	85.3	277	86.3
	radiotherapy	5	3.3	4	2.4	9	2.8
	no treatment	14	9.3	21	12.4	35	10.9
First-line chemotherapy status	CT was given	132	87.4	147	86.5	279	86.9
	no CT	19	12.6	23	13.5	42	13.1
First step chemotherapy protocols		19	12.6	23	13.5	42	13.1
	BEP 2 cycle	18	11.9	32	18.8	50	15.6
	BEP 3 cycle	50	33.1	52	30.6	102	31.8
	BEP 4 cycle	59	39.1	55	32.4	114	35.5
	carboplatin single dose	0	0.0	2	1.2	2	0.6
	EP 3 cycle	0	0.0	1	0.6	1	0.3
	EP 4 cycle	3	2	4	2.4	7	2.2
	EP 6 cycle	1	0.7	1	0.6	2	0.6
	VIP: Etop + ifos + cisplatin	1	0.7	0	0.0	1	0.3
Marker status							
	normal	125	82.8	143	84.1	268	83.5
	high	15	9.9	15	8.8	30	9.3
Relapse	non-recurrent	97	64.2	137	80.6	234	72.9
	recurrent	48	31.8	26	15.3	74	23.1
Relapse place		103	68.2	144	84.7	247	76.9
	lung	10	6.6	6	3.5	16	5
	brain	2	1.3	1	0.6	3	0.9
	inguinal	0	0.0	1	0.6	1	0.3
	liver	4	2.6	0	0.0	4	1.2
	bone	4	2.6	1	0.6	5	1.6
	mediastinal lymph node	7	4.6	5	2.9	12	3.7
	retroperitoneal lymph node	21	13.9	12	7.1	33	10.3
Autologous transplant	done	21	13.9	19	11.2	40	12.5

BEP: Bleomycin-etopocyte-cisplatin, EP: Etoposide-cisplatin, VIP: Etoposide-ifosfamide-cisplatin, CT: Chemotherapy

to asymmetrical arrangement, the incidence and prognosis of diseases affecting the right and left locations in organs are different (10). During cancers development process in different organs of the body is evaluated, differences in development mechanisms and various clinical outcomes are observed. In a study conducted by Roychoudhuri et al. (7), the impact of

Table 2. Distribution of tumour according to localization of testicle						
		Right		Left		*p
		n	n%	n	n%	
Pathology	embryonal cell carcinoma	**8**	**5.3**	**9**	**5.3**	0.052
	immature teratoma	6	4	9	5.3	
	mixed non-seminoma	65	43	62	36.5	
	mixed seminom + non-seminoma	29	19.2	39	22.9	
	pure coriocarcinoma	12	7.9	20	11.8	
	teratoma	20	13.2	8	4.7	
Yolk sac tumour		11	7.3	23	13.5	
Metastasis	yes	76	50.3	70	41.2	0.100
	no	75	49.7	100	58.8	
	brain	5	3.3	5	2.9	
	multiple organ	22	14.6	15	8.8	
	other	5	3.3	8	4.7	
	liver	8	5.3	2	1.2	
	bone	3	2	3	1.8	
	pulmonary	32	21.2	30	17.6	
	supradiaphragmatic lymph node	2	1.3	4	2.4	
	marker status normal	125	82.8	143	84.1	
	high	15	9.9	15	8.8	
Relapse	-	6	4%	7	4.1	0.002
	non-recurrent	97	64.2	137	80.6	
	recurrent	48	31.8	26	15.3	
Relapse place	lung	103	68.2	144	84.7	0.020
		10	6.6	6	3.5	
	brain	2	1.3	1	0.6	
	inguinal	0	0.0	1	0.6	
	liver	4	2.6	0	0.0	
	bone	4	2.6	1	0.6	
	mediastinal lymph node	7	4.6	5	2.9	
	retroperitoneal lymph node	21	13.9	12	7.1	

tumour localization on survival of patients with breast, lung, kidney, testis and ovarian was evaluated. They found that patients with left testicular cancer have better survival rate. In our study, a significant difference was found between cases with right and left testicular tumour in terms of survival (n=337.6 months vs NR, p=0.001). Our results are in consonant with that of the only literature so far (11).

In this study, the median follow-up period was 88.3 (range: 1-386) months, while the median survival was 337 months in all cases. The 10 year survival rate was 74.1%, while the 20 year survival rate was 70.7%. According to a meta-analysis by van Dijk et al. (5) including ten different studies, the 5 year survival rate of non-seminomatous testicular cancer patients with intermediate and poor prognosis were 83% and 71%, respectively. The 10 and 20 year survival rates of patients included in our study were consistent with the aforementioned literature.

In a study including 769 diffuse large B cell lymphoma patients, the OS was 4.4 years in patients with left testicle cancer, and 4.7 years in patients with right testicle cancer (p=0.039) (11). Authors were of stated that their results were inconsistent with the findings of Roychoudhuri et al. (7). However, they did not provide reasons for these contradictory result.

In our study, we included 45 seminoma patients and investigated the effect of tumour localization on their survival. The survival of the patients with tumour originating from the left testis was significantly higher than that arising from the right testis (n=205.1 month vs NR, p=0.002). This finding indicates that patients whose tumour originated from the right testis had poor survival.

Study Limitations

This is the first study on the localization of a rare type of primary tumour conducted retrospectively. This study was single-centred as it was included a large group of patients having a long follow-up period.

Conclusion

The survival of patients with localized tumour in the right testis was significantly better than that of patients with localized tumours in the left testis. The effect of tumour localization on survival was independent of the metastasis, histopathology, site of metastasis, and disease stage, as at the time of diagnosis.

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Ethics

Ethics Committee Approval: Local ethics committee approval was obtained, and the study protocol conformed to the ethical guidelines of 1975 Declaration of Helsinki (approval number: 19/26, date: 12.02.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.Y., N.K., Design: B.Y., N.K., İ.E., Data Collection or Processing: B.Y., N.K., B.B.B., Analysis or Interpretation: E.E., B.B.B., Literature Search: N.K., B.B.B., R.A., Writing: B.Y., N.K., E.E.

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Original Article

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What is the Prostate Specific Antigen Cut-off Value to Detect Metastases in Ga-68 Prostate Specific Membrane Antigen Ligand Positron Emission Tomography/ Computer Tomography Imaging for Intermediate and High-risk Prostate Cancer?

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Abstract

Objective: The aim of this study was to detect a prostate specific antigen (PSA) cut-off value for metastases, and prevent unnecessary use of Ga-68 prostate specific membrane antigen (PSMA) ligand positron emission tomography/computer tomography (CT) imaging.

Materials and Methods: Between January 2016 and October 2017, patients with prostate cancer (PCa) who were staged using Ga-68 PSMA enrolled in this retrospective study.

Patients were divided into two groups: group 1 (G1) had Ga-68 PSMA for primary staging, and group 2 (G2) had Ga-68 PSMA for detection of metastases after treatment (secondary staging). PSA cut-off values were calculated for general, bone, lymph node and visceral metastases.

Results: A total of 181 patients were included in this study. PSA cut-off was 7.5 ng/mL for overall metastases in general. The PSA cut-offs for overall metastases using initial PSA were 8.98 ng/mL and 6.82 ng/mL for G1 and G2, respectively. For G2 patients the post-treatment PSA cut-off was 0.38 ng/mL. For bone metastases, the PSA cut-offs using initial PSA were 8.98 ng/mL and 10.7 ng/mL for G1 and G2, respectively. For lymph node metastases, the PSA cut-offs using initial PSA were 8.98 ng/mL and 6.71 ng/mL for G1 and G2, respectively. For visceral metastases, the PSA cut-offs using initial PSA were 16.4 ng/mL and 7.08 ng/mL for G1 and G2, respectively. The same analyses could not be calculated in subgroups of G2 due to small sample size.

Conclusion: These cut-off values do not suggest that Ga-68 PSMA is superior to using both CT and bone scintigraphy. It is an expensive test and its use is only reasonable when small lymph node metastases cannot be evaluated in CT.

Keywords: PSA, prostate cancer, Ga-68 PSMA ligand PET/CT

Introduction

Prostate cancer (PCa) is the most detected cancer and the second most common cause of cancer death among men in USA (1). The detection of PCa increased after the first reported use of prostate specific antigen (PSA) by Catalona et al. (2) in 1991, and the verification of PSA for cancer detection by the Food and Drug Administration in 1994 (3). PCa represents a broad-spectrum illness ranging from slow to aggressive disease (1). The major aim of PCa treatment is to convert the disease to an indolent form, as much as the treatment regimen allows. To select the most appropriate treatment modality, patients are categorised as low, intermediate and high-risk for PSA recurrence using the clinical stage, Gleason score and serum PSA level (4). Current the European Association of Urology guidelines suggest imaging with contrast-enhanced computerized tomography (CT) and bone scan (BS) for intermediate and high-risk patients to detect possible metastases. In addition, for high-risk patients, multiparametric magnetic resonance imaging of prostate (MP-MRI-P) is also recommended for detection of local enlargement

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(4). However, CT is not a disease-specific imaging technique, and BS is mostly suitable when the patient has bone pain and a serum PSA level of >10 ng/mL (5).

Prostate specific membrane antigen (PSMA) is a type 2 transmembrane glycoprotein found in normal prostatic epithelium and overexpressed when PCa develops in normal prostatic tissue (6). Ga-68 PSMA ligand positron emission tomography (PET)/CT imaging is the name of radiotracer labelled with the Ga-68 radionuclide substance. It is endocytosed and collected beyond the cell membrane of PCa (7). It is an emerging imaging technique that could combine the advantages of CT and BS. After the initial diagnosis, Ga-68 PSMA can be used for both primary and secondary staging. For primary staging, conventional imaging techniques may not detect metastases: CT could omit some lymph nodes (5), and BS could omit bone metastases when PSA is <10 ng/mL (7,8). These factors may play a role in choosing the treatment modality. For secondary staging, conventional techniques could fail to detect metastases unless the biochemical PSA recurrence reaches high levels (9).

In this study, our aim was to detect a PSA cut-off value for metastases and prevent unnecessary use of Ga-68 PSMA.

Materials and Methods

The ethical acceptance of this study was approved by the local Ethics Committee Private Koru Hospital and followed ethical standards described in the Helsinki Declaration (date: 05.01.2018).

Between January 2016 and October 2017, a total of 207 men with PCa who were staged using Ga-68 PSMA enrolled in this retrospective study (prospectively collected data reviewed retrospectively). The indications for Ga-68 PSMA were: PCa with the Gleason score >6, or any suspicion of metastases after any treatment for PCa.

For primary patients, the algorithm from elevated PSA level to application of a Ga-68 PSMA started from a transrectal ultrasound prostate biopsy when PSA was ≥4 ng/mL, or abnormal palpation of prostate on rectal digital examination in patients with more than 10 years life expectancy. A minimum of a 12-core prostatic biopsy was taken with an 18 gauge Tru-cut biopsy needle.

For secondary patients who were treated for PCa, the algorithm started with the suspicion of metastases in an imaging modality or with an elevated PSA level.

Patients with serum creatinine and bilirubin levels higher than two times of upper limit of normal, and patients with liver transaminase levels higher than three times of upper limit of normal were not directed to Ga-68 PSMA.

Twenty-six patients were excluded from the study due to excessive incomplete information. Patients were divided into two groups: group 1 (G1) had Ga-68 PSMA for primary staging, and group 2 (G2) had Ga-68 PSMA for detection of metastases after a treatment modality (secondary staging). Patients in G2 were divided into six groups: G2a had radical prostatectomy (RP), G2b had radiotherapy (RT) plus hormonotherapy (HT), G2c had HT alone, G2d had chemotherapy plus HT, G2e had RP plus RT, and G2f had RT plus chemotherapy.

The PSA value, pathology results, metastatic sites and maximum standard uptake value (SUV_{max}) for metastatic sites were noted and compared. A PSA cut-off value was calculated for general, bone, lymph node and visceral metastases.

Radiopharmaceutical and Imaging Protocols

All PSMA PET/CT evaluations were performed at a single centre. Ga-68 PSMA-11 was prepared using a fully automated radiopharmaceutical synthesis device based on a modular concept (Eckert & Ziegler Eurotope, Berlin, Germany). Briefly, a TiO_2-based commercially available Ge-68/Ga-68 generator (Eckert & Ziegler Eurotope) was eluted with 0.1 N hydrochloric acid and a 1.2 mL fraction was added to 5 nmol of PSMA (ABX GmbH, Radeberg, Germany); pH was adjusted to 3.5-4.0 by adding 1 mol/L sodium acetate solution. The reaction was carried out at room temperature for 120 s. The reaction solution was passed over a C18 cartridge (Sep-Pak; Waters Associates, Milford, Massachusetts, USA), washed with 5 mL of water, and finally eluted with 0.5 mL 95% ethanol, which was followed by saline through a 0.2 µm sterile filter. Radiochemical purity, as determined by high performance liquid chromatography, exceeded 95% in all cases.

For image acquisition after the preparation and quality control of the radiotracer, all patients received 65 to 178 MBq (mean 113.3±21.2 MBq, <2 nmol PSMA ligand) of Ga-68 PSMA-11 according to the yield of the radiolabeling. Whole-body images acquired 45 to 60 minute post-injection of radiotracer using integrated PET/CT scanners: Discovery PET/CT 690 (GE Healthcare, Milwaukee, Wisconsin, USA). The patients were placed on the scanner table in a supine position and a CT transmission scan without intravenous contrast enhancement was acquired with a low tube current (130 kVp, 48-76 mAs), a slice thickness of 4.0 mm, 0.6 s gantry rotation, and a collimator width of 6×3 mm. Then, PET emission scanning with duration of 3 minute per bed position was performed with an identical transverse field of view in the caudocranial direction. For attenuation correction, CT transmission images were used and an iterative method was used for image reconstruction.

Statistical Analysis

Statistical analysis was done using Statistical Package for Social Sciences 20.0 Software (SPSS 20.0 for MAC). Descriptive statistics of nominal samples were expressed with numbers and percentiles. Descriptive statistics of scale samples were expressed as mean ± standard deviation (minimum-maximum). Shapiro-Wilk, Kurtosis and Skewness tests were used to assess the variables' normalisation. The Mann-Whitney U test was used to compare the pre and post procedure independent scale parameters without normal distribution. The Paired Sample t-test was used to compare the pre and post procedure dependent scale parameters with normal distribution. Pearson chi-square test was used to compare the independent nominal parameters. Pearson Correlation test was used to correlate two scale samples. Receiver operating characteristic (ROC) curve was used to detect a PSA cut-off. Probability of $p<0.05$ was accepted as statistically significant.

Results

A total of 181 patients were included in this study. G1 and G2 included 71 and 110 patients, respectively. The mean patient age was 69.46±8.22 (range 53-86) years in G1 and 68.21±9.44 (41-88) years in G2. The median PSA value was 15.0 (3-3000) ng/mL in G1, and 18.21 (1.02-1260) ng/mL in G2 at the initial diagnosis of PCa. After the treatment modalities, the median PSA value was 0.78 (0.01-81) ng/mL in G2. The median PSA values were 0.24 (0.01-0.53) ng/mL, 13.63 (0.01-81) ng/mL, 0.26 (0.01-0.3) ng/mL, 3.84 (0.24-13.8) ng/mL, 3.44 (0.21-8) ng/mL, and 17.85 (0.01-69.2) ng/mL in G2a, G2b, G2c, G2d, G2e and G2f, respectively.

The pathologic results and pathologic Ga-68 PSMA uptake in detail for each site of body is expressed in Table 1. The most common metastatic regions were the lymph nodes and bone in G1 and G2, respectively. The most common metastatic bone sites were the sternum and costa, with 15 (21.1%) and 41 (37.3%) metastases, respectively (p=0.002). The most common metastatic lymph node regions were the internal iliac, external iliac and obturator lymph nodes with 20 (28.2%) and 30 (27.3%) metastases, respectively (p=0.895). The third metastatic region was the visceral organs, and the most common metastatic visceral organ was lung with 2 (2.8%) and 12 (10.9%) pathologic uptake in G1 and G2, respectively (p=0.042) (Table 1).

The mean SUV_{max} values were 21.55±5.64 (10-29.9) and 25.4±18.9 (2.4-74) for bone metastases (p=0938); 28.9±17.39 (10.9-52) and 25.69±18.02 (7-59) for lymph node metastases (p=0.902); and 19.1±9.44 (41-88) and 21.30±29.7 (7-82) for visceral metastases (p=0.571) in G1 and G2, respectively. There was a significant correlation between PSA and SUV_{max} values for bone (p=0.001) and lymph node (p=0.015) metastases in G1 (Figure 1). There was a significant and non-significant correlation for bone (p=0.004) and lymph node (p=0.304) metastases in G2. The correlation could not be calculated for visceral metastases due to small sample size. For G1 patients, there was a linear correlation between PSA and SUV_{max}. For G2 patients, the linear correlation was only significant when the PSA was between 24-26 and 14-25 ng/mL.

The overall area under curve value of the ROC curve formed using PSA to detect any metastases in the body was 0.727, and the PSA cut-off was 7.5 ng/mL with 80% sensitivity and 60% specificity. The area under curve values were 0.78 and 0.68 in G1 and G2, respectively (Figure 2). The PSA cut-offs for overall metastases using initial PSA were 8.98 ng/mL and 6.82 ng/mL with 80% sensitivity and 60% specificity for G1 and G2. For G2 patients the post-treatment PSA cut-off was 0.38 ng/mL. For G2a, G2b, G2d, G2e and G2f, the post-treatment PSA cut-offs were 0.31 ng/mL, 0.95 ng/mL 0.27 ng/mL, 1.71 ng/mL and 0.05 ng/mL, respectively. For G2c, a post-treatment PSA cut-off could not be detected due to sample size (Table 2).

For bone metastases, the PSA cut-offs using initial PSA were 8.98 ng/mL and 10.7 ng/mL for G1 and G2, respectively. For lymph node metastases, the PSA cut-offs using initial PSA were 8.98 ng/mL and 6.71 ng/mL for G1 and G2 at first diagnosis. For visceral metastases, the PSA cut-offs using initial PSA were 16.4 ng/mL and 7.08 ng/mL for G1 and G2 at first diagnosis (Table 2). The same analyses could not be calculated in subgroups of G2 due to small sample size.

Discussion

New techniques and developments in the detection of clinically significant PCa to determine treatment modality have been the main topics of reports in the last decade. The most commonly used imaging techniques for staging PCa are CT, BS and MP-

Table 1. The pathologic results and metastatic sites of patients

	G1 (n, %)	G2 (n, %)	p*
Gleason 3+3	4 (7)	2 (4)	0.009
Gleason 3+4	4 (7)	3 (6)	
Gleason 4+3	18 (33)	10 (21)	
Gleason 4+4	8 (14)	9 (20)	
Gleason 4+5	11 (20)	30 (23)	
Gleason 5+3	2 (3)	2 (4)	
Gleason 5+4	1 (1)	4 (8)	
Gleason 5+5	6 (2)	6 (14)	
Visceral metastasis	4 (5.6)	16 (14.5)	0.062
Lymph node metastasis	25 (35.2)	44 (40)	0.517
Parotis gland metastasis	0	1 (0.09)	0.521
Submandibular gland metastasis	0	0	-
Lacrimal gland metastases	0	1 (0.09)	0.608
Tiroid metastasis	0	3 (2.7)	0.222
Supraclavicular lymph node metastasis	2 (2.8)	6 (5.5)	0.327
Lung metastasis	2 (2.8)	12 (10.9)	0.042
Hiler lymph node metastasis	10 (14.1)	18 (16.4)	0.424
Hepatic metastases	2 (2.8)	6 (5.5)	0.327
Spleen metastasis	0	0	-
Kidney metastases	0	0	-
Paraaortic + paracaval + aortocaval lymph node metastasis	12 (16.9)	24 (21.8)	0.418
Internal + external iliac + obturatuar lymph node metastasis	20 (28.2)	30 (27.3)	0.895
Inguinal lymph node metastasis	5 (7)	6 (5.5)	0.445
Multiple abdominal lymph nodes metastasis	9 (12.7)	17 (15.5)	0.603
Pararectal metastasis	12 (6.9)	10 (9.1)	0.119
Prostatic uptake	56 (78.9)	32 (29.1)	0.001
Bone metastasis	18 (25.4)	63 (57.3)	0.001
Multiple bone metastasis	13 (18.3)	42 (38.2)	0.005
Cranial metastasis	5 (7)	22 (20)	0.016
Vertebral metastasis	13 (18.3)	51 (46.4)	0.001
Sternal and costa metastasis	15 (21.1)	41 (37.3)	0.02
Acatabular metastasis	11 (15.5)	40 (36.4)	0.02
Pubis metastasis	14 (19.7)	38 (34.5)	0.031
Sacral metastasis	11 (15.5)	36 (32.7)	0.009

G1: Group 1, G2: Group 2, *Pearson chi square test

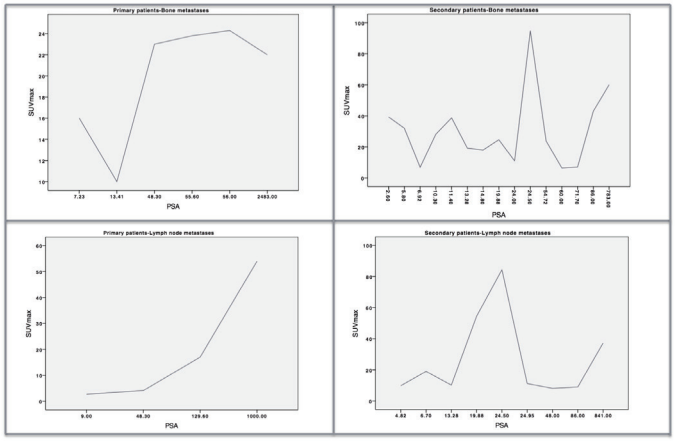


Figure 1. The correlation between PSA and SUV_{max}

PSA: Prostate specific antigen, SUV: Standardized uptake value

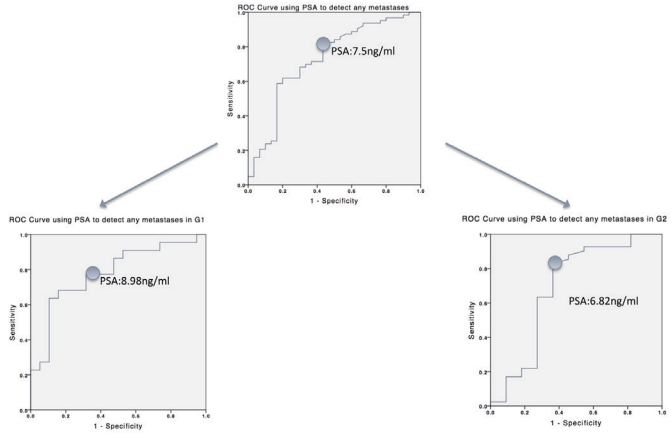


Figure 2. The PSA cut-off using initial PSA for primary and secondary patients

PSA: Prostate specific antigen, ROC: Receiver operating characteristic, G1: Group 1, G2: Group 2

MRI-P. However, they have some limitations. CT has reported to have lack in T staging due to low contrast uptake in soft tissue, and lack in N staging due to not detecting small lymph nodes. Eighty percent of lymph node metastases in PCa are reported to be <8 mm (10). BS is used to examine the skeletal metastases, but it has a low specificity and low detection rates when PSA is <7 ng/mL (8). MP-MRI-P is considered the best imaging technique to evaluate close structures surrounding the prostate (11). However, in a series of 40 prostate lesions, 32 lesions had significant uptake outside the lesion detected in MP-MRI-P (12).

An imaging technique detecting skeletal, lymph node and visceral metastases in a single setting, also evaluating the prostatic lesions and neighbourhood of prostate would be reasonable for PCa staging. For this reason, Ga-68 PMSA is a significant step for patients with Gleason score occurrence of biochemically PSA recurrence. However, Meyrick et al. (6) examined the Ga-68 PSMA for primary staging and reported a 34% detection rate of metastatic disease. They also reported a 50% rate of nodal metastases, and a 17% rate of skeletal metastases in these patients, but they did not explain the metastatic disease well

Table 2. The detailed prostate specific antigen cut-off values for primary and secondary patients

Metastases	**Initial PSA cut-off (ng/mL)**	**Sensitivity (%)**	**Specificity (%)**
Any site for overall	7.5	80	60
Metastases	**Initial PSA cut-off (ng/mL)**	**Sensitivity (%)**	**Specificity (%)**
Any site for G1	8.98	80	60
Bone for G1	8.98	80	40
Lymph node for G1	9.98	80	60
Visceral for G1	16.4	100	40
Metastases	**Initial PSA cut-off (ng/mL)**	**Sensitivity (%)**	**Specificity (%)**
Any site for G2	6.82	80	60
Bone for G2	10.7	80	60
Lymph node for G2	6.71	80	40
Visceral for G2	7.08	80	40
Metastases	**Post-treatment PSA cut-off (ng/mL)**	**Sensitivity (%)**	**Specificity (%)**
Any site for G2	0.38	81	79
Bone for G2	0.27	84	55
Lymph node for G2	0.38	80	50
Visceral for G2	0.38	70	48
Subgroups of G2			
Metastases	**Post-treatment PSA cut-off (ng/mL)**	**Sensitivity (%)**	**Specificity (%)**
Any site for G2a	0.31	100	100
Any site for G2b	0.95	75	75
Any site for G2c	-	-	-
Any site for G2d	0.27	70	100
Any site for G2e	1.71	100	100
Any site for G2f	0.05	100	45

PSA: Prostate specific antigen, G1: Group 1, G2: Group 2

in material methods section and did not examine the skeletal and nodal metastases in a setting separate from metastatic disease. In our study, we detected 5.6%, 35.2% and 25.4% of visceral, nodal and bone metastases, respectively, in primary staging. Our detection rate is similar to that of Meyrick et al. (6) if we describe metastatic disease as the combination of visceral, nodal and skeletal metastases. According to Gleason score, our patients had less aggressive disease than those of Meyrick et al. (6). They reported 31%, 28% and 32% patients with Gleason score <7, <8 and >9, respectively (9% missing). In our series, the same parameters were 47%, 14% and 26% (13% missing). The same study revealed that patients with higher PSA values have more metastases in Ga-68 PSMA after categorising the PSA as 0-5 ng/mL, 5-10 ng/mL and >10 ng/mL. However, they could not provide a p value due to inability to correlate a scale sample with a nominal sample. Our results are compatible with

the mentioned study. Differently from the mentioned study, we correlated the PSA and SUV_{max}, and in our findings, the linear correlation between PSA and SUV_{max} showed that higher PSA value increased the detection rate of bone and lymph node metastases in primary staging of PCa. The other studies of Ga-68 PSMA and primary staging have insufficient patient size or are inappropriate to compare to our study (7).

For secondary staging, Mena et al. (12) reported 60% overall recurrence using F18-PSMA in patients with detected PSA recurrence after primary local therapy. The locations of the progressions were prostate bed, lymph nodes and distant sites (12). Sanli et al. (13) reported 51 local recurrence, 42% lymph node metastases, and 50% bone metastases in their series of 109 patients with PSA recurrence. Afshar-Oromieh et al. (14) reported 86.5% organ recurrence; Eiber et al. (15) reported a 58% metastasis detection rate for PSA levels below 0.5 ng/mL, and a 73% detection rate for PSA levels below 10 ng/mL; Budaus et al. (16) reported 33% sensitivity and 100% specificity for detection of lymph node metastases using Ga-68 PSMA. In our series, there were 68.2%, 14.5%, 40% and 57.3% overall, visceral, nodal and bone metastases in secondary staging, respectively. Our results are similar to the literature. However, due to the heterogeneous structure of studies above, it is difficult to make an exact comparison. The median reported Gleason score was 7 in the studies about secondary staging (13,14,17). According to Gleason score, our patients seem to have more aggressive disease than the studies in literature. In our study, most of our patients had Gleason score 9 PCa. The studies examining PSA and Ga-68 PSMA uptake for secondary staging reported that a higher PSA recurrence value led to detection of more metastases with Ga-68 PSMA (13,15). However, they could not make an exact correlation. We correlated the PSA and SUV_{max}, and the significant correlation between PSA and SUV_{max} for oligometastases in secondary staging. The same outcome could not be concluded for lymph node and visceral metastases.

The primary goal of our study was to determine PSA cut-off values for Ga-68 PSMA. To our knowledge, no one reported a PSA cut-off in Ga-68 PSMA for primary staging of PCa. In our study, we detected 8.98 ng/mL as a cut-off for overall metastases in primary staging. Examining in detail, 8.98 ng/mL was a cut-off for bone and lymph node metastases. However, for visceral metastases it was detected to be 16.4 ng/mL. For secondary staging, there are many reports trying to find out a PSA cut-off. Mena et al. (12) reported 0.78 ng/mL as a cut-off for overall detection of metastases; Sanli et al. (13) reported 0.67 ng/mL, 1.23 ng/mL, 0.68 ng/mL and 2.35 ng/mL as cut-offs for overall, local recurrence, lymph node and bone metastases, respectively; Ceci et al. (17) reported 0.83 ng/mL as a cut-off for overall metastases in secondary staging. The differences between our study and the above-mentioned studies are the evaluation of the initial PSA value to create a cut-off, and the classification of patients according to their treatment regimens. We thought that the initial PSA value could be an indicator for evaluating the patients after a treatment modality, and that different regimens could cause different PSA decrease in follow-up. We detected 6.82 ng/mL, 10.7 ng/mL, 6.71 ng/mL and 7.08 ng/mL as cut-offs using initial PSA for overall, bone, lymph node and visceral metastases in secondary staging, respectively. We also detected 0.38 ng/mL as a cut-off using post-treatment PSA for overall metastases. Our post-treatment PSA cut-off value seems lower than the studies above. In subgroups of secondary staging, the post-treatment PSA cut-offs were 0.31 ng/mL, 0.95 ng/mL, 0.27 ng/mL, 1.71 ng/mL and 0.05 ng/mL for overall metastases in G2a, G2b, G2d, G2e and G2f, respectively. For G2c, a post-treatment PSA cut-off could not be detected due to sample size. In addition, we also could not calculate the cut-off values using post-treatment PSA for bone, lymph node and visceral metastases separately in subgroups of secondary staging due to small sample size.

Over all of these conditions, the cost-effectiveness is a major problem. Using both CT and BS for staging is extremely cheaper than Ga-68 PSMA alone, and the PSA cut-off values we detected do not make it superior than BS for bone metastases. We think that its use is only reasonable when small lymph node metastases cannot be evaluated in BT.

Study Limitations

There are many limitations of our study. Firstly, our series consists of heterogeneous subgroups. Studies examining the subgroups with more patients will reveal better results than ours. Secondly, the detected metastases in our series were not proven using histological or radiographic methods. However, it was impractical and unethical to guide every patient to biopsy for staging of PCa, and using conventional imaging sectioning concomitantly with Ga-68 PSMA would not be cost-effective.

Conclusion

The PSA cut-off for overall metastases was detected as 8.98 ng/mL for primary staging. The PSA cut-off using initial PSA for overall metastases was detected as 6.82 ng/mL for secondary staging. The PSA cut-off using post-treatment PSA for overall metastases was detected as 0.38 ng/mL for secondary staging.

These cut-off values do not make it extremely superior than using both CT and BS and it is an expensive test. We think that its use is only reasonable when small lymph node metastases cannot be evaluated in CT.

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Ethics

Ethics Committee Approval: The ethical acceptance of this study was approved by the local Ethics Committee Private Koru Hospital and followed ethical standards described in the Helsinki Declaration (date: 05.01.2018).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Supervision: M.G., N.A., Critical Review: M.G., N.A., Concept B.K., T.E., Design: B.K., T.E., Data Collection or Processing: E.K., E.A., Analysis or Interpretation: M.Z., M.Ö.E., Literature Search: S.B., Writing: B.K., T.E., E.K.

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Original Article

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Efficacy and Safety of Monopolar Transurethral Resection of the Prostate on Bleeding Control in the Treatment of Benign Prostatic Obstruction: Is It Still a Good Option in Developing Countries?

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Abstract

Objective: The objective of this study is to investigate the bleeding control safety along with the need for preoperative blood preparation and postoperative blood transfusion in the transurethral resection of the prostate with monopolar system (M-TURP) for the treatment of benign prostatic obstruction (BPO).

Materials and Methods: We retrospectively analysed 379 patients with BPO who underwent M-TURP procedure between January 2016 and December 2019 at a single centre. Importantly, we collected the demographic data, use of 5-alpha-reductase inhibitor (5-ARI), postoperative haemoglobin (Hb) and haematocrit levels, platelet counts, and transfusion rates of these patients.

Results: The minimum, maximum and the mean ages of the patients were 43, 79 and 67.44±7.74 years, respectively. The minimum, maximum and the mean prostate volumes of the patients measured via transrectal ultrasonography were 30, 95 and 53.42±18.12 mL, respectively. In total, 99 patients (26.1%) had received 5-ARI for at least three months before surgery. The mean decrease of the preoperative Hb in the postoperative 48th hour was 0.99±0.87 gr/dL. Only 9 patients (2.4%) received the transfusion of blood products (erythrocytes or fresh frozen plasma). The preoperative Hb level was inversely and significantly correlated with the decrease in postoperative Hb and the need for transfusion ($p<0.05$). The preoperative use of 5-ARI was not associated with postoperative decrease in Hb and the need for transfusion. The preoperative cut-off value of Hb for predicting a substantial decrease in Hb and transfusion need after M-TURP was calculated as 12.45 gr/dL with a sensitivity and specificity of 77.8% and 86.8%, respectively.

Conclusion: M-TURP is still a safe and effective option in BPO treatment in developing countries. Importantly, we do not recommend the routine preoperative blood preparation in index patients with Hb level higher than 12.45 gr/dL.

Keywords: Benign prostatic obstruction, bleeding control, haemoglobin, monopolar transurethral resection, transfusion

Introduction

Transurethral resection of the prostate (TURP) is the gold standard in the treatment of lower urinary tract symptoms caused by benign prostatic obstruction (BPO) (1). With the observation of its long-term efficacy in randomised controlled trials, TURP has maintained its success in the surgical treatment of BPO (2).

Bleeding is one of the most severe complications of TURP. Its persistence may necessitate blood transfusion and can lead to clot retention in the postoperative period (3). Although TURP is one of the most common and currently performed urological procedures, there are some doubts as to whether the routine tests for blood group or antibody screening should be conducted on these patients. The major international urological associations do not have specific recommendations regarding the routine tests for blood group or antibody screening before TURP and post-TURP haemoglobin (Hb) control; however, these tests are performed routinely in many hospitals (4).

Despite the technological improvements in the endoscopic surgery of BPO, TURP with monopolar system (M-TURP) is

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commonly performed in developing countries because of the economic reasons. The purpose of this study is to assess the effects of M-TURP on bleeding control, the need for blood transfusion after M-TURP and the problems of preoperative blood preparation.

Materials and Methods

Study Design

Due to the fact that this study is a retrospective, ethical committee approval was not obtained. We retrospectively collected the records of the patients with the diagnosis of BPO (after other failed medical treatment) who underwent M-TURP between January 2016 and December 2019.

Inclusion and Exclusion Criteria

This study included patients with BPO who were resistant to medical treatment, aged between 40 and 79 years, and underwent M-TURP. The exclusion criteria of this study were: age equal or greater than 80 years, presence of haematuria, antithrombotic/anticoagulant use, heart failure, patients with platelet (Plt) count and/or function anomaly, additional urinary tract disease such as bladder tumour or bladder stone, and inadequate data. Few patients who had a prostate gland volume (PV) equal or greater than 100 mL and who underwent the M-TURP procedure were not included because within the study period nearly all of the patients who had a PV equal or greater than 100 mL underwent open prostatectomy.

We collected the information regarding the age of the patients, use of 5α-reductase inhibitor (5-ARI) and other medications, demographics, PV measured by transrectal ultrasonography, complete blood count preoperatively and in the postoperative 48th hour, and transfusions. In four patients, who were re-hospitalised because of late bleeding after discharge, the complete blood count in the 48th hour of the second admission was used in the calculations.

The patients were grouped according to their age, older or younger than 65 years, and whether blood transfusion was performed or not. We compared the study parameters among these groups. Additionally, we assessed the correlation between Hb changes from the preoperative period to the postoperative 48th hour and the other study parameters.

Blood Transfusion

We adopted a restrictive transfusion strategy (5). No transfusion was performed in the patients with a Hb level greater than 10 g/dL, whereas all the individuals with a Hb level lower than 7 g/dL received erythrocyte suspension (ES) transfusion. Between these threshold Hb levels, the decision of transfusion was made according to the concurrent organ ischaemia, predicted consequences of the bleeding, intravascular volume status of the patient and the risks arising out of inadequate oxygenation. Fresh frozen plasma (FFP) was administered in the patients who received high amounts of ES to prevent dilutional coagulopathy. Other blood products were not used in the study.

Surgical Technique

All the surgical procedures were performed in a routine manner by specialist urologists with an experience of performing more than 100 TURP operations. M-TURP was conducted in a standard manner by using the 26 Fr continuous flow resectoscope (Karl Storz GmbH & Co. KG, Tuttlingen, Germany) or 24 Fr single-flow resectoscope (Karl Storz GmbH & Co. KG, Tuttlingen, Germany) with a monopolar loop electrode. The electrocautery system (Valleylab Force FXTM, Boulder, CO, USA) was used with the power settings of 120 and 80 Watts for cutting and coagulation, respectively. About 0.5% mannitol solution [Rezosel® (OSEL, Istanbul, Turkey)] was used as irrigation fluid during surgery. Postoperatively, a 22 Fr three-way latex Foley catheter was placed in all the patients, and the catheters were removed 48-72 h after the operation.

Statistical Analysis

We conducted statistical analyses by using IBM SPSS Statistics 22 (IBM SPSS, Turkey) computer program. We controlled the normal distribution of the data by Shapiro-Wilks test. Besides the descriptive statistical methods (mean, standard deviation and frequency), we used Mann-Whitney U test for comparison because of the non-normal distribution of the qualitative data. We used Fisher's exact test for analysing the quantitative data. We investigated the correlations between the non-normally distributed data by Spearman's rho correlation analysis. The best cut-off point was calculated with the receiver operating characteristic (ROC) curve analysis. A p value of less than 0.05 was considered statistically significant for this study.

Results

We enrolled 379 patients in this study. The mean age of patients was 67.44±7.74 years; moreover, 135 (35.6%) patients were younger than 65 years and 244 (64.4%) were equal to or older than 65 years. In total, 99 (26.1%) patients were taking 5-ARI treatment for at least three months before surgery (Table 1). The minimum, maximum and mean PV measured via transrectal ultrasonography were 30, 95 and 53.42±18.12 mL, respectively.

Transfusion (erythrocytes and FFP) was performed in only 9 (2.4%) of the 379 patients. The age, PV, Plt count, international

Table 1. Demographic data and laboratory findings of the patients who underwent transurethral resection of the prostate with monopolar system

		Min-max	Mean ± SD
Age (year)		43-79	67.44±7.74
PV (mL)		30-95	53.42±18.12
Hb (preoperative) (g/dL)		10.1-18	14.21±1.48
Plt (10^3/mm^3)		101-450	219.95±59.94
INR (0.8-1.2)		0.73-1.20	1.03±0.8
Hb decrease (g/dL)		0.1-6	0.99±0.87
		n	%
5α-reductase inhibitor use	Yes	99	26.1
	No	280	73.9
Blood product transfusion	Yes	9	2.4
	No	370	97.6

PV: Prostate volume, Hb: Haemoglobin, Plt: Platelet, INR: International normalised ratio for prothrombin time, Min: Minimum, Max: Maximum, SD: Standard deviation, α: Alpha

normalised ratio (INR) for prothrombin activity and the use of 5-ARI of the patients were not different between the transfusion and non-transfusion groups (p>0.05). The preoperative Hb level of the transfusion group was significantly lower than that of the non-transfusion group (p=0.004) (Table 2). The mean decrease of preoperative Hb in the postoperative 48th hour was 0.99±0.87 gr/dL. The preoperative Hb level was found to be inversely correlated with the postoperative decrease in Hb (p=0.000). The decrease in Hb was not associated with age, PV, Plt count, INR and use of 5-ARI (p>0.05) (Table 3).

The patients were grouped according to their age: whether they were younger than 65 years or not. The decrease in Hb was not different between the groups (p>0.05). The transfusion rates were 3% and 2% in the younger and older groups, respectively. There was no statistically significant difference between the groups (p>0.05). The correlations between decrease in Hb and other study parameters in both the groups were investigated individually, and the preoperative Hb level was found to be inversely correlated with postoperative decrease in Hb in both younger and older groups (p=0.000 and p=0.022, respectively) (Table 3).

The area under curve (AUC) was 0.777, and the standard error was 0.11 in the ROC curve analysis for the preoperative Hb level, which predicted significant Hb decrease and need for transfusion after M-TURP. The AUC was significantly higher than 0.5 (p=0.015). The cut-off value for preoperative Hb level, which predicted significant Hb decrease and need for transfusion after M-TURP, was calculated as 12.45 gr/dL with a sensitivity and specificity of 77.8% and 86.8%, respectively (Figure 1).

Table 2. Observed parameters in the transfusion and non-transfusion groups

	Transfusion		p
	(–)	(+)	
	Mean ± SD	Mean ± SD	
Age (Year)	67.45±7.66	66.67±11.17	[1]**0.873**
PV (mL)	53.39±18.21	54.67±14.95	[1]**0.579**
Hb (preoperative) (g/dL)	14.26±1.44	12.32±2.07	[1]**0.004***
Plt (10^3/mm^3)	219.77±59.73	227.22±71.53	[1]**0.585**
INR (0.8-1.2)	1.03±0.08	1.05±0.05	[1]**0.425**
Hb decrease (g/dL)	0.95±0.8	2.89±1.46	[1]**0.000***
5α-reductase inhibitor use n (%)			
No	274 (%74.1)	6 (%66.7)	[2]**0.702**
Yes	96 (%25.9)	3 (%33.3)	

[1]Mann-Whitney U test, [2]Fisher's exact test, *p<0.05, PV: Prostate volume, Hb: Haemoglobin, Plt: Platelet, INR: International normalised ratio for prothrombin time, SD: Standard deviation

Table 3. Correlations between haemoglobin decrease and observed parameters

	Hb decrease					
	<65 years		≥65 years		Total	
	r	p	r	p	r	p
Age (year)					-0.004	[1]0.945
PV (mL)	-0.032	[1]0.715	0.077	[1]0.231	0.034	[1]0.508
Hb (preoperative) (g/dL)	-0.300	[1]0.000*	-0.147	[1]0.022*	-0.194	[1]0.000*
Plt (10^3/mm^3)	-0.088	[1]0.310	-0.089	[1]0.164	-0.087	[1]0.091
INR	0.068	[1]0.436	0.070	[1]0.276	0.069	[1]0.177
5α-reductase inhibitor use		[2]0.359		[2]0.307		[2]0.791

[1]Spearman Rho Correlation analysis, [2]Mann-Whitney U test, *p<0.05, PV: Prostate Volume, Hb: Haemoglobin, Plt: Platelet, INR: International normalised ratio for prothrombin time

Discussion

Since the 1970s, TURP has been the gold standard for the treatment of BPO after the failure of other medical treatments. TURP is a relatively safe procedure because of advancements in the surgical technique, instrumentation and perioperative management including anaesthesia (6). Postoperative complications such as haematuria or clot retention may prolong the length of hospital stay and increase the estimated medications for treating the complications. Even blood transfusions may be required because of acute haemorrhage.

The incidence rate of transfusion-requiring bleeding after M-TURP was 0.4-7.1% in the trials conducted before 2010 (7,8). A recent randomised controlled study reported the incidence rate of transfusion-requiring bleeding after M-TURP to be 6.3% (9). The most common causes of the bleeding after TURP are inadequate bleeding control during the procedure, anticoagulant drug use, comorbidities such as ischaemic heart disease, uncontrolled hypertension in the postoperative period,

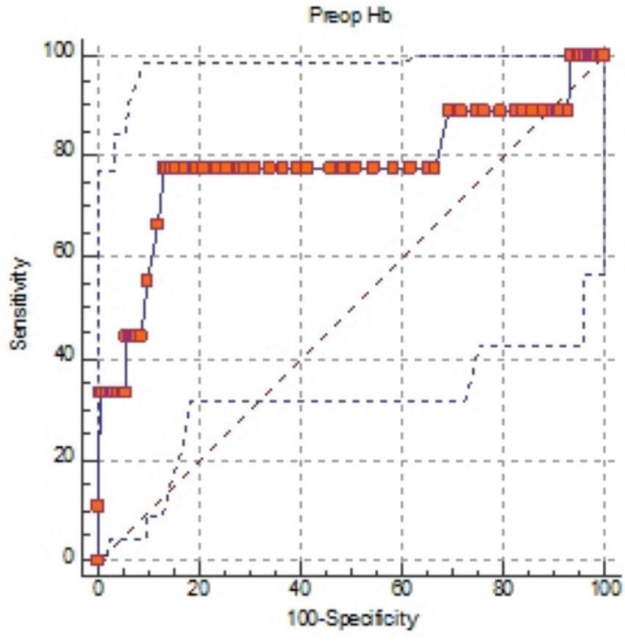


Figure 1. ROC analysis results and AUC for the preoperative Hb cut-off value predict the substantial decrease in Hb and transfusion need after M-TURP

ROC: Receiver operating characteristic, AUC: Area under curve, M-TURP: Transurethral resection of the prostate with monopolar system, Hb: Haemoglobin

exercises increasing the intra-abdominal pressure, coughing and constipation. In addition to all these factors, the preferred TURP method may be the determinant of bleeding. There are several studies demonstrating that bleeding, clot retention and need for transfusion are more common in M-TURP as compared to bipolar TURP (10,11,12). However, it is reported that these two methods are comparable in terms of bleeding, clot retention and need for transfusion (9). A randomised controlled study reported that the long-term outcomes of M-TURP, photoselective vaporisation of the prostate and need for postoperative transfusion were not different between the two methods (13). The modified M-TURP methods, which reduce bleeding and transfusion rates as compared to the standard M-TURP, are also in use (14).

The mean Hb decrease with M-TURP was 0.99±0.87 gr/dL in our study and in nearly all of the patients; importantly, we did not encounter any clinically important bleeding. The incidence rate of transfusion-requiring bleeding rate 2.4% with M-TURP in our study, which was consistent with the literature. Among all the parameters, only the preoperative lower Hb level was found to be associated with clinically important bleeding. The cut-off value of preoperative Hb level for predicting the substantial decrease of Hb and the need for transfusion after M-TURP was calculated as 12.45 gr/dL. Of the nine patients who underwent transfusion, seven (77.8%) had a preoperative Hb level lower than this cut-off level.

It is apparent from the literature that the patients undergoing TURP are older than 65 years and are likely to be on multiple medications due to the various co-existing chronic conditions thus more susceptible to postoperative complications (15). These complications may result in more serious conditions due to the delicate physiologies of the older patients (16). In our study, 64.4% of our patients were equal to or older than 65 years. The patients were grouped according to their age, that is, whether they were younger than 65 years or not. Contrary to the literature, the decrease of Hb and transfusion rates did not differ between the groups. We believe that this may be due to the study design that included only the index patients after the exclusion of patients who were older than 80 years of age, receiving antithrombotic/anticoagulant drugs, and who had comorbidities.

The preoperative PV, perioperative excessive resection of the prostate and prolonged duration of the operation may increase the risk of bleeding after TURP (17). Reich and colleagues reported that the risk of transfusion-requiring intraoperative/postoperative bleeding increased with resection weight. Transfusion rates for resection weights greater than 60 grams, 30-60 grams and less than 30 grams were 9.5%, 3.4% and 2.0%, respectively (18). Some studies showed correlations between the mean resected prostate weight and transfusion rates (4,19). PV in our study ranged widely from 30 to 95 mL with a mean PV of 53.4 mL. The resected PV was not measured routinely in this study; therefore, it is not shown in the analyses. In our study, preoperative PV measured via transrectal ultrasonography was not found to be associated with a decrease in Hb in the postoperative 48th hour and transfusion.

Several studies (from 2005 to present) demonstrated that the preoperative use of 5-ARI reduced perioperative bleeding (3,20,21,22). However, there were also reports of contrary results (23,24,25). In our study, 99 (26.1%) patients were on 5-ARI treatment for at least three months before surgery, and a decrease in Hb in the postoperative 48th hour and transfusion was not associated with the preoperative use of 5-ARI.

There are few studies investigating the need for blood preparation before TURP and the routine control of Hb level after TURP. Shah and Nethercliffe (26) demonstrated that Hb decrease in 48 hours after TURP was negligible and except for clinical deterioration, the routine control of Hb level was unnecessary. Additionally, Hakeem et al. (4) reported that routine biochemical analyses were significantly expensive ($45), and these analyses should be performed selectively rather than on a routine basis for a standard TURP procedure.

In our clinic, the preoperative blood group analysis, antibody screening and postoperative Hb level control were performed routinely because of legal concerns in the study period. However, these tests and controls did not yield the expected benefits in the management of the patients, and nearly all of the patients were discharged without necessity of transfusion. These tests, which are performed because of legal concerns and are under debate in terms of medical indications, appeared to cause a great waste of resources in four years.

As a clinical consequence, patients should not routinely be tested for blood group or antibody screening before M-TURP, except for the following clinical conditions: Hb level lower than 12.4 g/dL preoperatively, the absence of an active transfusion unit of the centre where the operation is performed, or rare blood group of the patient.

Study Limitations

The retrospective design of this study and the heterogeneity between groups are some limitations of this study. Additionally, a separate statistical evaluation could not be made for this group of patients because the number of cases for M-TURP with PV over 80 mL was not sufficient to obtain a good-quality statistical data.

Conclusion

M-TURP is still a safe and efficient method for bleeding control in BPO treatment in developing countries despite some potential risks. Additionally, routine tests for blood group or antibody screening do not alter the clinical management. The authors recommend selective blood testing based on the clinical need of patients.

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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: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Supervision: Ö.Y., H.H.T., Critical Review: Ö.Y., Concept: S.A., Design: S.A., C.E., Data Collection or Processing: E.Ö., M.P., Analysis or Interpretation: C.E., K.K., Literature Search: H.H.T., Writing: S.A., C.E.

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Case Report
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Impact of Neoadjuvant Sunitinib Treatment on Tumour Thrombi in the Inferior Vena Cava in Metastatic Renal Cell Carcinoma

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Abstract

The authors report cases of metastatic renal cell carcinoma with level III-IV tumour thrombi in the inferior vena cava (IVC). Cases were treated with three courses of neoadjuvant sunitinib to reduce the thrombus level before surgery.
Nephrectomy and tumour thrombectomy were performed, and sunitinib treatment continued after the operation.
Cases 1 and 3 showed regression of lung metastases, but the size of the primary renal tumour and thrombus remained the same. The progression-free survival of the cases was 35 months and 24 months, respectively. In case 2, the primary renal tumour, metastases and thrombus showed regression. The upper limit of the thrombus decreased by 3 cm. In this case, the progression-free survival was 15 months, and the cancer-specific survival was 18 months.
The neoadjuvant sunitinib treatment had a limited effect on downsizing the extent of tumour thrombi in the IVC.
Keywords: Inferior vena cava, neoadjuvant sunitinib, metastatic renal cancer, radical nephrectomy, tumour thrombus

Introduction

Progression of renal cancers into the inferior vena cava (IVC) is relatively rare and is sometimes associated with presence of distant metastases. The conventional treatment for metastatic renal cancer with a tumour thrombus in the IVC is radical nephrectomy with concomitant tumour thrombectomy, followed by targeted molecular therapy. Currently, there are relatively limited publicised data on the impact of neoadjuvant sunitinib therapy on tumour thrombi in the IVC (1,2,3,4,5).

Case Presentation

We report a series of patients who received neoadjuvant sunitinib treatment for metastatic renal cell carcinoma with a tumour thrombus in IVC. Tumour thrombus levels were determined according to Novick's classification. The tumours were in the intermediate risk group based on Memorial Sloan Kettering Cancer Center criteria. Patients received three courses of neoadjuvant sunitinib treatment, 50 mg/day for 4 weeks followed by a 2-week break before surgery. Afterward sunitinib treatment, the patients underwent abdominal and chest computed tomography (CT) exams and were evaluated according to the response evaluation criteria in solid tumours (RECIST) 1.1 criteria.

Case 1

A 66 year old male patient had macroscopic haematuria and an abdominal ultrasound described an 8 cm tumour in the left kidney. Abdominal and chest CT exams showed a suprahepatic tumour thrombus in the IVC (level IV), multiple lung metastases and metastases in the left adrenal gland. Renal biopsy revealed clear cell renal carcinoma. After neoadjuvant sunitinib treatment, the CT control showed a regression of lung metastases, but the size of the primary renal tumour did not change. The upper level of the tumour thrombus also did not decrease (Figure 1) (Table 1).

Radical nephrectomy and tumour thrombectomy were performed and histologic analysis revealed grade 2 clear cell carcinoma with pT3c, pN0, pM1 stage.

After the surgery, sunitinib therapy was continued according to the protocol with follow-up CT exams performed every two cycles. The actual progression-free survival (PFS) of the patient was 35 months.

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Case 2

A 50 year old female had a deep vein thrombosis and a routine abdominal ultrasound discovered a 14 cm tumour in the right kidney. The CT exam revealed a renal tumour with a tumour thrombus extending into the right atrium (level IV), as well as multiple liver and retroperitoneal lymph node metastases. Renal biopsy revealed clear cell renal carcinoma. After neoadjuvant sunitinib treatment, the follow-up CT showed partial regression of both the renal tumour and liver metastases. The upper limit of the thrombus decreased by 3 cm, but it remained a level IV thrombus (Figure 2). Radical nephrectomy was performed, but tumour thrombectomy was unsuccessful. Histology of the resected tumour revealed grade 2 clear cell renal carcinoma with pT3a, pN0 stage. Following radical nephrectomy, sunitinib treatment was continued according to the protocol. Fifteen months after the radical nephrectomy, the control CT demonstrated a new liver metastasis, and sunitinib therapy was ceased. The patient's PFS was 15 months and the cancer-specific survival was 18 months.

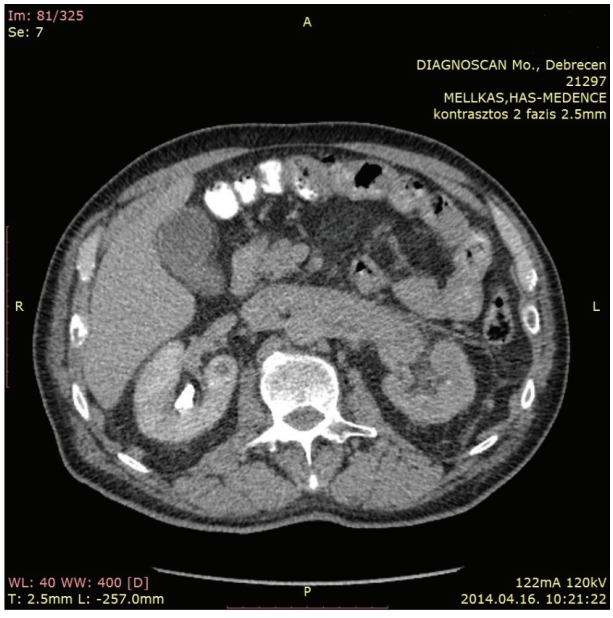


Figure 1. Abdominal computed tomography after the neoadjuvant sunitinib treatment in Case 1 (axial section)

Table 1. Control computed tomography findings after the neoadjuvant sunitinib treatment	
Case 1	**Tumour response**
Renal tumour	Stable
Lung metastases	Regression
Tumour thrombus	No change
Case 2	
Renal tumour	Regression
Liver metastases	Regression
Tumour thrombus	Decreased by 3 cm
Case 3	
Renal tumour	Stable (but necrosis)
Lung metastases	Regression
Tumour thrombus	No change

Case 3

A 52 year old male patient had a visible mass protruding from the upper right abdomen. Ultrasound showed a 22 cm tumour in the right kidney. Chest and abdominal CT exams showed a renal tumour with multiple lung and retroperitoneal lymph node metastases, as well as an intrahepatic tumour thrombus in the IVC (level III). Renal biopsy revealed clear cell carcinoma. After neoadjuvant sunitinib therapy the follow-up CT showed partial regression of lung metastases. The CT did not show changes in the bulk size of the renal tumour or the thrombus (Figure 3). Surgery was performed and the histology revealed grade 2 clear cell carcinoma with pT3c, pN2 stage. After the operation, sunitinib therapy was continued according to the protocol. CT

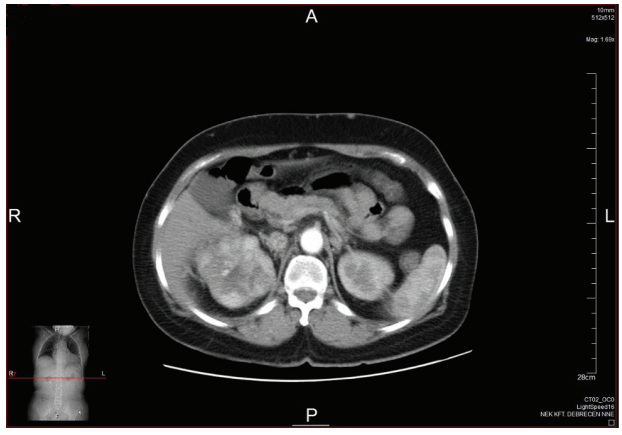


Figure 2. Abdominal computed tomography after the neoadjuvant sunitinib treatment in Case 2 (axial section)

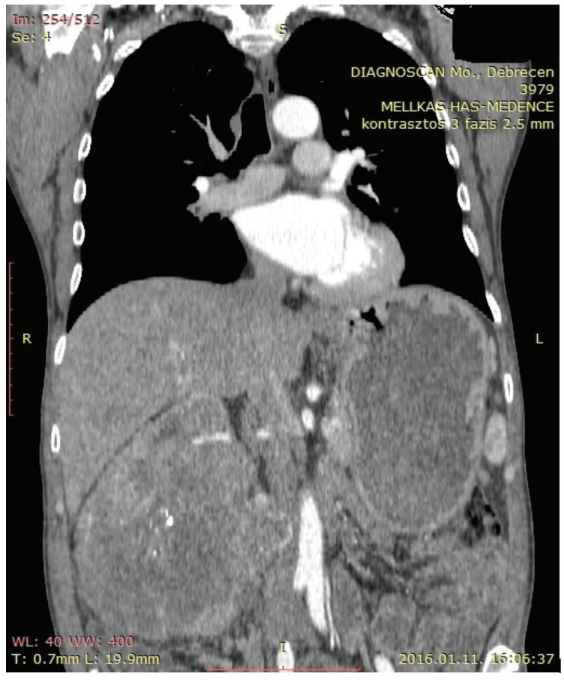


Figure 3. Abdominal computed tomography after the neoadjuvant sunitinib treatment in Case 3 (coronarial section)

control follow-up exams showed a stable disease on RECIST 1.1, with a PFS of 24 months.

Discussion

Surgery of renal tumours with IVC thrombi has a relatively high complication rate, ranging from 12% to 46%. Several physicians have tried to reduce the size of tumour thrombi with administration of neoadjuvant targeted molecular therapy to decrease the rate of complications.

Current literature only provides a few publications in which neoadjuvant therapy has been used to downsize tumour thrombi in the IVC. Generally in these patients, two to four cycles of the targeted therapy were administered before the operation. Of the limited publications, the majority consist of case reports. Some authors described regression of tumour thrombi after neoadjuvant sunitinib therapy in their individual cases (6,7,8). Karakiewicz et al. (7) were the first to report a significant decrease of the thrombus level in the IVC (from level IV to level II) after sunitinib therapy, facilitating easier surgical procedure. Peters et al. (8) described a case in which there was a significant reduction in primary tumour size and metastatic sites, and the IVC thrombus downstaged from level IV to level III according to Novick classification as a result of preoperative sunitinib treatment.

However, in contrast to the mentioned cases, other reports have showed that neoadjuvant therapy was not always successful at downstaging the IVC thrombus level, and progression of the thrombus level was observed (3,9).

Cost et al. (3) studied the efficacy of targeted molecular therapy at decreasing the level of renal cell carcinoma vena cava tumour thrombi in 24 patients. Their data showed that the thrombus level remained unchanged in 21 patients (84%), decreased in three patients (12%) and increased in one patient (4%) during the treatment. Of the three cases that showed thrombus regression, only one case had enough of an impact to affect the surgical procedure (level IV to III). During the study, the size of the primary tumour increased in 10 patients (40%), decreased in 12 (48%), and did not show any change in three (12%) cases.

Bigot et al. (1) performed a retrospective analysis of 14 patients with renal cell carcinoma with IVC thrombus treated with neoadjuvant sunitinib therapy before the surgery. In the study, six (43%) patients had a measurable decrease in thrombus size, six (43%) had no change, and two (14%) had an increase. In regard to the thrombus size, 12 patients (85%) had stable thrombus, one patient (7%) had a downstage of thrombus level, and one patient (7%) had an upstage of thrombus level. In the one patient who demonstrated a downstaging of the thrombus (level II to level I), the downstaging was not significant enough to affect the surgical intervention. Follow-up CT exams after the neoadjuvant sunitinib treatment showed that the primary renal tumour remained stable in five patients (36%), showed regression in seven patients (50%), and showed progression in two patients (14%) (1).

In our cases, regression of the tumour thrombus was detected in only one case, but the tumour thrombus level in that case remained the same (level IV). Neoadjuvant treatment resulted in regression of the distant metastases in all cases, but the size of the primary tumour decreased in only one patient.

Conclusion

Effective downstaging of the tumour thrombus in the IVC was not achieved in our cases with neoadjuvant sunitinib treatment. Although sunitinib treatment had noticeable effects on primary tumour size, metastases and survival, it had a limited effect on downsizing the extent of tumour thrombus in the IVC and did not affect the overall surgical outcome in this regard.

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Ethics

Informed Consent: Retrospective study.

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Authorship Contributions

Supervision: T.S., Concept: C.B., Design: T.F., C.B., Data Collection or Processing: A.B., Analysis or Interpretation: T.S., Literature Search: B.J., Writing: A.B., T.F., B.J.

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Video Article

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Laparoscopic Extraperitoneal Radical Prostatectomy

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Abstract

Radical prostatectomy (RP) involves removing the entire prostate with its capsule intact and the seminal vesicles (SV). In this video article, we summarized the extraperitoneal laparoscopic RP with pelvic lymph node dissection procedure along with a video presentation of a case. The patient is placed in a Trendelenburg position. Through a small transverse infraumblical incision, the anterior rectus aponeurosis is identified and incised. The extraperitoneal surgical field is developed bluntly by a balloon dilator, and a 10 mm trocar is placed for the camera. CO_2 insufflation at a 12-15 mmHg pressure is established, and the remaining trocars are placed. The fatty tissue is swept laterally to create a wide operative field. The endopelvic fascia is incised on both sides. The levator ani muscle fibers are separated from the lateral surface of the prostate. Dorsal vascular complex (DVC) is ligated with 2 consecutive sutures. Identification of the bladder neck (BN) is critical for proper dissection between the prostate and the BN. BN is incised until the catheter is seen. The urethral catheter is removed and a Bougie dilator is inserted through the urethra to elevate the prostate. With posterior oblique dissection, the vasa deferentia are exposed and clip-ligated, and SVs are identified and freed. Then, lateral pedicles are ligated with hemoclips and divided. Lateral dissection proceeds with an anterolateral incision from the base to the prostatic apex. The neurovascular bundles lie posterolateral to the prostate. Apical dissection and division of the DVC and urethra is a critical step to ensure a safe surgical margin and good postoperative erectile function and continence. The urethra is divided with a small rim on the prostate. The gland is totally freed, put into an endobag, and extracted. The vesicourethral anastomosis is done using two 3-0 monocryl sutures in a running fashion, starting from the posterior in both direction and tied together at the 12 o'clock position, anteriorly.

Keywords: Prostate cancer, radical prostatectomy, extraperitoneal, laparoscopy

Radical prostatectomy (RP) involves removing the entire prostate with its capsule intact and the seminal vesicles (SV). The surgical technique has evolved from open to a laparoscopic and robot-assisted technique. RP is mostly indicated for the treatment of intermediate-risk and high-risk localized prostate cancer. In this video article, we summarized the extraperitoneal laparoscopic RP with pelvic lymph node dissection procedure along with a video case presentation.

The patient is placed in a Trendelenburg position with a 25° head-down tilt. The surgeon stands on the left and the assistant on the right side. Through a small transverse incision just caudal to the umbilicus, the anterior rectus aponeurosis is identified and incised. The extraperitoneal surgical field is developed bluntly first by finger dissection and then a balloon dilator. A 10 mm trocar is placed for the camera. CO_2 insufflation at a 12-15 mmHg pressure is established and the remaining trocars are placed under direct visual control in a reverse V configuraiton.

The fatty tissue is swept laterally to create a wide operative field until the myopectineal area is seen. The endopelvic fascia that is cleaned from fatty tissue is incised on both sides. The levator ani muscle fibers are separated from the lateral surface of the prostate. The puboprostatic ligaments are exposed and divided. Dorsal vascular complex (DVC) is ligated with 2 consecutive sutures (30 mm polyglactin MH 2/0).

Identification of the bladder neck (BN) is critical for proper dissection between the prostate and the BN, for which caudal traction of the catheter balloon can be helpful. BN is incised horizontally with a hook dissector or ultrasonic scsissors until the catheter is seen. The urethral catheter is removed and a Bougie dilator is inserted through the urethra to elevate and fix the prostate. Posterior BN is incised horizontally. Caution should be exercised while dissecting to avoid entry into the prostate. With posterior oblique dissection, vasa deferentia are exposed and clip-ligated. SVs are identified and freed from the surrounding fatty tissues. Thermal energy should be kept at minimum to avoid thermal damage to the nearby nerve bundles. Then, lateral pedicles are ligated with hemoclips and divided.

Anterior traction of the SVs and vasa deferentia helps with the identification and in developing the posterior plane correctly, between the two layers of Denonvilliers fascia (i.e. interfascial

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dissection). Dissection continues bluntly in the caudal direction to the prostatic apex and laterally to the medial aspect of the neurovascular bundles.

Lateral dissection proceeds with an anterolateral incision from the base to the prostatic apex. The neurovascular bundles lie posterolateral to the prostate. With the prostatic fascia kept intact, the bundles are released from the prostate.

Apical dissection and division of the DVC and urethra is a critical step to ensure a safe surgical margine and good postoperative erectile function and continence. As the anatomy of the apex is highly variable, visualization and careful dissection is needed. The urethra is divided with a small rim on the prostate. The gland is totally freed, put into an endobag, and extracted at the end of the operation.

The vesicourethral anastomosis is done using two 3-0 monocryl sutures in a running fashion, starting posteriorly in both directions and tied together at the 12 o'clock position, anteriorly. The urethral catheter is removed on the 8-10th postoperative day.

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