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

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

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

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

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Instructions to Authors

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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.

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

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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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3. Peer-Review Process

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

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

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

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

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

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

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

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

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-Abbreviations:

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

-Units of Measurement:

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

-Statistical Evaluation:

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

-Language:

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

5. Article Types

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

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

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

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

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

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

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

3) References

4) Figure legends

5) Short Quiz for review articles.

Tables and figures should be uploaded separately.

Also, "Acknowledgements Form" should be uploaded separately.

A. Original Research Articles

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

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

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

-Introduction

- Materials and Methods

- Results

- Discussion

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

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

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

C. Review Article

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

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

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-Introduction

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

-Conclusions

-References

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

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

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

D. Literature Review

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

E. Editorial Commentary

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

F. Letters to the Editor

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

G. Surgery Videos on Urooncology (Video-urooncology)

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

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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

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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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Example:

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

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

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

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

D. Tables and Figures

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Dear Reviewer

Danny Darlington is selected to be the best reviewer of the year as he has vigorously made evaluations for The Bulletin of Urooncology within the year. Thanks a lot for your contributions to our journal.

We wish you success in your academic career.

Sincerely

Review

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Current Approach in Radiation Therapy for Prostate Cancer

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Abstract

Prostate cancer is one of the most common malignancies in men. Radiotherapy is one of the main treatment modalities in the treatment of prostate cancer. The reflection of technological advances in the field of radiation oncology enables the safe application of higher doses of radiotherapy in the treatment of prostate cancer. In addition, improvements in normal tissue preservation are reflected in patients' quality of life. Radiotherapy can be applied in all stages of prostate cancer and postoperative radiotherapy can be applied in appropriate indication. Side effects are expected to be observed more in patients undergoing postoperative radiotherapy. The treatment decision should be based on personal preference after informing the patient about the advantages and disadvantages of each treatment approach.

Keywords: Prostate cancer, radiotherapy, treatment

Introduction

Prostate cancer (PC) is one of the most common malignancies in men. Radical prostatectomy (RP), external beam radiotherapy (EBRT), brachytherapy (BCT) are different options that can be applied in patients with limited disease. Surgery and radiotherapy (RT) are considered standard in the treatment of localized PC. Treatment decision should be made with the patient after a multidisciplinary evaluation of the patient's age, performance status, accompanying diseases, life expectancy and possible side effects of the treatment. In addition to life expectancy, quality of life is also important in patients. The patient should also be informed that RT may be needed after surgery and that side effects may increase.

The reflection of technological developments in Radiation Oncology has enabled increased sensitivity in determining tumor sites, to reflect these identified areas to treatment at high accuracy rate [Image-guided Radiotherapy (IGRT)], to decrease margins given to tumors (Intensity-Modulated Radiotherapy-IMRT), and thus to preserve more normal tissue (1). As a result of the increase in sensitivity and accuracy, the increase in doses administered and the application of high doses within a short period of time [Stereotactic Body Radiotherapy (SBRT)] is possible and the treatment times are shortened. Thanks to all these developments, both high tumor control and increased life expectancy, as well as a decrease in normal tissue toxicity of patients and the resulting increase in quality of life have been achieved.

The RT used in PC is EBRT and BCT. Current approaches in RT techniques are IMRT and SBRT. The form of treatment, dose and hormone therapy (HT) vary according to the risks and stages of PC. Curative RT of localized PC is administered in doses between 74-81 Gy for 7-9 weeks with conventional fractions (1.8-2 Gy/day) as standard and 5 days per week. It is possible to apply higher doses to the tumor with fewer side effects in parallel with technological developments in imaging methods and computer software.

Very Low Risk PC; T1c, grade group 1 (GS 6), prostate specific antigen (PSA) <10, 1 or 2 quadrant positivities and ≤50% for each quadrant positivity and PSA density ≤0.15 ng/mL. Magnetic resonance imaging and genomic tests may be performed to rule out high-grade disease in patients younger than 62 years. Active follow-up is often recommended except this group of patients.

Low Risk PC; T1c/T2a, grade group 1 (GS 6), PSA <10. Treatment options are ERT and BCT. EBRT can be applied as standard fractionation (2 Gy per day) with 78-80 Gy, as Hypofractionated RT (HRT); 70 Gy (2.5 Gy per day), 60 Gy (3 Gy per day) or as SBRT; 36-40 Gy (7.25-8 Gy per day). BCT can be applied as Low-dose-rate (LDR): I-125, Pd-103, Cs-131 (with permanent source placement) or High-dose-rate (HDR) (with Ir-192 catheters, 4 times). D'Amico et al. (2) showed that the results of treatment with RP, EBRT and BCT were similar in patients with low-risk PC. BCT studies showed results ranging from 95% to 85% in 5-10-year PSA controls in different series (3,4,5,6). In the Spirit trial, BCT and RP were compared in

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terms of quality of life and there were statistically significant less urinary leakage and better sexual outcomes in BCT (7). Donovan et al. (8) compared quality of life results between RP and EBRT in the "Prostate Testing for Cancer and Treatment" (Protect) trial and showed that RP had better results in terms of intestinal functions and nocturia, while EBRT had better results in terms of incontinence and erectile dysfunction.

HRT (daily fraction dose 2.4-4 Gy, total treatment duration 4-6 weeks). The total duration of treatment for PC due to its radiobiological characteristics can be shortened by increasing the fraction dose, i.e. hypofractionation. The results of studies comparing moderate hypofractionation with standard fractionation were found to be similar (Table 1). The meta-analysis showed similar results except for higher acute gastrointestinal (GI) side effects with conventional EBRT (16). Therefore, moderately HRT is recommended in low and moderate risk PC (17). In Ultra HRT (SBRT), fraction doses between 4-10 Gy per day are generally applied in ≤5 fractions with a total dose of 35-50 Gy. The studies are shown in Table 2.

SBRT can cause more side effects than moderately HRT. The Swedish study, a phase III randomized study, compared 42.7 Gy (6.1 Gy per day) SBRT with 78 Gy (2 Gy per day) conventional

Table 1. Trials comparing moderate hypofractionation with external beam radiotherapy

Trial	n	Trial design	Trial arms	Risk groups	HT	Median follow-up	Cancer control	Acute GU SE	Acute GI SE	Late GU SE	Late GI SE
Dearnaley et al. (9)	3216	Multicenter Non-inferiority Biochemical or clinical failure rate	74 Gy (2 Gy) 60 Gy (3 Gy) 57 Gy (3 Gy)	15% Low 73% Intermediate 12% High	97% 3-6 months	5.2 years	60 Gy/74 Gy same 57 Gy was worse than 74 Gy	Similar	Increased risk with hypofractionation 25%/38%	Similar	Similar
Catton et al. (10)	608	Multicenter Non-inferiority Biochemical or clinical failure rate	78 Gy (2 Gy) 60 Gy (3 Gy)	Intermediate	No	6 years	Hypofractionation was non-inferior	Similar	Increased risk with EBRT 10%/16%	Similar	Reduced risk with hypofractionation 11%/7%
Lee et al. (11)	1115	Multicenter Disease-free survival	7380 cGy (1.8 Gy) 70 Gy (2.5 Gy)	Low	No	5.8 years	Hypofractionation was non-inferior	Similar	Similar	Increased risk with EBRT 23%/30%	Increased risk with EBRT 14%/22%
Incrocci et al. (12)	820	Çok merkezli Recurrence-free survival	78 Gy (2Gy) /78 Gy 6460 cGy (3.4Gy) / 87 Gy	26% Intermediate 74% High	67%	5 years	Non-significant difference	Similar	Increased risk with BRT 31%/42%	39%/41%	18%/22%
Shaikh et al. (13)	303	Single center Biochemical failure	76 Gy (2 Gy) /76 Gy 7020 cGy (2.7Gy) / 84 Gy	66% Intermediate 33% High	46%	5.7 years	Non-significant difference			Similar	Similar
Hoffman et al. (14)	206	Single center Disease-free survival	7560 cGy (1.8 Gy) /71 Gy 72 Gy (2.4 Gy) / 84 Gy	28% Low 71% Intermediate	%24	8.4 years	Hypofractionation improved cancer control			Similar	Increased trend 5%/13% p=0.08
Valeriani et al. (15)	168	Single center Late toxicity	80 Gy (2 Gy) 62 Gy (3.1 Gy) /81 Gy	High	All	9 years	Non-significant difference	Similar	Increased trend 21%/35% p=0.07	Similar	Similar

HT: Hormone therapy, GU: Genitourinary, SE: Side effect, GI: Gastrointestinal, EBRT: External beam radiotherapy

Table 2. Trials of stereotactic body radiotherapy

Trial	n	Median follow-up (years)	Dose	EQD2	GS 6	Acute G3+		Late G3+			5-year BDFS
						GU	GI	GU	GI	ED	
Pham et al. 2010 (18) (Abstract)	40	5yıl	34 Gy (5 frc)	82 Gy	100%	2%	0%	3%	0%	50%	93%
Kupelian et al. 2013 (19) (Abstract)	135	5	35/40 Gy (4-5 frc)	8650-11060 cGy	80%	NR	NR	NR	NR	NR	97%
Mantz, 2014 (20)	102	>5	40 Gy (5 frc)	11060 cGy	69%	2%	0%	NR	0%	NR	100%
Hannan et al. 2016 (21)	91	4.5	45-50 Gy (5 frc)	13800-16800 cGy	47%	0%	2%	5%	7%	26%	99%
Musunuru et al. 2016 (22)	84	6.2	35 Gy (5 frc)	8650 cGy	100%	1%	0%	0%	1%	43%	97%
Zimmerman et al. 2016 (23)	80	6.9	45 Gy (9 frc)	8470 cGy	100%	NR	NR	4%	13%	NR	96%
Total	532				80%	1.2%	0.6%	3%	2.6%	37%	98%

BDFS: Biochemical disease-free survival, ED: Erectile dysfunction, EQD2: Dose equivalent to 2 Gy fraction, Frc: Fraction, GI: Gastrointestinal, GU: Genitourinary, NR: Not reported

RT in patients with intermediate and high risk PC. Biochemical relapse-free survival rate (83.8% vs. 83.7%), late urinary side effects (3.5% vs. 2.5%) and rectal (2.3% vs. 1.3%) side effects were similar in 5-year follow-up (24). The PACE B randomized study compared 36.5 Gy (7.25 Gy per day) SBRT and 78 Gy (2 Gy per day) EBRT in 858 patients with low and intermediate risk PC. No difference was detected in terms of acute side effects (25). A meta-analysis of 6116 patients showed that SBRT increased biochemical control (p=0.018) but were associated with more grade 3 or above genitourinary (GU) side effects (p=0.014) (26). In light of the studies, SBRT may also be recommended, especially for low-risk patients.

Intermediate Risk PC; Good intermediate risk: <50% biopsy positivity (presence of only 1 moderate risk factor T2b/c or GS (3+4) or PSA:10-20 ng/mL). Good intermediate risk tends to be treated like a low risk group. BCT, EBRT or moderately HRT can be performed. Poor intermediate risk: GS (4+3), contains ≥50% biopsy positivity or many intermediate risk factors. Short term (4-6 months) HT with EBRT, BCT boost with EBRT (and/or short term HT) can be applied. Studies on dose increase in intermediate risk PC are going on. In the GETUG-14 trial, 377 patients with intermediate risk PC were treated with 80 Gy EBRT either alone or in combination with HT for 4 months. Five-year biochemical failure rates were 21% and 10% in the groups (p=0.02) and no difference was detected in terms of toxicity (27). In the ASCENDE-RT trial, medium and high risk patients were either given dose-escalated EBRT boost to 78 Gy (2 Gy per day) or LDR BCT (115 Gy I125) boost. Biochemical failure rates in the BCT arm were found to be statistically significantly 2 times better for medium and high risk patients (28).

High Risk PC; EBRT and HT (1.5-3 years) or EBRT, BCT boost and HT (1-3 years) are recommended. In 3 randomized studies, biochemical recurrence-free survival was found to be statistically significantly higher with dose-escalating EBRT and BCT (28,29,30).

Table 3. Phase III trials comparing external beam radiotherapy plus hormone therapy with external beam radiotherapy

Trials	Risk groups	Trial arms	5-year results	10-year results
Standard dose EBRT				
D'Amico et al. (31)	Intermediate/high-risk PC	Arm 1= EBRT Arm 2= EBRT + HT (6 months)	CSS= 94/100 OS= 77/88 BPFS= 55/79	OS= 61/74 (8 years) DSS= 84/78 (8 years) OS= 28/35NS (15 years)
Pilepich et al. (32)	High-risk PC	Arm 1= EBRT Arm 2= EBRT + HT	BRFS= 21/55 DM= 29/15 CSS= 87/91 OS= 71/76	DM= 39/24 CSS= 78/84 OS= 39/49 BPFS= 9/31 LF= 38/23 DSS= 78/84
Bolla et al. (33)	High-risk PC	Arm 1= EBRT Arm 2= EBRT+HT (3 years)	CSS= 79/94 BPFS= 45/76 DM= 29/10 OS= 62/78 LF= 1/7	DFS= 23/48 OS= 40/58 CSS= 70/90 DSS= 10/30
Pilepich et al. (34)	High-risk PC	Arm 1= EBRT Arm 2= EBRT+ HT (4 months)	BRFS= 10/28 CSS= 80/85 DM= 39/29 OS= 68/72NS	OS= 34/43NS BRFS= 80/65 DM= 27/35 CSS= 64/77 DSS= 23/36
Jones et al. (35)	Low/intermediate/high-risk PC	Arm 1= EBRT Arm 2= EBRT+ HT (4 months)	LF= 39/21 (2 years)	BRFS= 59/47 OS= 57/62 CSS= 92/96 DM= 8/6
Dose-escalating EBRT				
Bolla et al. (36)	Intermediate/high-risk PC	Arm 1 = EBRT (70, 74, 78 Gy) Arm 2 = EBRT (70, 74, 78 Gy) + HT (6 months)	BRFS= 70/83 DM= 4/8NS OS= 88/91NS	NR
Nabid et al. (37)	Intermediate-risk PC	Arm 1= EBRT (70 Gy) + HT (6 months) Arm 2= EBRT (76 Gy) + HT (6 months) Arm 3 = EBRT (76 Gy)	BF= 7/2/14* DFS= 93/97/86* OS= 90/94/91NS *=NS between arms 1-2	BF= 22/22/33* DFS= 78/78/67* OS= 63/72/75NS *=NS between arms 1-2
Dubray et al. (27)	Intermediate-risk PC	Arm 1= EBRT (80 Gy) Arm 2 = EBRT (80 Gy) + HT (4 years)	BRFS= 76/84 OS= 94/93NS	NR
Dearnaley et al. (38)	Low/intermediate/high-risk PC	Arm 1 = EBRT (64 Gy) + HT (3-6 months) Arm 2 = EBRT (74 Gy) + HT (3-6 months)	-	BPFS= 43/55 OS= 71/71*

EBRT: External beam radiotherapy, HT: Hormone therapy, OS: Overall survival, DM: Distant metastasis, LF: Local failure, NR: Not reported, BRFS: Biochemical recurrence-free survival, CSS: Cause-specific survival, NS: Not significant, DSS: Disease-specific survival, DFS: Disease-free survival, Gy: Gray, BF: Biochemical failure, PC: Prostate cancer, BPFS: Biochemical progression-free survival, *: NS between arms 1-2

In the ASCENDE-RT trial, 398 patients were randomized to a standard arm with 12 months of androgen deprivation therapy, pelvic irradiation to 46 Gy, followed by a dose-escalated EBRT boost to 78 Gy, or an experimental arm that substituted a LDR-BCT boost (28). Nine-year biochemical recurrence-free survival was significantly better in the BCT boost arm (p=0.004). In addition, grade ≥ III urinary toxicity was found lower in the BCT boost arm (19% vs. 5%, p<0.001). In numerous phase III randomized trials, neoadjuvant and adjuvant HT have been proven to be beneficial in combination with EBRT (≥70 Gy) in the treatment of high risk PC (31,32,33,34,35), (Table 3).

Adding HT has significantly reduced the risk of biochemical failure, clinical progress, local recurrence and distant metastasis without increasing the risk of death due to cardiac problems, GU toxicity and GI toxicity. A meta-analysis has shown that adding HT to ERT reduces the risk of death from PC by 24% and the risk of death from other causes by 14% (39). Numerous randomized studies have shown that dose-escalating EBRT (≥74 Gy) improves biochemical outcomes compared with conventional doses (40,41). The EORTC 22991 trial showed that adding short-term HT (ST-HT) to dose-escalating ERT improved 5-year biochemical progression-free survival (BPFS) (36). The results of other phase III dose-escalating-EBRT trials have shown that addition of ST-HT still provides a benefit in intermediate risk patients (27,36). Adding ST-HT to dose-escalating-EBRT in patients with intermediate risk PC improves BPFS and reduces distant metastasis, and PC-specific mortality (PCSM) (37). MRC RT01 showed that dose-escalation from 64 Gy to 74 Gy improved BPFS, even when both arms were given ST-HT (38). Long-term (LT)- HT is used in the treatment of patients with high risk PC (42).

This recommendation is largely based on EORTC 22961 and RTOG 9202 trials (45,46). In both trials, it was shown that cancer-specific survival and overall survival were increased with LT-HT (28-36 months) compared to ST-HT (4-6 months) (Table 4).

DART01/05 trial, a trial comparing the duration of HT with Dose-escalating EBRT, found that LT-HT (28 months) improved biochemical control, distant metastasis-free survival and overall survival compared to ST-HT (4 months) (Table 4) (48). The PCS IV trial compared ST-HT (18 months) and LT-HT (36 months) and concluded that ST-HT was as effective as LT-HT and improved quality of life (49). The use of genomics in the future to find out which patients should be given personalized treatment is the topic on the agenda for high risk PC. Mahal et al. (50) showed

Table 4. Trials comparing different hormone therapy durations with conventional or dose-escalating external beam radiotherapy

Trials	Risk groups	Trial arms	5-year results	10-year results
Conventional dose EBRT				
Denham et al. (43)	Intermediate-risk PC	Arm 1= EBRT Arm 2= EBRT + HT (3 months) Arm 3= EBRT + HT (6 months)	BRFS=32/49/52 DM=19/22/13* CSS=91/92/94 *NS between arms 1-2 LF=28/17/12	BRFS=70/60/53 CSS=78/81/8* OS=57/63/71* *NS between arms 1-2
Pisansky et al. (44)	Intermediate-risk PC	Arm 1= EBRT+HT (9 months) Arm 2= EBRT+HT (4 months)	NR	BRFS= 73/73NS DM= 6/6NS CSS= 96/95NS OS= 67/66NS
Bolla et al. (45)	High-risk PC or Locally advanced disease	Arm 1= EBRT+HT (6 months) Arm 2= EBRT+HT (36 months)	OS=81/85 DSS= 95/97 CSS=91/97 DM=6/14	NR
Horwitz et al. (46)	High-risk PC or Locally advanced disease	Arm 1= EBRT+HT (4 months) Arm 2= EBRT+HT (28 months)	BRFS=44/72 DM=17/12 CSS=95/97 OS=79/80NS	BRFS= 32/48 DM= 23/15 CSS= 84/89 OS= 51/54NS LF= 22/12 DSS= 84/89
Denham et al. (47)	Intermediate/high-risk PC	RT (66,70,74 Gy or 46 Gy +BCT) +HT (12 months) +/- Z RT+ADT (6 months) +/- Z	PCSM (7.8/7.4/4.1/7.8)NS CSS (19.4/13.9/17/18.9)NS PSAP (29.2/26//34.2/39.6) DP (14.2/11.1/14.7/17.3)NS	PCSM 9.7/13.3 DP 20.7/27.5 PSAP 34/45.9
Dose-escalating EBRT				
Zapatero et al. (48)	Intermediate/high-risk PC	Arm 1 = EBRT (70, 74, 78 Gy) + HT (4 months) Arm 2 = EBRT (70, 74, 78 Gy) + HT (28 months)	BRFS= 81/90 DMFS= 83/94 OS= 86/95	NR
Nabid et al. (49)	High-risk PC	Arm 1= EBRT+HT (36 months) Arm 2= EBRT+HT (18 months)	CSS= 97/95NS OS= 91/86NS	CSS= 4/84NS OS= 62/59NS

EBRT: External beam radiotherapy, HT: Hormone therapy, OS: Overall survival, DM: Distant metastasis, LF: Local failure, TROG: Trans-tasman radiation oncology group, NR: Not reported, DSS: Disease-specific survival, BRFS: Biochemical recurrence-free survival, CSS: Cause-specific survival, NS: Not significant, CSS: Cancer-specific survival, Gy: Gray, Z: Zoledronate, BCT: Brachytherapy, ADT: Androgen deprivation therapy, PCSM: Prostate cancer-specific mortality, PSAP: Prostate specific antigen progression, DP: Distant progression, DMFS: Distant metastasis-free survival, *: NS between arms 1-2

that there was a statistically significant relationship between the rate of metastasis and Decipher score >0.6 (p<0.001). The genomic risk group and the National Comprehensive Cancer Network risk group have been evaluated together and clinical-genomic risk group classification has been established (51). In high risk patients; treatment schemes have been established: LT-HT and RT or ST-HT and RT in patients with low genomic risk and LT-HT and RT or ST-HT and RT with LT abirateron or LT apalutamide arms in patients with high genomic risk (NRG GU 1864 Clinical Trial).

Postoperative RT; Positive surgical margin is recommended in disease at level of pathological T3 or higher (52). In SWOG randomized trial, it was found that the addition of postoperative RT provided a survival advantage in patients with pT3 or positive surgical margin (53). Genomic classification can tell us about the timing of postoperative RT (54). The results of randomized trials (RADICALS-HT for its necessity and duration, RAVES-RT for its timing) on postoperative RT timing (early or early salvage) are expected. The 5-year results of the RAVES randomized trial were reported at ASTRO 2019. Starting adjuvant RT at 4-6 months was compared with early salvage RT when PSA was ≥0.2 ng/mL. Five-year results showed no difference in terms of BPFS and locoregional and distant metastasis free survival rates. In the RTOG 96-01 randomized trial, salvage RT and/or 2-year HT was compared with salvage RT alone in 771 patients who had PSA rising after RP in 13-year follow-up. Salvage RT and/or 2-year HT was associated with lower development of metastasis (11% vs. 19%), lower PCSM (4.5% vs. 10.1%) and longer overall survival (82% vs. 78%), (p<0.01, p=0.036 and p<0.001, respectively). In subgroup analysis; this advantage was increased in those with PSA >1.5 ng/mL and surgical margin positivity (55). In the GETUG/AFU-16 randomized trial, there was statistically significant difference between EBRT in combination with 6-month HT and EBRT alone in terms of 5-year BPFS (62.1% vs. 79.6%, p<0.001 and survival (56). After RP, 1107 patients with lymph node positivity were retrospectively evaluated. Eight-year cancer-specific mortality rates were statistically significantly lower in the postoperative RT and HT group than the HT alone group in patients with lymph node positivity <4 (57).

Oligometastasis PC; Ost et al. (58) compared the patients who were treated for metastasis and the patients who were not in a phase II randomized trial. Sixty two patients with ≤3 bone or lymph node metastases were examined. BPFS and cancer-specific mortality were better in the group undergoing treatment for metastasis (p=0.03). In the Stampede phase III randomized trial, 2061 patients with metastatic PC were evaluated. The addition of RT to the treatment of metastatic patients initially was found to increase disease-free survival and overall survival, especially in patients with low metastasis load (p<0.0001 and p=0.007, respectively) (59). In the Horrad randomized trial, 432 patients with bone metastasis (<5) were evaluated and the time to PSA progression was found to be longer (p=0.02) in patients who received RT to prostate and bones, but there was no difference in terms of survival (60). Burdett et al. (61) showed in their meta-analysis that patients who received RT to prostate and HT had 7% longer 3-year survival compared with patients who took only HT in patients with less than 5 bone metastases. Fifty four patients were evaluated in the Oriole phase II trial. The patients with 1-3 bone metastases (≤5 cm lesion) were randomly assigned to SBRT or observation arms. In the early 24 months early results, the time to progression-free survival was longer at the 6th month.

Studies are going on the use of neoadjuvant or adjuvant chemotherapy, immunotherapy and next generation HT agents in combination with EBRT. In the RTOG 0521 randomized study, standard HT (2 years) and RT (72.0-75.6 Gy) arm was compared with RT, HT and docetaxel (adjuvant 6 cures after RT is completed) in 612 patients. In 6-year follow-up, general and disease-free survival rates significantly increased in favor of the docetaxel-added arm (p=0.03 and p=0.05, respectively) (62).

Proton and heavy ion therapy can reduce the amount of radiation used in RT that goes beyond the target. However, more data are needed on this issue. There are ongoing studies.

Conclusion

It is possible to safely perform RT at all stages of PC. With advances in imaging methods and treatment in RT, it has become possible to apply higher doses to the tumor with fewer side effects. In addition, hypofractionation applications increase the fraction dose and decrease the total treatment time. Postoperative RT can also be applied in appropriate indication by looking at clinical and pathological features after surgery. The results of studies in metastatic disease and lymph node positive patients are promising. Studies are ongoing with the use of neoadjuvant or adjuvant chemotherapy, immunotherapy and next-generation hormotherapies in combination with RT.

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Questions

1. What are the treatment options for low risk prostate cancer?

a. Brachytherapy

b. External beam radiotherapy

c. Hypofractionated radiotherapy

d. Stereotactic body radiotherapy

e. All of them

2. Which of the following are not indications of postoperative radiotherapy ?

a. Positive surgical margin

b. pT3 tumor

c. p lymph node positivity

d. pT2 and surgical margin negativity

e. pT4 and seminal vesicle invasion

3. Which of the following is the standard radiotherapy treatment in high risk prostate cancer?

a. External beam radiotherapy +/- brachytherapy+ hormone therapy for 1-3 years

b. Stereotactic body radiotherapy

c. External beam radiotherapy

d. Brachytherapy

e. External beam radiotherapy + hormone therapy for 6 months

Original Article

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Comparison of Three Different Antibiotic Protocols Used as Prostate Biopsy Prophylaxis in Terms of Infectious Complications

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Abstract

Objective: Development of urinary infection and sepsis following prostate biopsy procedure is the main problem. Despite use of antibiotic prophylaxis, which becomes a routine procedure in prostate biopsy, urinary infection and sepsis may significantly be observed. Furthermore, there is no consensus in terms of the type and duration of prophylaxis. This study aimed to compare the incidence of infectious complications, which developed during 3 different prophylaxis protocols used in our institution.

Materials and Methods: Four hundred and eighteen prostate biopsy procedures performed in our institution between 2010 and 2017 were evaluated retrospectively. Patients were divided into 3 groups based on their prophylactic antibiotic protocols. First group patients (n=136) were given ciprofloxacin and gentamicin 80 mg. Second group patients (n=180) were given cefpodoxime and gentamicin 80 mg. Third group patients (n=102) were given cefpodoxime and gentamicin 160 mg. Three groups were compared in terms of post-biopsy infectious complications. SPSS 20 statistical program was used for data evaluation.

Results: There was no statistically significant difference between the groups in terms of age, prostate specific antigen level and prostate volume. Urinary tract infection following the prostate biopsy was seen in 11 (8.1%) patients in group 1, 8 (4.4%) patients in group 2 and, 2 (1.9%) patients in group 3. Five of these patients were hospitalized due to deterioration of their overall health status and fever. When 3 groups were statistically compared, infection incidence was significantly different between the first and the third group ($p<0.05$).

Conclusion: Bacterial resistance against fluoroquinolones is particularly increasing day by day. Fluoroquinolone resistance in *Escherichia coli* strains in our country is reported between 39-63%. In this study, infectious complications were found to be less in cefpodoxime plus gentamicin 160 mg prophylaxis, when compared to ciprofloxacin plus gentamicin 80 mg. Replacing quinolones with cefpodoxime and gentamicin in the antibiotic prophylaxis protocols used before prostate biopsy can minimize risk of infection.

Keywords: Prophylactic antibiotic, prostate biopsy, urinary tract infection

Introduction

Prostate cancer is the most common type of male cancer in developed countries as a result of increase in life expectancy (1). The standard diagnostic method of prostat cancer is transrectal ultrasound (TRUS) guided prostate biopsy (2). Although complications such as hematuria and hematospermia following prostate biopsy are common, they recover spontaneously. However, severe complications such as febrile and non-febrile urinary tract infection, epididymitis, acute prostatitis and sepsis may also be observed (3,4). Antibiotic prophylaxis before the biopsy procedure in routine practice, can minimize these severe infectious complications. However, incidence of post-biopsy urinary infection and sepsis is increasing due to increase in bacterial antibiotic resistance (4). Furthermore, there is no consensus in terms of the type and duration of prophylaxis. This study aimed to compare the incidence of infectious complications, which developed during 3 different prophylaxis protocols used in our institution for the patients undergoing TRUS-guided prostate biopsy.

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Materials and Methods

Four hundred and eighteen patients, who underwent TRUS-guided prostate biopsy in our institution between 2010 and 2017, due to elevated prostate specific antigen (PSA) level and suspicion of prostate cancer following digital rectal examination were retrospectively evaluated.

Selection and Description of Participants

Re-biopsied patients and patients with any systemic chronic or immunosuppressive disease (Diabetes Mellitus, congestive heart failure, chronic renal failure, chronic liver failure, etc.) were excluded. Patients, who underwent standard 12-core prostate biopsy, were divided into 3 groups based on their prophylactic antibiotic protocols. First groups patients (n=136) received 5-day course oral ciprofloxacin 500 mg, which started one day before the scheduled biopsy, and a single dose gentamicin 80 mg, which was administered intramuscularly 30 minutes before the procedure. Second group patients (n=180) received 5-day course oral cefpodoxime 200 mg (oral 3rd generation cephalosporin), which started one day before the scheduled biopsy, and a single dose gentamicin 80 mg, which was administered intramuscularly 30 minutes before the procedure. Third group patients (n=102) received 5-day course oral cefpodoxime 200 mg, which started one day before the scheduled biopsy, and a single dose gentamicin 160 mg, which was administered intramuscularly 30 minutes before the procedure.

Technical Information

General Electric Healthcare, LOGIQ C2 ultrasound machine and biplane rectal probe were used during the biopsy procedure. Rectal enema was applied to the patients 2 hours before the biopsy for colon cleansing. TRUS-guided periprostatic block was applied to the patients with 2% prilocaine (CitanestR) before the biopsy for local anesthesia. All procedures, including the biopsy, were performed while the patient was in left lateral decubitus position with the knee and hip at flexion. Before the biopsy, the prostate was examined at the transvers and sagittal planes and the zonal anatomy and the ultrasonographic characteristics of the tissue were examined from the base to the apex of the prostate. Biopsy was performed with an 18-gauge, 22-25 cm biopsy needle and a biopsy gun with a suitable attachment. Patients were informed about potential complications in detail. First post-biopsy emergency admissions or admissions to the institution within the first month were evaluated in terms of infectious complications. Sepsis definition was based on the 2001 International Sepsis Definitions Conference Criteria (5).

Statistical Analysis

Three groups were compared in terms of post-biopsy infectious complications. SPPS 20 (IBM Corp. Released 2011. IBM SPSS Statisticsfor Windows, Version20.0. Armonk, NY:IBM Corp.) statistical program was used for the evaluation of data. Median ± standard deviation, percentage and frequency values were used for the variables. In addition to this, Levene's test was used to assess equality of variances, as a precondition of parametric tests. Assumption of normality was tested by Shapiro-Wilk test. Unidirectional variance analysis was used for comparing 3 or more groups, and when preconditions for parametric test were not met with the multiple comparison test Tukey Honestly Significant Difference, Kruskal Wallis and multiple comparison test, Bonferroni-Dunn, were used. Relationship between categorical variables was analyzed with Fisher's exact test and chi-square test. When expected frequencies were smaller than 20%, Monte Carlo Simulation Method was used to include these frequencies in the analysis. For statistical significance, $p<0.05$ and $p<0.01$ were considered as the thresholds. .

Results

Mean age of patients in group 1, 2 and 3 was calculated as 65.7, 67.2 and 66.8 years, respectively and there was no statistically significant difference between the groups in terms of mean age ($p=0.31$). Mean PSA level of patients in group 1, 2 and 3 was calculated as 9.99, 19.97 and 14.26 ng/dL, respectively and there was no statistically significant difference between the groups in terms of PSA levels ($p=0.056$). Mean prostate volume for the patients in group 1, 2 and 3 was calculated as 38.47, 42.16 and 44.27 mL, respectively and there was no statistically significant difference between the groups in terms of mean prostate volume ($p=0.274$). Urinary tract infection associated with biopsy was confirmed with urine culture. It developed in 11 (8.1%) of 136 patients in the first group, 8 (4.4%) of 180 patients in the second group and 2 (1.9%) of 102 patients in the third group. Twenty one (5.02%) patients out of a total of 418 patients developed urinary tract infection. Five (1.19%) of these patients were hospitalized due to deterioration of their overall health status and fever. *E.coli* colonization was identified in the urine culture of 19 patients and *Klebsiella spp*. in 2 patients. Rate of resistance of *E.coli* against fluoroquinolone, aminoglycoside and 3rd generation cephalosporin was identified in the antibiograms 80%, 42% and 28%, respectively. When 3 prophylaxis groups were compared between each other in terms of post-biopsy infectious complications, no statistically significant difference was found between group 2 and the other groups. However, infectious complications were observed statistically less in group 3, when compared to group 1 ($p<0.05$).

Discussion

Prostate biopsy is an invasive urological intervention commonly applied in the present urology practice for diagnosis of prostate cancer. It may be applied with transperineal and transrectal approaches with similar complication rates (6). The most common complication following prostate biopsy is hematospermia (37.4%) (4). Post-biopsy infectious complications are generally reported following 5-7% of procedures (7). The most common type of infectious complication is symptomatic urinary infection, which manifests without fever or with mild fever mainly associated with lower urinary tract symptoms (8). Febrile urinary tract infection requiring hospitalization and parenteral treatment, bacteremia and sepsis were reported following 0.64-3% of procedures (7,8,9).

Most commonly isolated pathogen in symptomatic infections after prostate biopsy is *E.coli* (7,10). Although there is consensus for use of prophylactic antibiotic, it is not clear yet which

antibiotic to use and for how long. Furthermore, antimicrobial resistance rates vary from country to country (11). Concentration of the drug selected for antibiotic prophylaxis, in the prostatic parenchyma, periprostatic spaces and blood circulation, should not exceed the minimum inhibitor concentration of the uropathogens diffused during the procedure. Besides, drug of choice must be safe, cheap, easy to administer and efficacious against both Gram-negative and Gram-positive bacteria (12). In general, fluoroquinolones are mostly preferred for antibiotic prophylaxis. However, in selection of antibiotics, it is recommended to consider the regional and local antibiotic resistance patterns (4). In our country, there is fluoroquinolone resistance in *E.coli* strains, which is steadily increasing and has reached to 63% in the recent years (13). In general, while resistance against cephalosporins in *E.coli* strains in our country varies between 12% and 42.9%, resistance against gentamicin is reported between 8% and 24% (13,14). Although there are regional differences, infectious complication rate in prostate biopsy will steadily increase in parallel to increasing rate of bacterial resistance (4). This requires the need for different prophylaxis protocols including single or combined antibiotics. There are several different prophylaxis protocols in the literature (7,10,15). Furthermore, targeted antimicrobial prophylaxis based on measuring regional *E.coli* resistance rates by taking pre-biopsy rectal culture is also reported (10). Baldissera-Aradasa et al. (16) reported a significant reduction in infectious complication rates and treatment cost of these complications with the use of targeted antimicrobial prophylaxis. However, in a study investigating 3953 targeted prophylaxis treatments in 15236 prostate biopsies, it was found that targeted prophylaxis did not have a significant effect in preventing sepsis. Fluoroquinolone resistance of *E.coli* was reported as 28.5% (10).

There was nearly two times difference between group 1 and 2 in terms of infection after biopsy, but the difference did not reach statistically significance. We think that antibiotic prophylaxis could change in favor of cefpodoxime by performing studies with larger sample size. A statistically significant difference among the group 1 and group 3 in terms of infection rates after biopsy suggested that increased dose of gentamicin (160 mg) in group 3 provided an additional contribution to cefpodoxime in infection prophylaxis.

Study Limitations

The limitations of this study were its retrospective design and lack of group including ciprofloxacin + gentamicin with escalating doses. If such a group had been included in the study, the relationship between increased gentamicin dose and infection rates could have been made clearer.

Conclusions

In our study, taking into account fluoroquinolone resistance rates for *E.coli* strains in our country, we evaluated the efficacy of cefpodoxime and gentamicin prophylaxis. Although urinary infection rates in each of our 3 prophylaxis groups were in general similar to the results reported in the literature, there was a significant decrease in infection rates in cefpodoxime and gentamicin groups, with the increasing dose of gentamicin. The limitation of our study was that cefpodoxime resistance was not checked in routine culture-antibiogram practice of our institution and no comment was provided on the resistance rates of our patients against cefpodoxime. Cefpodoxime is safe and easy to administer for prostate biopsy prophylaxis and is efficacious against both Gram-negative and Gram-positive bacteria, however, it is disadvantageous in terms of cost when compared to fluoroquinolones. Gentamicin has the challenge of parenteral administration. However, decrease in infectious complication rates with the use of cefpodoxime and gentamicin prophylaxis will in its turn reduce the cost of treatment for complications. Steady increase in fluoroquinolone resistance rate in our country and the results of our study support that cefpodoxime and gentamicin can be an alternative prophylaxis protocol in prostate biopsy. Randomized controlled studies to be conducted in larger patient groups including cost-effectiveness analysis will further shed a light upon the choice of prophylactic antibiotic.

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Original Article

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A Technical Modification to Reduce Potential Contamination in Transperineal Prostate Fusion Biopsy

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Abstract

Objective: Prostate fusion biopsy could be performed either transrectal or transperineal route. Interestingly, the risk of infective complications after transperineal approach does not seem fewer than transrectal approach. Even when transperineal approach is chosen surgeons may have to deal with fecal contents during the biopsy procedure. We have developed a simple modification to minimize perineal contamination during transperineal prostate fusion biopsy. In this study, the results of patients who underwent transperineal fusion biopsy by using our novel technique were presented.

Materials and Methods: Targeted prostate fusion biopsy was performed in 91 patients who underwent mutliparametric magnetic resonance imaging (Philips İntera 3.0 T) and had Prostate Imaging Reporting and Data System 3 or higher lesions, under general anesthesia, with the guide of transrectal ultrasonography (SmartUS, Telemed), with the help of transperineal stepper (CIVCO, EX3) by using MIM Symphony (MIM Software, Cleveland) software between May 2016 and May 2019 with a suspicion of prostate cancer. In the first 24 patients, both targeted fusion biopsy and systematic biopsy were taken only by transperineal approach, while in the 67 patients who were followed up, fusion biopsy was taken by transperineal method and systematic biopsy was taken by transrectal method. In the original technique, a condom filled with 120 mL saline was placed into the rectum; whereas in our modified technique, initially an empty condom was placed into the rectum and filled with 100 mL ultrasound gel and then fixed to the anus by using a standard ileostomy adapter.

Results: We performed only transperineal biopsy in 24 patients and both transperineal and transrectal biopsies in 67 patients. A total of 139 lesions with an average size of 9.6-4.4 mm (4-25) were sampled by transperineal route in 91 patients. The mean number of core biopsies was 5.2-1.7 (2-13) for each of 139 lesions. Pathological examination revealed prostate adenocarcinoma in 33 lesions (23.7%) out of 139 lesions. None of the patients had fever or urosepsis after transperineal approach however, only 1 (p=0.43) patient who underwent transperineal and transrectal biopsies developed urosepsis symptoms and treated with intravenous antibiotic in the hospital.

Conclusion: Our novel and simple technique to reduce infective complications after transperineal biopsies seems feasible and safe. Further comparative studies with larger number of patients are needed to demonstrate its clinical benefit.

Keywords: Prostate biopsy, fusion biopsy, urosepsis

Introduction

Combining imaging modalities such as mutliparametric magnetic resonance imaging (mpMRI) and transrectal ulrasonography (TRUSG) has entered clinical practice as an exciting innovation, potentially increasing the diagnostic capacity of TRUSG-guided standard biopsy.

mpMRI/USG fusion biopsy can be applied transrectal or transperineal, depending on the software platform used. In transrectal practice, prostatitis and urosepsis are observed in approximately 5% due to the unavoidable flora of the rectum and rectal inoculation, and it has been reported that this rate has increased in recent studies due to increased fluoroquinolone resistance (1). Interestingly, it has been shown that although there are no bacteria in the perineum as much as the rectum and there is no transrectal inoculation, there is no difference between transperineal and transrectal approach in terms of prostatitis and urosepsis rates (2,3). One potential explanation

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may be that the perineum is contaminated with a transrectal ultrasound probe that is moved through the rectum during the procedure.

In this study, a simple modification technique to reduce perineal contamination during transperineal prostate fusion biopsy was demonstrated and it was aimed to present the results of the patients to whom this technique was applied.

Materials and Methods

Targeted prostate fusion biopsy was performed in 91 patients who underwent mpMRI (Philips İntera 3.0 T) and had Prostate Imaging Reporting and Data System (PI-RADS) 3 or higher lesions, under general anesthesia, with the guide of transrectal USG (SmartUS, Telemed), with the help of transperineal stepper (CIVCO, EX^3) by using MIM Symphony (MIM Software, Cleveland) software between May 2016 and May 2019 with a suspicion of prostate cancer. In the first 24 patients, both targeted fusion biopsy and systematic biopsy were taken only by transperineal approach, while in the 67 patients who were followed up, fusion biopsy was taken by transperineal method and systematic biopsy was taken by transrectal method.

In the standard transperineal biopsy approach performed in lithotomy position under general anesthesia, the condom filled with 100-120 mL of saline is attached to the transrectal ultrasound probe and the probe is placed in the rectum in connection with this condom. During this procedure, the perineum is exposed to continuous rectal contamination by the manipulation of the probe. In the technical modification we have developed, 50 mL ultrasound gel is injected into the rectum at the lithotomy position under general anesthesia with the help of a irrigation syringe. Then the empty condom is placed in the rectum and filled with 100 mL ultrasound gel and then the condom is mounted on the ileostomy adapter, the portion over the perineal region is tangentially cut off so that the adapter is fixed to the anal region. The perineal area is cleaned with batticon and then covered with sterile off-site. Only the portion of the off-site inside the ileostomy adapter is cut, thus providing a completely sterile surgical area (Figure 1). After this stage, the transrectal ultrasound probe moves comfortably back and forth in the rectum, preventing the perineum from being re-contaminated with the rectal content.

After this procedure under general anesthesia, all patients were discharged on the same day.

Statistical Analysis

Statistical analysis in this study was made using the SPSS v.20 (IBM Corp.) package program. The chi-squared test was used to compare the relationship between variables with two categories.

Results

Of the total 91 patients, 24 only underwent transperineal biopsy and 67 underwent both transperineal fusion biopsy and transrectal systematic biopsy. In 15 of the 24 patients who underwent only transperineal biopsy, both transperineal fusion biopsy and transperineal systematic sampling were performed. In 9 of the 24 patients, only a targeted transperineal fusion biopsy was performed. The mean prostate volume was 55±21.6 cm^3 (20-120), the mean age was 61±7.9 years (42-85) and the mean prostate specific antigen (PSA) value was 7.7±8.2 ng/mL (1.15-64). In 14 patients (15%),digital rectal examination was positive. Eighteen patients (20%) had a history of standard biopsy. A total of 139 lesions with an average size of 9.6±4.4 mm (4-25) were sampled in 91 patients. The percentages of the lesions located in the apex, mid, base, anterior, TZ, apex-mid and base-mid regions were 18.7%, 36%, 18.7%, 1.4%, 9.4%, 8.6% and 7.2%, respectively. Of the lesions, 51.8% (72/139) were classified as PI-RADS 3, 36% (50/139) as PI-RADS 4, and 12.2% (17/139) as PI-RADS 5. An average of 5.2±1.7 (2-13) core biopsies was taken from each lesion by transperineal route. As a result of pathological examination, prostate adenocarcinoma was detected in 33 (23.7%) of 139 lesions. The mean duration of anesthesia for patients was 60 minutes (45-100).

While no post-op urosepsis was observed in 24 patients who underwent only transperineal biopsy, only 1 (p=0.43) patient who underwent both transperineal and transrectal systematic biopsies developed signs of urosepsis within 48 hours of post-op period and the patient was hospitalized and treated with intravenous antibiotics. In addition, 1 patient also developed hematuria and urinary retention due to the process.

Through our technical modification, the contamination of the perineum with rectal content has been completely eliminated while at the same time the transrectal ultrasound image quality has been subjectively improved.

Discussion

Prostate cancer is the most common cancer among men and the second most common cause of death from cancer (4). Transrectal ultrasound assisted biopsy is still the most common method in the diagnosis of prostate cancer. Although transrectal ultrasound is useful for showing specific anatomical regions of the prostate or targeting identifiable lesions, it alone is insufficient to detect localized cancer within the prostate (5). Recent studies have shown that mpMRI obtained before biopsy increases the rate of detection of clinically important prostate cancer and limits the detection of innocent disease (6). Now, in many centres in our country, mpMRI/USG fusion biopsy is used when there is suspicion of clinical prostate cancer, even in the first biopsy. mpMRI/USG fusion biopsy can be done cognitively as well as with software. In the fusion biopsy technique performed using computer software, 2 different approaches are applied, depending on the software being transrectal or transperineal.

In the Global Prevalence study which investigated the infection rate after transrectal prostate biopsy in 702 men from 84 centers around the world showed that symptomatic urinary tract infection (3.5% had fever, 3.1% required hospitalization) was observed in 5.2% of the patients, despite 90% of patients were given prophylactic fluoroquinolone (7). In our country, Şimşir et al. (8) examined urosepsis rates after more than 2000 transrectal biopsies performed in their centers and showed that 3.06% of patients developed urosepsis within the first 5 days after the procedure. After 72500 TRUSG assisted biopsies performed in the UK in 2008, 2.5% to 3.6% of patients were

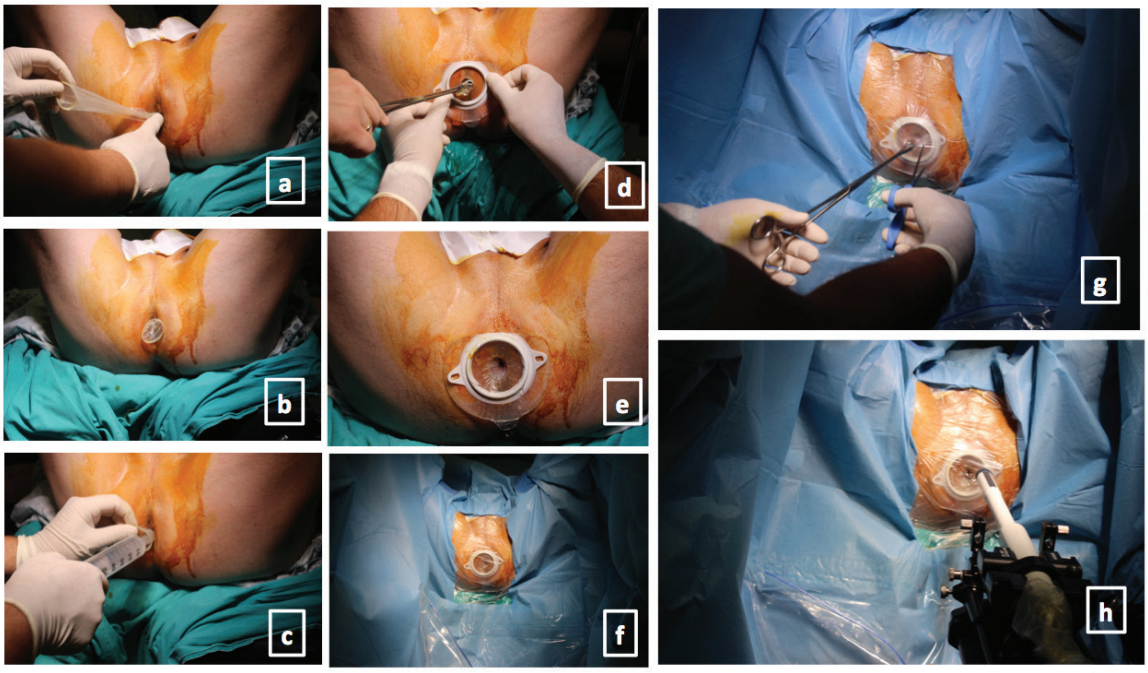


Figure 1. Technical modification to minimize perineal contamination in transperineal prostate biopsy. The empty condom is placed in the rectum which has been filled with 50 mL ultrasound gel (a-b). The inside of the condom is filled with 100 ml ultrasound gel (c). The condom is mounted on a tangentially cut ileostomy adapter which will fix to the perineum region, thus allowing the adapter to be fixed to the anal region (d-e). The perineal area is cleaned with batticon and then covered with sterile off-site (f). Only the part of the off-site that comes into the ileostomy adapter is cut off, thus providing a completely sterile surgical area (g-h).

re-admitted in the hospital due to the process-related infection and the annual cost of this complication was estimated to be approximately £ 1 million (9). Çam et al. (10) showed that after TRUSG assisted biopsies performed in our country, 2% of the patients were hospitalized due to infection.

Fluoroquinolone resistance has increased not only in gastrointestinal or urinary tract infections, but in many infectious diseases, such as skin infections or sexually transmitted diseases, and has become a global problem (11). More than 75% of *E.coli*, which causes infections after prostate biopsy, have been shown to be quinolone resistant in our country (12). Factors that increase fluoroquinolone resistance can be classified as patient-related and process-related factors (1). Patient-related factors are co-morbidities such as diabetes or chronic obstructive pulmonary disease, travel to foreign countries, benign prostatic hyperplasia, urogenital infection, history of recent antibiotic use (especially fluoroquinolone), the presence of a urethral catheter, having recently been hospitalized or being a hospital employee and positive culture before biopsy. A large number of biopsies, repeated biopsies and contaminated ultrasound gel are factors related to the process. The presence of a fluoroquinolone-resistant microorganisms in rectal swab culture is also an important predictor of infection development after prostate biopsy (13). In the light of all this information, whether it is transrectal or transperineal, the complication of infection after prostate biopsy is undeniably serious and costly. The fact that fluoroquinolone-resistant microorganisms are growing globally and nationally suggests that this problem will also appear as an important clinical problem in the coming years.

Several strategies have been applied to prevent infective complications after prostate biopsy. First of all, patients should be evaluated individually before the procedure and the risk factors such as accompanying co-morbidity, urologic attempt history, the use of antibiotics in the last 6 months, history of international travel and being a health care worker should be questioned (14). In addition, strategies such as bowel cleansing with povidone-iodine, prophylactic antibiotics before the procedure, or target-oriented antibiotic prophylaxis due to the result of culture from a rectal swab sample have also been developed (14). Other factors such as contamination from multi-use ultrasound gel containers, contamination of the tip of the biopsy needle during transfer of tissue samples to pathological tubes or pads, or contamination via multi-use needle guide should also be considered (1,14).

Another strategy for preventing infection complications due to prostate biopsy is the use of a perineal approach instead of a microorganisms-rich rectal approach. A recently published meta-analysis revealed that there was no difference between the two approaches in terms of complications (3). A potential explanation for this paradox is that despite the pre-operative peraparation of the perineum, it has been re-contaminated with a continuously manipulated ultrasound probe during the procedure placed in the rectum. Supporting this explanation, in our series, 24 patients who underwent only transperineal biopsy had no procedure-related infection as a complication.

Study Limitations

One of the most important limitations of this study was that it was done with a limited number of patients and that it was a

retrospective study. In addition, according to our knowledge, the absence of a similar application to reduce the infectious complicatios in the transperineal approach in the literature makes our study unique.

Conclusion

Infectious complication after prostate biopsy is a major health problem that has the potential to occur more frequently today due to increased fluoroquinolone resistance. Even in the transperineal approach, which is commonly used especially in fusion biopsies, the rate of this complication is not less than the transrectal approach. This simple technical modification, which we have put into clinical practice for the first time, appears to be a new, effective and safe strategy for reducing the complication of infection after transperineal prostate biopsies. Comparative studies with a larger number of patients are needed to demonstrate the clinical benefit of this technical modification.

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Authorship Contributions

Concept: S.S., C.Y.B., Design: A.E., S.S., C.Y.B., Data Collection or Processing: A.G., Analysis or Interpretation: A.G., S.S., C.Y.B., Literature Search: A.G., S.S., C.Y.B., Writing: A.G., S.S., C.Y.B.

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Original Article

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Evaluation of Histopathologic Results of Testicular Tumors in Antalya: Multi Center Study

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Abstract

Objective: Testicular tumors constitute 1% of all malignancies in men. Being a relatively uncommon tumor, there are few descriptive studies in the literature. The aim of this study is to retrospectively investigate the histopathological results of testicular tumors in our region.

Materials and Methods: In this descriptive multicenter study, we evaluated the histopathologic results of 124 patients who underwent radical or partial orchiectomy with a diagnosis of testicular tumor between 2011 and 2019 in the region of Antalya, Turkey. All specimens were examined by the pathologists in a single center. Data pertaining to patient age, type of operation, histopathological tumor type, tumor size, and pathological stage of the primary tumor (pT) were analyzed.

Results: The mean age of the 124 patients included in the study was 35.14±15.3 (2-80) years. Most (98.4%) of the analyzed specimens were radical orchiectomy materials, while only 1.6% were partial orchiectomy materials. Mean tumor size was 4.01±2.29 (0.5-11) cm. Tumor size was ≤2 cm in 29 (23.4%) specimens and ≥2 cm in 95 (76.6%) specimens. In terms of histopathology, 76.8% were germ cell tumors, 6.4% were gender cord-stromal tumors, 4.8% were ductal canal and rete testis tumors, and 12% were secondary tumors of the testis. Pathological stage of the pT was pT1 in 46%, pT2 in 39%, and pT3 in 15% of the patients.

Conclusion: Although patient age and histopathological distribution of testicular tumors were generally consistent with the literature, the average tumor size in the orchiectomy materials was notably large. Initiatives are required to increase public awareness of the importance of early detection. In addition, our findings suggest that urologists feel hesitant to practice testis-sparing surgery despite recommendations in international guidelines.

Keywords: Testis, tumor, cancer, seminoma, orchiectomy

Introduction

Although testicular cancers account for only 1% of all malignancies in males, they are the most common organ malignancies in men aged 20-40 years (1). Incidence and mortality rates for testicular cancer show significant geographical variation. While the incidence rate is 9.9/100,000 in Scandinavian countries and only 1.3-4/100,000 in the region that includes Turkey, the mortality rates in these areas are 0.27/100,000 and 0.53/100,000, respectively (2). While testicular tumors are still relatively uncommon malignancies, their incidence has increased in the past two decades for unknown reasons (3). Major known risk factors for testicular cancer include undescended testes, a family history of testicular cancer, and the presence of germ cell cancer in the contralateral testis (4). Today, complete cure rates in testicular cancer are close

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to 100%, primarily due to early diagnosis and its highly chemo- and radiosensitive nature. The numerous histopathological variations of testicular tumors prompted the World Health Organization (WHO) to update the classification of testicular tumors in 2016 (5). Traditionally, germ cell tumors are the most common histopathological type of testicular cancer. Other tumor types are very rare. In fact, some histopathological types appear in the literature only as case reports. Being relatively uncommon, there are few descriptive studies on testicular cancers in the literature. The aim of this study is to evaluate the histopathologic results of testicular tumors in our region and compare our findings with the literature.

Materials and Methods

This descriptive multicenter study was approved by the local ethics committee and included six hospitals in the Antalya region. The histopathologic results of 124 patients who underwent radical or partial orchiectomy (PO) due to a diagnosis of testicular tumor between June 2011 and May 2019 were analyzed retrospectively. All specimens were examined by the pathologists in a single center. Data pertaining to patient age, type of operation, pathological tumor type, tumor size, and pathological stage of the primary tumor (pT) were collected. Tumor size was determined by measuring the maximum diameter of the tumor in centimeters. Pathological staging of pT was done according to the 7th edition of the tumor node metastasis (TNM) staging system for testicular cancer by the American Joint Committee on Cancer (AJCC). This study was designed according to the ethical rules of the 1975 Declaration of Helsinki. Ethics committee approval was received for this study from the ethics committee of Antalya Medical Park Hospital (Complex No: 2019/05 Date: 22.07.2019). Written infromed consent was obtained from patients who participated in this study before surgery.

Statistical Analyses

All statistical analyses were performed using SPSS statistical software (SPSS for Windows version 16.0 SPSS Inc., Chicago IL, USA). Age and tumor size were expressed as mean ± standard deviation, while age distribution based on histopathological subgroups was expressed as median (minimum - maximum).

Results

The mean age of the 124 patients included in the study was 35.14±15.3 (2-80) years. The distribution of tumors according to age group is shown in Figure 1. Most (98.4%) of the analyzed specimens were radical orchiectomy materials, while only 1.6% were PO materials. Mean tumor size was 4.01±2.29 (0.5-11) cm. Tumor size was ≤2 cm in 29 patients (23.4%) and ≥2 cm in 95 patients (76.6%). Mean tumor size of the seminomas was 4.85±2.12 (0.6-9) cm. Histopathologically, germ cell tumors accounted for 76.8% of all the testicular neoplasms and 87.2% of the primary testicular tumors. Gender cord-stromal tumors accounted for 6.4% and collecting duct and rete testis tumors for 4.8% of the patients, while 12% were secondary tumors of the testis (Table 1). Pathological stage of the pT was pT1 in 46%, pT2 in 39%, and pT3 in 15% of the patients. None of the patients had pTis or pT4.

Discussion

Tumor size is becoming increasingly important in the clinical course of testicular cancers. Especially for seminoma, which is the most important form of testicular cancer, tumor size is recognized as a risk factor in both staging and occult metastatic disease. One of the important changes in the AJCC 8th edition TNM classification is that in seminomas, pT1 tumors are divided into two subgroups. A tumor size of 3 cm is determined as the cut-off value. Tumors <3 cm are subclassified as pT1a and those >3 cm as T1b (6). In addition, a tumor size of >4 cm and/or the presence of rete testis involvement in stage 1 seminomas was also shown in meta-analyses to be a risk factor for metastatic disease (7,8). The average seminoma size was 4.85±2.12 cm in the present study, which was not reassuring. In another study on testicular tumors conducted approximately 2 decades ago in our region, the mean tumor size in seminoma specimens was 4.92±3.03 cm (9). This demonstrates that unfortunately, there

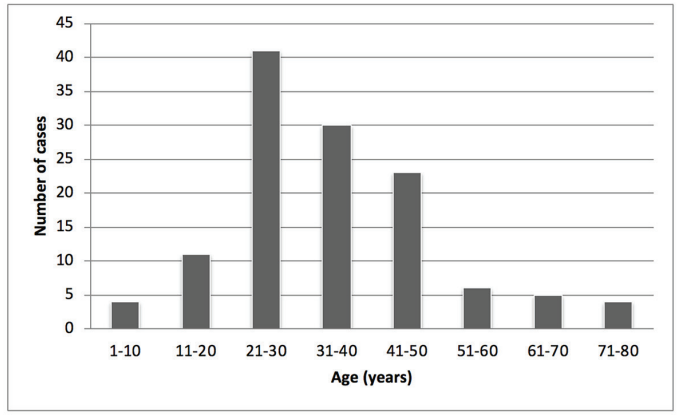


Figure 1. Age distribution of patients with testicular tumors

Table 1. Histopathological distribution of testicular tumors		
Testis Tumors	% (n)	Age (median)
A) Germ Cell Tumors	**76.8%**	
Seminoma	32.3% (40)	35 (24-62)
Embryonal Carcinoma	15.3% (19)	28 (18-46)
Mixed Germ Cell Tumors	22.6% (28)	26.5 (17-52)
Yolk Sac Tumors	4% (5)	20 (2-28)
Teratoma	2.4% (3)	27 (7-40)
B) Gender Cord-Stromal Tumors	**6.4%**	
Leydig Cell Tumors	4% (5)	40 (25-80)
Sertoli Cell Tumors	1.6% (2)	50.5 (31-70)
Fibroma	0.9% (1)	43
C) Collecting Duct and Rete Testis Tumors	**4.8%**	
Adenomatoid Tumors	4.8% (6)	45.5 (27-72)
D) Secondary Tumors	**12%**	
Lymphoma	6.4% (8)	54 (36-74)
Leukemia	4% (5)	11 (7-45)
Urothelial Carcinoma Metastases	1.6% (2)	71.5 (71-72)
	100% (124)	

has been no improvement in tumor size at time of diagnosis over the past two decades.

Tumor size is also important in surgical planning. Although radical orchiectomy is currently the gold standard treatment for testicular tumors, PO is a good alternative in selected patients. The preservation of testicular functions with PO is valuable for sustaining testosterone production and spermatogenesis. Mid- and long-term follow-up studies have suggested that PO is not associated with any significant risk of local or distant recurrence that may cause progression (10). Keske et al. (11) reported that of 13 patients who underwent PO due to testicular tumors, only 1 exhibited local recurrence during an average follow-up period of 44 month. The American Urological Association 2019 guidelines state that PO can be considered for tumors ≤2 cm in size in the presence of normal serum tumor markers (β human chorionic gonadotropin and α-fetoprotein), a functionally or anatomically solitary testis, or bilateral synchronous testicular tumors (12). The recent European Urology Association guidelines do not specify a size but states that only masses smaller than 30% of the testis are candidates for PO (4). However, urologists still seem hesitant about this surgical method. It was reported in a large series in the United States that PO was performed in only 2.21% of 5,365 patients with tumors 2 cm or smaller (13). In our series, PO was successfully performed in 2 (6.9%) of the 29 (23.4%) patients with testicular tumors ≤2 cm in size that were eligible for PO. We believe that urologists have reservations regarding PO, and that rates of testis-sparing surgery will increase as the results of large series with follow-up are published.

The most important point here is the size of the testicular tumors at the time of diagnosis. Testicular tumors are known to be painless masses, which is the main factor responsible for patients' late presentation to a physician. In our study, the mean testicular tumor size was 4.01±2.29 cm, with 76.4% being ≥2 cm in size. This suggests that patients seek medical attention quite late and highlights the importance of raising public awareness, especially among men in the at-risk age group. Testicular self-examination is the easiest and cheapest way to scan testicular tumors (14). Especially raising awareness of regular testis self-examination among men aged 15-45 years will facilitate the detection of tumors when much smaller in size.

The prevalence of secondary tumors of the testis varies considerably according to previous publications. In some studies, only testicular metastases of solid organ tumors were considered secondary tumors, while hematologic malignancies were not included (15). When analyzed in that way, secondary tumors of the testis account for less than 2% of all testicular tumors (16). In earlier studies, it was shown that prostate adenocarcinoma was the most common pT with testicular metastases (15,16). This was because bilateral orchiectomy was performed routinely in the treatment of advanced prostate adenocarcinoma in the past. In our series, 12% of the tumors were secondary. If we excluded hematological malignancies, the rate of secondary tumors in the form of organ metastasis was compatible with the literature, which was 1.6% of all testicular tumors. Both of those cases were urothelial carcinoma metastases. Hematological malignancies represent the largest proportion of secondary testicular tumors. In our study, 87% of secondary tumors were hematological malignancies and 13% were solid organ metastases.

As mentioned above, testicular invasion by hematological malignancies constitutes a significant proportion of secondary tumors. There seems to be confusion regarding the definition here. Oncologists avoid defining testicular involvement of hematological malignancies as metastasis, instead describing it as involvement. In our study, about 10.4% of all patients were hematological malignancies. The relatively high rate of hematologic malignancies in this series might be due to the fact that two of the participating hospitals were regional referral centers for hematological malignancies.

Testicular lymphoma is caused by either primary or secondary infiltration of the testis by malignant/clonal lymphocytes. It accounts for 5% of all testicular tumors and is the most important cause of testicular masses after the age of 60. Primary testicular lymphoma is very rare and usually reported in the literature in case reports (17). In our series, patients with lymphoma were slightly younger compared to the literature, with a mean age of 54. One of the patients with lymphoma had primary testicular lymphoma and the others had relapses. Twenty percent of extramedullary lymphomas are located in the testes, which is an indicator of poor prognosis. Bilateral involvement is seen in up to 35% of patients (18). About 80-90% of testicular lymphomas are diffuse large B-cell lymphomas. All of the lymphomas in our study except in one patient were diffuse large B-cell lymphomas.

Leukemic infiltration is another hematological malignancy that involves the testes and is among the secondary testicular tumors. It represents an important place among testicular tumors, especially in the pediatric age group. As with lymphoma, the testes are also the most common site of extramedullary recurrence of leukemia after the central nervous system. In the pediatric patients with acute lymphoid leukemia, up to 5-8% of patients can have primary involvement or relapse in testis (19). Lymphoblastic cells that pass through the blood-testis barrier are protected from chemotherapeutic agents and involvement occurs as a result of their proliferation (20). In our study, patients with testicular leukemic infiltration had a mean age of 11 years and represented a remarkable 4% of all testicular tumors. In addition, all of the patients were diagnosed as having acute lymphoblastic leukemia. Orchiectomy or radiotherapy (RT) may be considered in the treatment of the leukemic involvement of the testes (19,21). Neither approach provides superior outcomes in patients with unilateral involvement. In principle, however, orchiectomy is advantageous because it definitively eliminates leukemic infiltration of the testes (22). Patients in whom RT is planned should be informed of the possibility of permanent deterioration of gonadal functions after RT (23).

Adenomatoid tumors are benign and they are the most common form of paratesticular tumors (24). Adenomatoid tumors are indistinguishable from malignant testicular tumors both in terms of clinical findings and imaging; therefore, radical orchiectomy is often performed in these tumors (25). Notably, adenomatoid tumors were seen in 6 patients and accounted for 4.8% of all testicular tumors in our study. In addition, only one of these patients underwent PO. Testis-sparing surgery should definitely be considered in these patients.

Testicular fibroma was observed in one patient in our study. Testicular fibroma is a benign tumor in the thecoma-fibroma group of gender cord-stromal tumors according to the 2016 WHO classification. Testicular fibroma is a very rare tumor, with fewer than 30 patients reported in the literature (26).

Study Limitations

This study had certain limitations. Only pathological tumor staging was done in patients with primary testicular tumor. The lack of clinical staging of the pT might be considered a limitation.

Conclusion

Although age and histopathological distribution of testicular tumors in our region were generally consistent with the literature, tumor size in the orchiectomy materials was remarkably large. Initiatives are required to increase public awareness of the importance of early diagnosis in testicular cancer, especially men between the ages of 15 and 45 years. In addition, despite recommendations in international guidelines, our findings show that urologists are hesitant to practice testis-sparing surgery.

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Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Antalya Medical Park Hospital (Complex No: 2019/05 Date: 22.07.2019).

Informed Consent: Written infromed consent was obtained from patients who participated in this study before surgery.

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Authorship Contributions

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

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Original Article

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Renal Cell Carcinoma: Epidemiological Profile and Histopathological Features

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Abstract

Objective: Nowadays, with the use of advanced imaging methods, the incidence of renal cell carcinomas (RCCs) has increased steadily and they have become recognizable at early stage. Morphologically and immunophenotypically, RCCs are divided into many different types and are divided into three main subtypes. Each type has differences in terms of genetics, biology, and behavior. The objectives of this study is to investigate the histopathological features of tumor specimens of patients operated with diagnosis of RCC.

Materials and Methods: The pathology specimens and reports of 77 patients with RCC who underwent radical or partial nephrectomy were reviewed retrospectively. Descriptive and clinical data of the patients were obtained. The size, lateralization, focality, histopathological type, Fuhrman nuclear grading system (NGS), sarcomatoid change, renal sinus and vein invasions, perirenal fat tissue invasion, hilar fatty tissue invasion, ureter surgical margin, and primary tumor stage of RCC were determined.

Results: According to the histopathologic type, 77.9% of the patients had clear cell RCC, 10.4% chromophobe RCC, 9.1% papillary RCC, and 2.6% multilocular RCC. The Fuhrman NGS values were 5.2% for grade 1, 61% for grade 2, 26% for grade 3, and 7.8% for grade 4. There were sarcomatoid features in only 7.8% of the patients. There were 6 patients (7.8%) with renal sinus invasion, 3 patients (3.9%) with renal vein invasion, 8 patients (10.4%) with perirenal adipose tissue invasion, 2 patients (2.6%) with hilar fat tissue invasion, and 2 patients (2.6%) with tumors at the ureter surgical margin. Pathological changes were significantly differentiated according to gender except for the primary tumor stage.

Conclusion: RCCs are divided into many different types and each type has differences in terms of genetics, biology, and behavior. Due to this, the pathologist must differentiate cell types routinely by morphology and immunohistochemical markers as well as by cytogenetic and molecular genetic analysis particularly when the cell type is equivocal.

Keywords: Renal cell carcinoma, histopathology, kidney tumors

Introduction

Prevalence of renal cell carcinomas (RCCs) is approximately 2% among adult cancers and RCC accounts for about 85% of all parenchymal kidney tumors. Among urological cancers, RCC is the 3rd most common cancer after prostate and bladder tumors. RCC is the 6th leading cancer type in men and the 10th in women, worldwide (1,2). RCCs do not respond to conventional chemotherapy and have the highest mortality rate (more than a third of the patients will die from RCC) among the genitourinary cancers and RCC is the 13th most common cause of cancer death worldwide. Surgical resection of the tumor with minimal risk of recurrence is applied during early stages. Nowadays, with the use of advanced imaging methods, RCCs are recognizable at early stage. With the use of advanced imaging methods and incidental detection of renal masses, the incidence of RCCs has increased steadily (3,4).

Nomenclature, categorization, and standardization of RCC have been made by many organizations such as The International Society of Urological Pathology, The World Health Organization (WHO) (5), The College of American Pathologists (6), and The American Joint Committee on Cancer (AJCC) (Staging Manual) (7) and revisions are ongoing. Morphologically and immunophenotypically, RCCs are divided into many different types and are divided into three main subtypes (≥5% incidence) with the malignant course: Clear cell, papillary, and chromophobe RCCs. Each type has differences in terms of

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genetics, biology, and behavior (8). The remaining subtypes are very rare (each with ≤1% total incidence) and in cases where a tumor does not fit any subtype's diagnostic criteria, it is designated as unclassified RCC (9,10).

Clear cell RCC, also called conventional RCC, is the most common and malignant renal tumor, accounting for approximately ~75% of all RCCs. It is thought to arise from the epithelium of the proximal tubule (11). Papillary RCC is observed at frequency of ~15% and is thought to arise from the epithelium of the proximal tubule, like clear cell RCC. Chromophobe RCC makes up ~5% of kidney tumors and is believed to derive from the distal nephron, probably from the epithelium of the collecting tubule (3,9). The pathologist differentiates cell types routinely by morphology and immunohistochemical markers as well as by cytogenetic and molecular genetic analysis particularly when the cell type is equivocal. Of RCCs, 3-5% cannot be classified and are termed unclassified RCC (3).

These tumors, which are detected in early period, are usually small in size and are low-grade. Prognostic models are being developed for this purpose. In these models, the Fuhrman nuclear grading system (NGS) has an important role along with prognostic parameters such as tumor node metastasis (TNM) stage and performance score. Fuhrman NGS, which has been defined by Fuhrman et al. (12) and has been the most widely used histopathologic grading system since 1982, has been shown to be an independent prognostic factor of RCC survival (5,13).

The objectives of this study is to investigate the histopathological features of tumor specimens of patients operated with RCC diagnosis.

Materials and Methods

Data collection and ethical permission: The study was performed at a university hospital. The pathology specimens and reports of 77 patients with RCC who underwent radical or partial nephrectomy between the years 2010 and 2018 were reviewed retrospectively. Descriptive and clinical data of the patients (age, gender, hospital admission complaints, surgical procedure) were obtained. The study was approved by the University for the Non-interventional Clinical Research Ethics Board (Date: 08.08.2019, Decision No: 17).

Pathological parameters including the size, lateralization and focality of tumors were obtained from the pathology reports. The largest tumor diameter was determined from macroscopic examination. Histopathological type, Fuhrman NGS, sarcomatoid feature, renal sinus, and vein invasions, peri-renal fat tissue invasion, hilar fatty tissue invasion, ureter surgical margin, and primary tumor stage of RCC were determined by re-examination of preparations. Fuhrman NGS was used to define the tumor cell differentiation (14,15) and histological subtype classification was made using 2016 WHO scheme (10,16).

Fuhrman et al. (12) evaluated the effects of nuclear grade, tumor size, renal vein invasion, stage, tumor pattern and histopathological tumor type on survival. The most significant difference of this evaluation from other rating systems is evaluation of nucleolus visibility and size of the nucleolus under a light microscope. Accordingly, Fuhrman NGS is classified into four groups.

Grade 1: The tumor nucleus is small (10 μ in diameter), round, and uniform. No or inconspicuous nucleoli resemble lymphocyte nuclei (very rare).

Grade 2: The tumor nucleus is approximately 15 μ in diameter, has slightly irregular borders and open chromatin (40% of tumors). Nucleolus can be seen at 400 magnifications.

Grade 3: The tumor nucleus is about 20 μ (large) in diameter, has markedly irregular borders and open chromatin (30-40% of tumors). The large nucleolus can be seen even at 100 magnifications.

Grade 4: Tumor nuclei are similar to the nuclei in grade 3 and they are bizarre and multi-lobated. The cells are pleomorphic. The cells may have multiple nuclei and chromatin coarseness. They have macro-nucleoli (15% of tumors) (mitosis findings).

A significant difference was found between grade 1 and grade 2-4 tumors in terms of metastasis. In the study, four different nucleus degrees were defined when evaluating survival, but when evaluating the results, group 2 and 3 were grouped together and it was reported that there was a statistically significant difference in terms of the survival among grade 1, grade 2+3 and grade 4. Although there was no statistically significant difference in terms of survival rates among the nucleus grades in this first study, the differences between Fuhrman NGS grades were revealed in subsequent studies (13,17).

Statistical Analysis

The data obtained from the study were analyzed using IBM SPSS Statistics 24 software program. Quantitative variables were expressed as mean ± standard deviation and categorical variables were expressed as number (n) and percentage (%). "chi-square test" and "Fisher's exact test" were used to compare qualitative data and "Studen's t-test" was used to compare independent groups. A p value <0.05 was accepted as significant. The binary logistic regression coefficient was calculated for the relationship analysis of RCC.

Results

Descriptive and clinical data of the patients included in the study are shown in Table 1. According to this table, the mean age of the patients was 61.29 years and the average size of the tumors was 7.65 cm. Twenty-five (32.5%) of the participants were female and 52 (67.5%) were male. Distribution of the signs and symptoms were as follows: Flank pain was found in 50 patients (64.9%), followed by hematuria in 17 (22.1%) and palpable mass in 10 (13%) patients. Sixty-six (85.7%) of the surgical procedures were radical nephrectomy and 11 (14.3%) were partial nephrectomy.

Table 2 shows the histopathological features of the RCC. Tumors were localized in the right kidney in 41 (53.2%) patients and left kidney in 36 (46.8%) patients. The majority of the patients had unifocal (n=75, 97.4%) tumor. According to the histopathologic type, 60 (77.9%) of the patients had clear cell RCC, 8 (10.4%) chromophobe RCC, 7 (9.1%) papillary RCC, and 2 multi-locular

Table 1. Descriptive and clinical data of 77 patients			
Age (years)		61.29±14.68	
Tumor size (cm)		7.65±3.84	
		n	**%**
Gender	Female	25	32.5
	Male	52	67.5
Complaint	Flank pain	50	64.9
	Hematuria	17	22.1
	Palpable mass	10	13.0
Surgical Procedure	Radical nephrectomy	66	85.7
	Partial nephrectomy	11	14.3

Table 2. Histological features of renal cell carcinoma			
Histological Features		**n**	**%**
Lateralization	Right	41	53.2
	Left	36	46.8
Focality	Unifocal	75	97.4
	Multifocal	2	2.6
Histopathological type	Clear cell	60	77.9
	Chromophobe	8	10.4
	Papillary	7	9.1
	Multilocular	2	2.6
Fuhrman NGS	1.00	4	5.2
	2.00	47	61.0
	3.00	20	26.0
	4.00	6	7.8
Sarcomatoid changes	Yes	6	7.8
	No	71	92.2
Renal sinus invasion	Yes	6	7.8
	No	60	77.9
	Could not be assessed	11	14.3
Renal vein invasion	Yes	3	3.9
	No	63	81.8
	Could not be assessed	11	14.3
Perirenal fat tissue invasion	Yes	8	10.4
	No	69	89.6
Hilar fatty tissue invasion	Yes	2	2.6
	No	64	83.1
	Could not be assessed	11	14.3
Surgical margin of ureter	Negative	64	83.1
	Positive	2	2.6
	Could not be assessed	11	14.3
Primary tumor stage	1a	13	16.8
	1b	19	24.7
	2a	19	24.7
	2b	12	15.6
	3a	14	18.1
NGS: Nuclear grading system			

RCC (2.6%) (Figure 1). The Fuhrman NGS values were 5.2% for grade 1,60% for grade 2, 26% for grade 3, and 7.8% for grade 4. There were sarcomatoid features in only 6 (7.8%) patients.

There were 6 patients with renal sinus invasion (7.8%), 60 patients (77.9%) without renal sinus invasion and 11 patients (14.3%) were not evaluated. Also, there were 3 patients with renal vein invasion (3.9%), 63 patients (81.8%) without renal vein invasion and 11 patients (14.3%) that could not be evaluated. There were 8 patients (10.4%) with perirenal adipose tissue invasion. There were 2 patients (2.6%) with hilar fat tissue invasion, 64 (83.1%) without hilar fat tissue and 11 (14.3%) patients that could not be evaluated. There were 2 patients (2.6%) with tumors at the ureter surgicalmargin, 64 patients (83.1%) without tumors at the ureter surgical margin and 11 patients (14.3%) that could not be evaluated. There were 13 patients with primary tumor stage 1a (16.8%), 19 patients stage 1b (24.7%), 19 patients stage 2a (24.7%), 12 patients stage 2b (15.6%), and 14 patients stage 3a (18.1%). (Figure 2)

The relationship between histopathological features and gender is shown in Table 3. Accordingly, pathological changes were significantly differentiated according to gender except for the primary tumor stage ($p<0.001$).

Table 4 shows the distribution of major histopathological types by age. The number of patients according to age groups "18-39", "40-59", and "60 or over" were 4 (3.9%), 28 (36.8%) and 45 (59.2%), respectively. In the 18-39 age group, there were 3 (75%) patients with clear cell RCC and 1 (25%) with chromophobe RCC. The most common type was found to be clear cell RCC (22 patients, 78.6%) in patients aged 40-59 years, followed by chromophobe (3 patients, 10.7%), multilocular (2 patients, 7.1%) and papillary (1 patient, 3.6%) RCC. The distribution of the types in the age group of ≥60 years was as follows; Clear cell RCC in 35 patients (77.8%), papillary RCC in 6 patients (13.3%), and chromophobe RCC in 4 patients (8.9%).

Table 5 shows the results of the regression analysis between the tumor lateralization and tumor size, histopathological type, and primary tumor stages. It was found that these 3 features did not have a predictive value on lateralization ($p>0.05$).

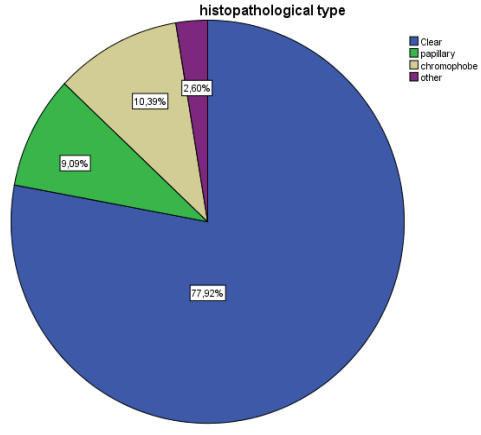


Figure 1. Distribution of patients according to tumor types

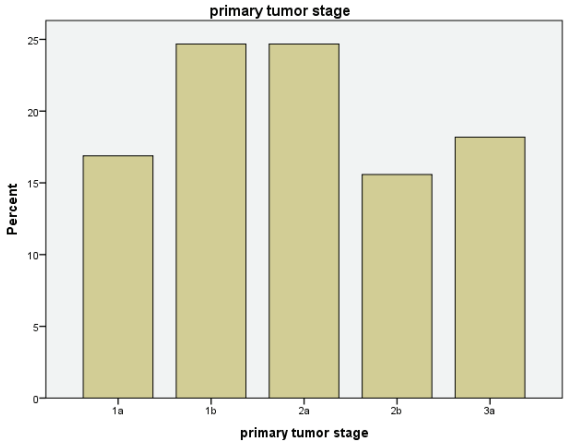


Figure 2. Graphical representation of the primary tumor stage

Table 3. The relationship between histopathological features and gender				
		Female	**Male**	**p**
Histopathological type	Clear cell	22 (88%)	38 (73.1%)	<0.001
	Chromophobe	1 (4%)	7 (13.5%)	
	Papillary	1 (4%)	6 (11.5%)	
	Multilocular	1 (4%)	1 (1.9%)	
Fuhrman NGS	1.00	1 (4%)	3 (5.8%)	<0.001
	2.00	16 (64%)	31 (%59.4)	
	3.00	6 (24%)	14 (26.9%)	
	4.00	2 (8%)	4 (7.7%)	
Sarcomatoid changes	Yes	3 (12%)	3 (5.8%)	<0.001
	No	22 (88%)	49 (94.2%)	
Renal sinus invasion	Yes No Could not be assessed	2 (8%) 18 (72%) 5 (20%)	4 (7.7%) 42 (80.8%) 6 (11.5%)	<0.001
Renal vein invasion	Yes	1 (8%)	2 (3.8%)	<0.001
	No	19 (72%)	44 (84.6%)	
	Could not be assessed	5 (20%)	6 (11.5%)	
Hilar fatty tissue invasion	Yes	1 (4%)	1 (1.9%)	<0.001
	No	19 (76%)	45 (86.5%)	
	Could not be assessed	5 (20%)	6 (11.5%)	
Surgical margin of ureter	Negative	20 (80%)	44 (84.6%)	<0.001
	Positive	0 (0%)	2 (3.8%)	
	Could not be assessed	5 (20%)	6 (11.5%)	
Primary tumor stage	1a	6 (24%)	7 (13.5%)	0.30
	1b	8 (32%)	11 (21.2%)	
	2a	6 (24%)	13 (25%)	
	2b	3 (12%)	9 (17.3%)	
	3a	2 (8%)	12 (23.1%)	
NGS: Nuclear grading system				

Discussion

Numerous prognostic factors have been identified in RCCs. Among these, the most important prognostic factors are stage, diameter, NGS, histologic subtype, presence of lympho-vascular invasion and presence of sarcomatoid component of the tumor (18).

The incidence of RCC increases markedly with age and is higher in men than women (the gender ratio approximately male:female is 2:1) (3,9). In a study conducted in Turkey, Turk et al. (18) examined the records of 230 patients with RCC and they found that the mean age of the patients was 57.5 years and the female/male ratio was 3/7. In the Surveillance, Epidemiology, and End Results database in the ultrasonography (USG), the median age of patients with RCC was 64 years. Also, it should be kept in mind that if RCC was diagnosed at younger ages (≤46 years), the possibility of a hereditary Kidney Cancer syndrome - which was 3-5% of all RCCs - should be considered (19). In our study, the mean age of the patients was 61.29 years. Of the patients, 32.5% were female and 67.5% were male. Our findings were consistent with the literature.

The early clinical manifestations of RCC are diverse and most are non-specific. Only 10% of individuals with RCC present with the classic triad of hematuria, flank pain, and mass (the tumor is already advanced in those with this triad). None of the 3 symptoms is present in more than 40% of individuals with RCC and the tumor is found incidentally in 60% of patients. This shift is a result of widespread use of non-invasive radiological techniques such as USG or abdominal computer tomography imaging performed for another reason (3,9). In our study, the most common complaints of patients were flank pain (64.9%), followed by hematuria (22.1%) and palpable mass (13%).

Early stage RCCs (T1-2, limited within the kidney) can be treated surgically. Radical nephrectomy is the traditional and preferred method. The radical nephrectomy is currently practiced using a

Table 4. Distribution of major histopathological groups by age			
Age	**Histopathologic Type**	**n**	**%**
18-39 (n=4)	Clear cell	3	75.0
	Chromophobe	1	25.0
40-59 (n=28)	Clear cell	22	78.6
	Papillary	1	3.6
	Chromophobe	3	10.7
	Multilocular	2	7.1
≥60 (n=45)	Clear cell	35	77.8
	Papillary	6	13.3
	Chromophobe	4	8.9

Table 5. Regression analysis						
		B	S.E.	Wald	Sig.	Exp (B)
Lateralization	Tumor size	0.138	0.095	2.091	0.148	1.148
	Histopathological type	0.062	0.306	0.042	0.838	1.064
	Primary tumor stage	0.088	0.243	0.133	0.716	1.092

conventional laparoscopic approach in most patients with stage I and II RCC, and the open surgery remains the gold standard in the treatment of more complex patients (9). However, nephron-sparing surgery which reduces the risk of premature death due to heart disease and late renal failure in small and localized tumors is also becoming widely used today (3). Turk et al. (18) reported that 88% of patients with RCC (n=230) underwent radical nephrectomy and 12% had nephron-sparing surgery. In our study, 85.7% of the surgical procedures were radical nephrectomy and 14.3% were partial nephrectomy in 77 patients. Our findings were consistent with the literature.

Turk et al. (18) found that the mean tumor diameter was 6.9 cm. In our study, the average size of the tumors was 7.65cm, the tumor was localized at the right kidney in 53.2% of patients and at left kidney in 46.8% of them, and the majority of the tumors (97.4%) were unifocal.

Clear cell RCC is the most common malignant renal tumor, accounting for approximately 70% of all renal cancers. At the macroscopic examination, the surface area of the clear cell tumors is golden yellow with mostly hemorrhagic, necrotic and cystic fields. At the microscopic investigation, clear cell RCC is consisted of tumor cells with clear cytoplasm arranged in nests or tubules surrounded by a rich vascular network. The clear presence of the cytoplasm is due to the accumulation of glycogen and lipids. A variable proportion of tumor cells with granular eosinophilic cytoplasm can be observed and, in some patients, these cells constitute the entire tumor mass (9,20). In their study, Turk et al. (18) found the rate of clear cell, papillary and chromophobe RCCs as 85%, 8%, and 3.5%, respectively (n=230). In our study, rate of clear cell RCC was was (77.9%) as histopathological type. This was followed by chromophobe (10.4%), papillary (9.1%), and multi-locular cell RCCs (2.6%).

In their study, Fuhrman et al. (12) evaluated RCC in 4 grades according to cell nucleus morphology (brief details were given in the method section). Fuhrman grades of I–IV have been shown to correlate with survival in clear cell and papillary RCCs but these grades do notcorrelate with survival in other histologic types (21,22). For better interobserver compliance; 2 working groups, Union Internationale Contre le Cancer and AJCC, published a report in 1997. It was suggested that the NGS should be used only in conventional (clear cell) and papillary RCCs and that in order to facilitate the reproducibility of Fuhrman NGS, grade 1 and 2 would be collected under a single group, thus there would be 3 groups (grade 1+2, 3, and 4) (22).

However, when grade 2 and 3 were grouped together (as grade 1, 2+3, and 4), there were also studies indicating statistically significant differences in terms of survival between groups (13,17). In many studies, double grouping (grade 1+2 and 3+4) and triple grouping (grade 1+2, 3, and 4 or grade 1, 2+3 and 4) were used instead of the classical quadruple Fuhrman NGS to achieve better interobserver agreement (13,17,23). In both univariate and multivariate analyses, it has been reported that classical quadruple Fuhrman NGS, double (grade 1+2 and 3+4) and triple (grade 1+2, 3 and 4) grouped NGSs have an independent prognostic value for survival in RCC (14,15). In our study, we used quadruple Fuhrman NGS scale. The rate of patients with Fuhrman grade 1, 2, 3 and 4 was 5.2%, 61%, 26%, and 7.8%, respectively. In other words, more than half of the patients were Fuhrman grade 2.

It should be kept in mind that all types of RCC may contain foci of high-grade malignant spindle cells (sarcomatoid differentiation). Sarcomatoid RCC is no longer considered as a true subtype since sarcomatoid changes represent undifferentiated cells associated with progression of disease in all RCC cell types (3,9). Turk et al. (18) found the rate of sarcomatoid variant as 3.5% in their study (n=230). In our study, sarcomatoid changes were found only in 6 subjects (7.8%).

In our study, renal sinus, renal vein, perirenal adipose tissue, hilar adipose tissue, and ureter surgical margin invasions were observed in 7.8%, 3.9%, 10.4%, 2.6%, and 2.6% of patients, respectively.

Pathologic stage, based on the diameter of the tumor and the extent of invasion, is the most important indicator of survival. The TNM staging system describes local extension of the primary tumor (T), involvement of regional lymph nodes (N), and presence of distant metastases (M). In the AJCC Cancer Staging guidelines, stage of RCC is defined as follows: T1a tumor is ≤4 cm in greatest dimension and limited to the kidney; T1b tumor is between 4 cm and 7 cm; T2a tumor is >7 cm but ≤10 cm in size and limited to the kidney; T2b tumor is >10 cm in size but confined within the kidney; T3 tumor extends into major veins or invades adrenal gland or perinephric tissues, but not beyond Gerota's fascia; and T4 tumor invades beyond Gerota's fascia (includes contiguous extension into ipsilateral adrenal gland) (24,25).

In a study on the incidence of RCC in the US between 1986 and 1998, 54% of patients had localized tumor (stage I and II), 21% had regional tumor (stage III), and 25% had advanced tumor (stage IV) (26). In their study, Turk et al. (18) reported that stage 1, 2, 3, and 4 (n=230) patients were 49%, 32%, 14% and 5%, respectively. In our study, the tumor stages of RCCs were mostly stage 1 and 2 and the ratio of each was 40%. Grade 3a was observed only in 18.1% of the patients, whereas grade 4 was oserved in none of the patients. We believe that early stage tumors can be diagnosed with advanced imaging techniques.

In our study; it was observed that all pathological changes were significantly differentiated by gender except for the primary tumor stage ($p<0.001$). The rates of tumor according to age groups were 3.9%, 36.8% and 59.2% in patients aged "18-39" (n=4), "40-59" (n=28) and "60 or above" (n=45) years, respectively. Clear cell RCC rates in these age groups were; 75%, 78.6% and 77.8%, respectively; chromophobe RCC rates were 25%, 10.7% and 8.9%, respectively; and papillary RRC rates were 0%, 3.4% and 13.3%, respectively. Multilocular RCC was observed only in 7.1% of the patients in 40-59 age group.

According to the results of the regression analysis between the tumor lateralization and tumor size, histopathological type, and primary tumor stages, it was found that these 3 features did not have a predictive effect on lateralization.

Study Limitations

Genetic factors (2-4% of RCC is hereditary), chronic kidney disease (and therefore long-term dialysis) kidney transplantation, and acquired cystic disease of kidney are major factors for the

etiology of RCC. Smoking, obesity, hypertension, and/or the use of medications associated with these diseases -although the risk is low - have been identified as risk factors. In our study, we focused on and discussed the pathological data. Therefore, some clinical data were not included in our study. For the same reason, we did not correlate survival rates with Fuhrman NGS.

Conclusion

RCCs are the 3rd most common cancer after prostate and bladder tumors among urologic cancers. Morphologically and immunophenotypically, RCCs are divided into many different types and are divided into three main subtypes (≥5% incidence) with the malignant course. Each type has differences in terms of genetics, biology, and behavior. Due to this, the pathologist must differentiate cell types routinely by morphology and immunohistochemical markers as well as by cytogenetic and molecular genetic analysis particularly when the cell type is equivocal.

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Ethics

Ethics Committee Approval: The study was approved by the University for the Non-Interventional Clinical Research Ethics Board (Date: 08.08.2019, Decision No: 17).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Supervision: S.H., S.G., Critical Review: S.H., S.G., Concept D.G., Design: D.G., İ.E.S., Data Collection or Processing: D.G., İ.E.S., S.G., Analysis or Interpretation: D.G., İ.E.S., Literature Search: D.G., İ.E.S., S.H., Writing: D.G.

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Original Article

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Laparoscopic Partial Nephrectomy for Renal Angiomyolipoma: A Retrospective Cohort Study

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Abstract

Objective: The aim of this study is to investigate the surgical and functional outcomes of laparoscopic partial nephrectomy (LPN) in patients with renal angiomyolipoma (RAML).

Materials and Methods: From April 2014 to February 2018, the data of a total of 346 patients who underwent LPN were retrospectively reviewed. Twenty-one patients with final pathology report indicating RAML were included in the study. Demographic data, operative indications, intraoperative and postoperative outcomes as well as complications were evaluated.

Results: Eighteen female (85.7%) and 3 male (14.3%) patients were included in this study. The mean age was 55.14±11.95 years. Of the RAMLs, 52.4% were in the right kidney and 47.6% in the left kidney. The mean tumor size was 31.38±16.72 mm and the mean RENAL Nephrometry score was 5.90±1.51 (4-10). RAML could not be differentiated from RCC in 12 patients (57.1%) by preoperative computer tomography and/or magnetic resonance images. In 4 patients, LPN was implemented by off-clamp technique whereas, in 17 patients it was implemented by global ischemia technique. The mean operation duration was 67.86±20.77 (40-110) minutes (min) and the mean estimated blood loss was 117.14±59.7 (30-220) milliliters. In 17 patients who underwent LPN by global ischemia technique, the mean warm ischemia time was 10.88±5.19 (6-22) min. According to the Modified Clavien-Dindo classification, grade 1 complications were detected in 3 patients, postoperatively. The most considerable renal functional changes were detected between preoperative and postoperative- 1st day levels. However, at the end of the first year, the difference was found to decrease.

Conclusion: LPN is a safe and effective treatment option for the treatment of RAMLs that are not able to be distinguished from renal cell carcinoma radiologically. Besides the definitive treatment, the exact pathological diagnosis can be ensured by LPN.

Keywords: Angiomyolipoma, laparoscopy, partial nephrectomy

Introduction

Angiomyolipoma (AML) is the most prevalent benign mesenchymal tumor of the kidney consisting of varying proportion of adipose tissue, blood vessel, and smooth muscle cells. The majority of AMLs occur in sporadic form with 4 times more in women than men however up to 20% of those may be accompanied by lymphangioleiomyomatosis (LAM) and tuberous sclerosis complex (TSC), which is an exceptional autosomal-dominant disorder related to over activation of the mammalian target of rapamycin pathway (1). The hereditary forms of RAMLs tend to be multifocal and bilateral in contrast to sporadic form which is more often specified as a solitary lesion (2).

The wide use of radiological imaging has increased the incidental detection of renal masses. The main considerable role of imaging is to differentiate RAMLs from renal cell carcinoma (RCC). As, the fat content of AML decreases, it is able to be difficult to differentiate it from RCC by computerized tomography (CT) and magnetic resonance image (MRI). It has been stated that approximately 5% of AMLs have devoid of adipose tissue to be identified in imaging. Therefore, biopsy or surgical resection may be needed to acquire the correct diagnosis (3).

Clinically, the majority of small AMLs are asymptomatic. However, increase in tumor size over time may lead to symptoms including flank pain, hematuria, palpable mass, retroperitoneal

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hemorrhage as well as shock. The indication for an active intervention of RAMLs has been recommended for patients with symptoms, tumor size >4 cm, suspicion of malignancy and for women of childbearing age. Treatment approaches include a wide range of options ranging from radical nephrectomy or partial nephrectomy to minimally invasive ablative therapies (4).

In this retrospective study, we aimed to evaluate the indications, intraoperative and postoperative outcomes in patients with RAML who underwent laparoscopic partial nephrectomy (LPN) in a tertiary care institution.

Materials and Methods

This was a single center retrospective cohort study and was conducted in compliance with the ethical principles of the Helsinki Declaration. Ethics approval was granted by the Ondokuz Mayıs University Clinical Research Ethics Committee (OMU KAEK 2019/157, February 14th, 2019). Informed consent was obtained from all patients prior to their database inclusion.

The current study was designed as a retrospective chart review of patients who underwent LPN from April 2014 to February 2018. The data of 21 patients who underwent LPN with final pathology report of AML were included in the study. Surgical indications were the presence of tumors that were indistinguishable from RCC on radiological imaging, increased tumor size, and/or changes in imaging characteristics in RAMLs ≥4 cm on follow-up and preference of surgery instead of selective artery embolization (SAE) by the patients. The patients who were managed by radical nephrectomy, open partial nephrectomy, active surveillance, SAE, and ablative therapies including cryoablation and radiofrequency ablation (RFA) were also excluded in this study. All patients were evaluated before the active surgical intervention with ultrasonography (USG), and CT or MRI. All LPNs were performed by a single surgeon (E.O) in a tertiary care institution via transperitoneal or retroperitoneal access which was previously described in the literature (5,6).

Follow-up consisted of measuring renal functions including serum creatinine (Cr) and estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation in the first-month postoperatively and 3 months thereafter (7). The initial radiologic evaluation by CT was performed in the 3rd month after surgery. USG was used as an imaging modality only if there were normal anatomical findings existed. CT was performed when necessary (8).

Demographic variables and tumor characteristics including age, gender, symptoms, comorbities, serum Cr, and eGFR, hemoglobin (Hb) level, American Society of Anesthesiologists score, tumor size, laterality, radiologic features, and RENAL Nephrometry score were recorded. Peroperative and postoperative data, including duration of operation, type of the ischemia, warm ischemia time (WIT), estimated blood loss, complications, post-operative Cr, Hb, eGFR, hospitalization, surgical margin status and final pathology report were also recorded. Demographic data, operative indications, peroperative and postoperative outcomes and complications were evaluated. Postoperative complications were also categorized according to the Modified Clavien-Dindo classification system. Moreover, trifecta was defined as negative surgical margin, WIT shorter than 20 min and complication free recovery.

Statistical Analysis

Patients' data were expressed as mean ± standard deviation (minimum-maximum). The data were analyzed using Statistics Package for Social Sciences version 24 (IBM SPSS®, Armonk, NY). The functional outcomes including serum Cr and eGFR were evaluated by two-way ANOVA. Hb values were compared with Paired-samples t test. A p value <0.05 was considered significant.

Results

The study included 18 women (85.7%) and 3 men (14.3%) patients whose age range was 29 to 71 years. The mean age was 55.14±11.95 years. While the renal masses were detected incidentally by routine radiological imaging in 20 patients (95.2%), only one patient with tumor size 50 mm and RENAL nephrometry score 8, (4.8%) presented with hematuria. All patients had only one renal mass, 52.4% of the masses were in the right kidney and 47.6% in the left kidney. The mean tumor size was 31.38±16.72 mm and the mean RENAL Nephrometry score was 5.90±1.51 (4,5,6,7,8,9,10). Hypertension was the most frequently detected comorbidity. Seven patients (33.3%) were receiving antihypertensive therapy. Nonetheless, one patient (4.8%) had Diabetes Mellitus and the other one (4.8%) also had coronary artery disease. Demographic data of patients are shown in Table 1.

In the surgical indication analysis, symptomatic RAML was determined in one patient (4.8%). While surgical intervention was performed in 8 patients (38.1%) due to tumor size ≥4 cm, inability to differentiate RAMLs from RCC in 12 patients (57.1%) by preoperative CT and/or MR images. LPN indications for RAMLs are shown in Table 2. Our general clinical management of RAMLs that have been radiologically confirmed as requiring active intervention is primarily the application of SAE. However, we applied LPN in patients who were indistinguishable from RCC radiologically or whose tumor diameter enlarged and

Table 1. Demographic data of patients

Age, years (min-max)	55.14±11.95 (29-71)
Gender, n (%)	
Female	18 (85.7%)
Male	3 (14.3%)
Comorbidity, n (%)	
Hypertension	7 (33.3%)
Diabetes Mellitus	1(4.8%)
Coronary Artery disease	1(4.8%)
Characteristics of the tumor	
>4 cm	7
≤4 cm	14
Mean size, mm	31.38±16.72 (10-60)
Polar	15
Central	6
RENAL score, mean (range)	5.9±1.5 (4-10)
ASA score	
ASA 1	9 (42.9%)
ASA 2	12 (51.7%)

ASA: American society of anesthesiologists, Min: Minimum, Max: Maximum, n: Number

radiological image characteristics changed. Another indication for LPN was the patient's preference.

While 18 (85.7%) patients underwent transperitoneal approach, 3 (14.3%) patients underwent retroperitoneoscopic partial nephrectomy (RPN). In 4 patients, LPN was implemented by off-clamp technique whereas, in 17 patients it was implemented by global ischemia technique. The mean duration of operation was 67.86±20.77 (40-110) minute (min), the mean estimated blood loss was 117.14±59.7 (30-220) milliliters (mL). In 17 patients who underwent LPN with global ischemia technique, the mean WIT was 10.88±5.19 (6-22) min. There was no intraoperative complication however; postoperative complication took place in 3 patients. Two patients were closely followed up in terms of Hemaglobin drop (grade 1), postoperatively. Yet, there was no need for blood transfusion in these patients. The drain of the third patient was withdrawn on the 4th postoperative day due to the prolonged drainage (grade 1). There was also no need for additional treatment or medication in that patient and only follow-up was enough. The mean hospital stay was 2.76±0.62 (2-5) days. All surgical specimens were revealed as AML in the final pathology result. However, the surgical margin was reported as positive in only 1 patient (4.8%). Trifecta was achieved in 18 (85.7%) patients. The mean follow-up was 43.0±26.0 (12-88) months. Intraoperative and postoperative outcomes are shown in Table 3.

In functional analysis, the mean preoperative eGFR value and postoperative 1st day, 1st month, 6th month and 1st year eGFR values were 102.46±23.31, 78.64±19.47, 83.11±18.93, 87.39±21.39, and 93.30±21.65, respectively. Furthermore, the mean preoperative serum Cr level and postoperative 1st day, 1st month, 6th month and 1st year serum Cr levels were 0.70±0.13, 0.88±0.15, 0.83±0.14, 0.80±0.13 and 0.75±0.12, respectively.

Table 2. Indication for laparoscopic partial nephrectomy

	n	%	p value[a]
Hematuria	1	4.8	0.012*
Suspicion of RCC	12	57.1	
Size ≥4 cm	8	38.1	
[a]: Chi-square test, *statistically significant. RCC: Renal cell carcinoma			

Table 3. Intraoperative variables and postoperative complications

Side (R/L), n (%)	10 (47.6%)/11 (52.4%)
Transperitoneal Retroperitoneal	18 (85.7%) 3 (14.3%)
Global ischemia Off-clamp (zero ischemia)	17 (81%) 4 (19%)
Operation time, min	67.86±20.77 (40-110)
Estimated blood Loss, mL	117.14±59.7 (30-220)
Warm ischemia time, min, (n=17)	10.88±5.19 (6-22)
Postoperative complications*	
Hb drop (grade1), n Prolonged drainage (grade 1), n Total	2 (9.5%) 1 (4.8%) 3 (14.3%)
Min: Minute, mL: milliliters, R: Eight, L: Left, *Clavien-Dindo classification, n: Number	

Both the changes in eGFR and serum Cr values were found to be statistically significant in all variance. P values were p=0.001, and p=0.001, respectively. Figure 1 shows eGFR changes and Figure 2 shows serum Cr changes according to time.

Discussion

It has been stated in a population-based screening study with ultrasound in Japan that RAMLs are not common in the general population and overall rate has been reported as 0.13 % in adults. It is also specified that %80 of RAMLs are detected sporadically, whereas 20% of RAMLs are related to TSC (4). The sporadic form of RAML tends to be solitary renal mass. In general, RAMLs have a female predominance. The vast majority of patients are asymptomatic. Nonetheless, the most frightening complication due to RAML is retroperitoneal hemorrhage that is called Wunderlich syndrome. This clinical condition may be sudden, life-threatening as well as painful. It is thought that micro and macro aneurysms that correlated to an increase in tumor size may cause retroperitoneal bleeding (9). Hematuria, flank pain, and palpable renal mass are the other symptoms related to RAMLs (10). Moreover, it has been reported as an exceptional condition that epithelioid AML may behave like a malignant tumor that causes vena cava thrombus (11). In this study, 18 (85.7%) of the 21 patients were female. Only 1 of the 21 patients had symptoms. In this 24-year-old female patient, the main complaint was an unclear loin pain and the detection of microscopic hematuria on urinalysis was the primary finding.

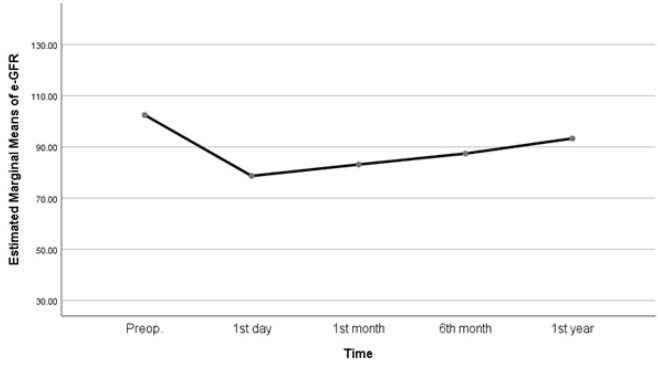


Figure 1. The changes in the mean eGFR values according to time
eGFR: Estimated glomerular filtration rate

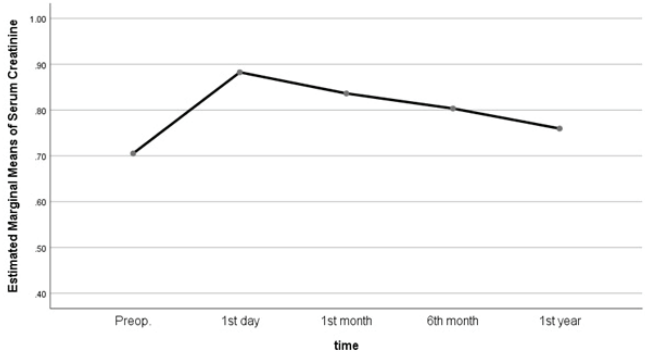


Figure 2. The changes in the mean serum creatinine values according to time

Although the tumor size smaller than 4 cm, LPN was applied upon the patient's preference.

Due to the widespread use of radiological imaging methods, renal masses are being detected earlier. It is declared that CT has a higher sensitivity and specificity to differentiate RAMLs from other renal malignant tumors. However, approximately 5% of RAMLs have devoid of adipose tissue. This is a challenging condition to distinguish oncocytoma and RAMLs with low-fat content from other malignant renal tumors by CT and MRI since fat-free RAMLs can easily imitate RCC (3,12,13). In the present study, RAMLs could not be differentiated from RCC in 12 patients (57.1%) by radiology.

Asymptomatic patients and patients with tumor size <4 cm RAMLs can be candidates for active surveillance. However, the indications for an active intervention for RAMLs are symptomatic masses, suspicion of malignancy, tumor size >4 cm, and women of childbearing age. Besides, patients with RAMLs with aneurysm >5 mm, patients with poor access to follow-up, patients with RAMLs associated with TSC, and patients with retroperitoneal hemorrhage are also candidates for an active intervention and patient's preference can also be an indication for an active intervention (4,14). The most considerable reason for the suggestion of LPN as an active intervention in our cohort was inability to differentiate RAMLs from RCC on radiologic imaging. The second significant reason for applying LPN in the patients was that tumor size was ≥4 cm in 8 patients (38.1%).

In recent years, advance in technology has increased the preference of nephron-sparing minimally invasive approaches including SAE (15), laparoscopic or robot assisted LPN (16,17), as well as laparoscopic or percutaneous cryoablation or RFA in the treatment of RAMLs (18,19). The aims of nephron-sparing approaches are relief of symptoms, preventing life-threatening acute hemorrhagic complications, preserving functional renal parenchyma, and also providing long-term kidney functions (20).

Given the effectivity of SAE, it is especially considered as a first-line treatment option for the management of RAMLs in patients with acute retroperitoneal bleeding, refractory hemodynamic instability or asymptomatic large RAMLs. However, it has been stated that the need for secondary intervention is high owing to recurrent hemorrhage, persistent symptoms or increased tumor diameter (21,22). It is also stated that this condition may be related to large tumor size and etiology (23). The ratio of secondary intervention including re-embolization and need for surgery were declared in the literature as 9.1-64.7% and 2.1-35.3%, respectively (24). Moreover, post-embolization syndrome characterized by fever, loin pain, vomiting or nausea, is the most common complication related to SAE and occurs in 85 % of patients (25). In this study, patients who underwent SAE and were followed up in our clinic were not included in the study. In the vast majority of patients who underwent SAE RAML had been diagnosed radiologically before the intervention. However, in 12 patients (57.1%) who underwent LPN RAML could not be differentiated from RCC by preoperative radiological imaging.

It has been stated that open or laparoscopic nephron-sparing surgery (NSS) for the management of renal tumors up to 4 cm in size in appropriate patients is a safe and effective treatment modality. Furthermore, it is stated that laparoscopic NSS is a safe and effective approach in the treatment of renal tumors larger than 4 cm (26). These recommendations may also be available for nephron-sparing treatment of RAMLs.

In the literature, one of the largest series of open NSS for the treatment of RAMLs was reported by Boorjian et al. (27) In this study, 58 patients with the mean tumor size of 3.9 cm (0.8-12) underwent open NSS with favorable functional results. It was stated that overall complication rate was 12.1%, the mean estimated blood loss was 350 mL (50-1200), and the recurrence rate was 3.4%. In a similar study, Minervini et al. (28) declared that the increase in tumor size was associated with higher intraoperative blood loss, longer ischemia time, and longer hospitalization. Despite the innovations in surgical technique, increase in surgical experience, and technological advances; intraoperative bleeding and WIT are still challenging parameters for LPN in the management of RAMLs. In recent years, it has been declared in a retrospective study that the implementation of SAE before LPN shortens duration of operation (93.7 vs 62.5 min), prolongs WIT (35.5 vs 21.6 min) as well as increases intraoperative blood loss (170 vs 40 mL) in patients with large (>8 cm) RAMLs (29). The outcomes of patients who underwent LPN with the diagnosis of either RCC or RAML were evaluated in two retrospective studies by Simmons et al. (30) (n=35) and by Msezane et al. (31) (n=14). It was stated that there was no difference in terms of duration of operation, blood loss, WIT and positive surgical margin. In a recent study reported by Liu et al. (8), data of 41 patients who underwent retroperitoneoscopic PN with the diagnosis of RAML were evaluated retrospectively. The median tumor size was 11.4 cm (8-23 cm). In 35 patients, the surgery ended up laparoscopically. Conversions to open surgery and to nephrectomy were 9.8% and 4.9%, respectively. The median duration of operation, WIT, and EBL were 167 min, 21 min, and 200 mL, respectively. Intraoperative complications occurred in 5% and postoperative complications occurred in 17.1% of patients. Furthermore, intraoperative blood transfusion was required in 8 patients.

In this study, unlike other studies cited above, a standard surgical approach was not applied to the patients. The transperitoneal or retroperitoneal approach was preferred according to the localization, size, RENAL score of the renal mass as well as the surgeon's preference. In addition, the non-ischemic LPN was performed in 4 patients according to the preoperative tumor and kidney anatomy and vasculature. The mean tumor size was 31.38±16.72 cm (10-60 cm). The mean duration of operation , WIT and EBL were 67.86±20.77 min, 10.88±5.19 min, and 117.14±59.7 mL, respectively. There was no need to convert to open surgery in any patient.

In this study, functional results of nephron-sparing PN in patients with RAML were found to be similar with previous literature (8,28,29). In a systematic review, preoperative renal function, the preserved renal parenchymal volume, WIT, tumor size, age, gender, and comorbidity have been specified as factors affecting functional outcomes after PN. Moreover, preservation of remnant renal parenchyma has also been remarked as more substantial than WIT (32). In this study, the decrease in eGFR and increase in serum Cr values were found

to be more prominent on the first postoperative day compared to preoperative values. The mean difference in eGFR was 23.82 mL/min [95% confidence interval (CI) (11.04-36.01)] when preoperative eGFR value and first postoperative day eGFR valuewere compared. Moreover, at the end of the 1st year, the mean difference was 9.1 mL/min [95% CI (1.06- 17.26)].

Study Limitations

The limitations of this study included small number of subjects, retrospective analysis of patients' data as well as consisting of only one group. Evaluation of preoperative and postoperative split renal functions on the affected kidney would have given precious information in terms of functional outcomes. However, the evaluation of renal functions with renal scintigraphy in patients who underwent PN was not being used in our routine practices. Therefore, a prospective study might be needed for this reason.

Conclusion

Minimally invasive PN is a safe and effective treatment option for the treatment of RAMLs that are not able to be distinguished from RCC radiologically, that are symptomatic and/or large in size (>4 cm).

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

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Ethics

Ethics Committee Approval: Ethics approval was granted by the Ondokuz Mayıs University Clinical Research Ethics Committee (OMU KAEK 2019/157, February 14th, 2019).

Informed Consent: Informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Original Article

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Effect of Multidisciplinary Approach in Diagnosis of Renal Sinus Fat Invasion in Renal Cell Cancer

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Abstract

Objective: In order to make the most appropriate treatment decision for kidney masses, accurate radiological evaluation is vital. In this study, we aimed to discuss how would be the concordance between a multidisciplinary approach to renal masses and the histopathological outcome.
Materials and Methods: Between June 2017 and July 2019, 75 patients who were evaluated for complex renal tumors at the Council of Uroradiology and treated at our clinic were included in the study and their clinical-pathological data were examined. After radiological reporting, all patients were re-evaluated in this council consisting of 4 urologists and 2 radiologists.
Results: Forty-three patients underwent partial nephrectomy and 32 patients underwent radical nephrectomy. Malignant histopathology was present in 85.3% of patients. The mass was solid in 35 patients and was of cystic nature in 40 patients. Cystic and solid component assessments were similar in both groups. There was no difference between the two groups in terms of tumor node metastasis staging. Subgroup analysis showed that the correlation between radiological T3 and pathological T3 was not significant in radiology reports. However, this correlation was significant in the council assessment ($p<0.001$).
Conclusion: As a result, the more important factor than the surgical method is which masses will be operated on and which masses will be monitored. Especially in complex patients, it is important to take this decision with a multidisciplinary approach and, if possible, with a team collaboration. Multidisciplinary evaluation has enabled us to achieve better results in determining the T3 stage, which is a factor that can change the surgical method and patient follow-up.
Keywords: Council, multidisciplinary, RCC, renal sinus invasion, uroradiology

Introduction

Renal cell cancer (RCC) accounts for 2-3% of all cancers. Along with improvements in imaging methods, there is an increase in incidental detection rates (1,2). Accurate clinical staging at the time of diagnosis by computerized tomography (CT) or magnetic resonance imaging (MRI) is very important for providing information about primary tumor spread, venous involvement, locoregional lymph nodes, adrenal glands, surrounding solid organs and the status of the kidney of the opposite side (3). Clinical staging is done according to the current "tumor node metastasis" (TNM) staging. Tumor size, renal sinus invasion (RSI), venous invasion, renal capsule involvement, adrenal involvement, lymph node metastasis and distant metastasis are the parameters that are used in classification (4). In particular, RSI stands out as the basic step to see the local spread of the tumor, indicating that the tumor has entered the T3a stage in the TNM classification (5). In predicting RSI by imaging methods, the most important factor is the involvement of the pelvicalyceal system (6). In the treatment of T3a stage tumors, radical nephrectomy is the first option.

Patient management based on decisions which are made by multidisciplinary teams is becoming increasingly common worldwide. Studies have shown that, thanks to multidisciplinary decisions, significant changes are achieved in diagnosis/staging, patient management (7,8) and even survival (9,10,11). In this study, the predictive role of evaluation made primarily at the Council of Uroradiology (CoU) on RSI was aimed to be seen. Second, it was aimed to see the superiority of the CoU in distinguishing the benign-malignant or cystic-solid nature of the masses.

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Materials and Methods

There were 212 patients who had renal mass detected at the urology outpatient clinic and re-evaluated at the CoU. Seventy five out of 212 patients who underwent radical or partial nephrectomy were included in the study between June 2017 and July 2019. Ethics committee approval was obtained from our institution. Informed consent form was taken from all of the patients. Pathological assessment was treated as a gold standard diagnosis. The most of first radiological evaluation was performed by the "service procurement" radiologists and 10% by our hospital's radiologist. Contrast enhanced CT or dynamic MRI imaging of the patients were evaluated for the second time at the CoU, which consisted of 4 experienced urologists and 2 experienced radiologists (Figure 1).

In this council; the data of radiological dimensions, side, localization, clinical RSI, clinical T stage, cystic nature (if present) and Bosniak classification, lymph node involvement and distant metastasis of the tumor were kept regularly. The same informations in the radiology report were retrospectively scanned and added to the data. In this way, two groups were formed as the radiology report and the CoU report. The patient's demographic data, surgical methods used, pathological histological diagnosis, pathological RSI, T stage, and Fuhrmann grade were scanned. Two groups were compared in terms of diagnostic sensitivity, specificity, positive and negative predictive values and in terms of diagnostic compatibility inside the group (Figure 2: Patient selection diagram).

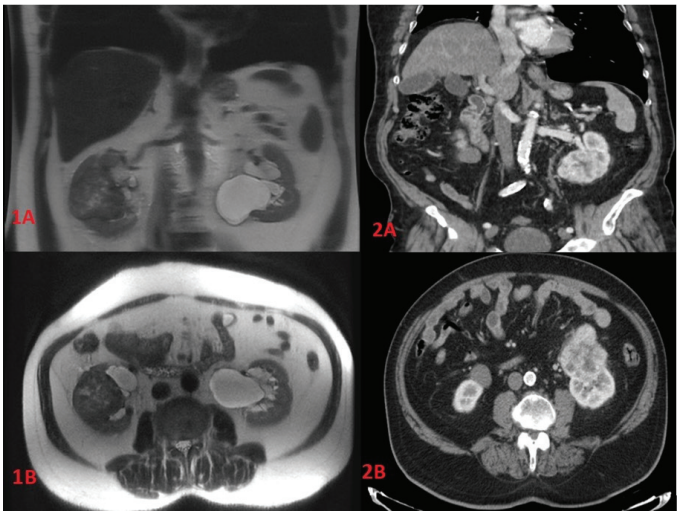


Figure 1. Renal masses with renal sinus invasion

1A: Coronal T2-weighted MR imaging, 1B: Axial T2-weighted MR imaging

2A: Coronal contrast enhanced CT imaging, 2B: Axial contrast enhanced CT imaging

MR: Magnetic resonance

CT: Computer tomography

Dynamic MR imaging of patient 1 who was a 63-year-old male: The mass in the mid-zone of the right kidney, which was 62 mm in size, was interpreted by the expert radiologist as T1b (group 1). It was interpreted as T3a in the CoU (group 2) and laparoscopic radical nephrectomy was performed. The pathology result was as follows: Clear cell RCC, Fuhrmann grade -1, stage T3a.

Contrast enhanced abdominal CT imaging of patient 2 who was a 77-year-old male: The mass in the lower pole of the left kidney, which was 90 mm in size, was interpreted by the expert radiologist as T2a (group 1). It was interpreted as T3a in the Council of Uroradiology (group 2) and laparoscopic radical nephrectomy was performed. The pathology result was as follows: Clear cell RCC, Fuhrmann grade -2, stage T3a.

Statistical Analysis

Pearson correlation analysis was performed to determine the compatibility between the two groups and it was considered significant when the p value was less than 0.05.

Results

Forty three of the patients underwent partial nephrectomy (57.3%) and 32 (42.7%) underwent radical nephrectomy. Fifty nine of these patients (78.7%) underwent laparoscopic surgery and 16 (21.3%) underwent open surgery. 35 (46.7%) of the tumors were solid and 40 (53.7%) were of cystic nature. Pathological evaluation of the patients revealed malignant histopathology in 64 patients (85.3%) and benign histopathology in 11 patients (14.7%). The most common histology, clear cell RCC, was found in 45 (60%) patients. Renal masses were most commonly found in the T1a stage in pathological diagnosis [30 patients (40%)], while 13 (17.3%) were found to be in the T3a stage (Table 1). Cystic and solid mass assessments and pathological findings were similar between both groups (Table 2). In predicting RSI, there was no correlation between radiological and pathological T3a in group 1, while there was correlation between them in group 2 ($p<0.0004$). In the first group, sensitivity was 15.4%, specificity was 93.9%, positive predictive value was 33.3% and negative predictive value was 84.1% for RSI. In the second group, sensitivity was 61.5%, specificity was 95.1%, positive predictive value was 72.7% and negative predictive value was 92.2% for RSI. When the correlation between the two groups was examined, the kappa coefficient (κ) was found to be - 3.1 (Table-3).

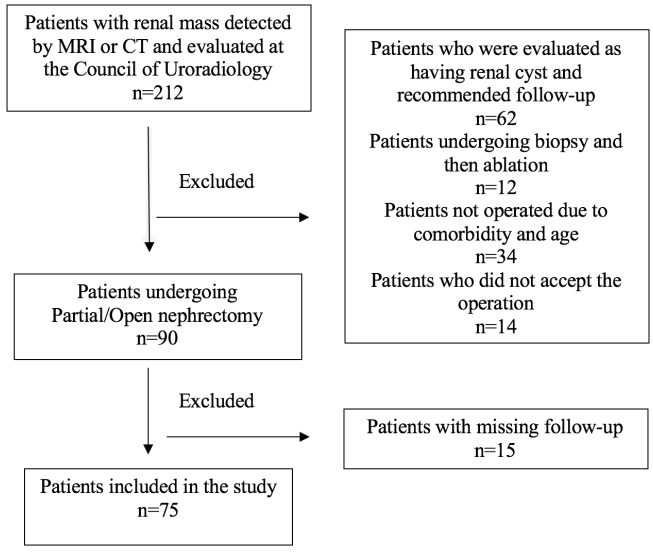


Figure 2. Patient selection diagram

MRI: Magnetic resonance imaging, CT: Computer tomography, n: Number

Table 1. Clinical and pathological features	
Age, mean	59.9±12.4 (30-81)
Radiological size, median (mm)	42.0±28.1 (18-190)
Pathological size, median (mm)	45±27.2 (12-170)
Gender Male/Female	48/27
Side, right/left	39/36
Localization, upper/middle/lower	22/35/18
Surgical technique, Open/Laparoscopic	16/59
Surgical method Partial Nephrectomy/Radical Nephrectomy	43/32
pT	
T1a	30
T1b	16
T2a	5
T2b	2
T3a	13
T3b	1
Histological Type	
Clear cell RCC	45
Papillary type-1 RCC	2
Papillary type-2 RCC	2
Chromophobe RCC	9
Other RCC	4
Oncocytoma	4
Angiomyolipoma	4
Other benign	3
Fuhrmann Grade	
Grade1	27
Grade2	17
Grade3	5
Grade4	1
Nonspecified	25
RCC: Renal cell cancer	

Table 2. Histopathological compliance of solid-cystic masses

1.Group: Radiologist-Pathology Compliance

Radiological Evaluation	Histopathological Evaluation		Total
	Malignant	Benign	
Solid Renal Mass	29 (82.9%)	6 (17.1%)	35
Cystic Renal Mass	35 (87.5%)	5 (12.5)	40
	64	11	75

2.Group: Council of Uroradiology and Pathology Compliance

Council of Uroradiology Evaluation	Histopathological Evaluation		Total
	Malignant	Benign	
Solid Renal Mass	31 (83.8%)	6 (16.2%)	37
Cystic Renal Mass	33 (86.8%)	5 (13.2%)	38
	64	11	75

Table 3. Intergroup correlation in detecting renal sinus invasion

1.Group: Radiologist-pathology Compliance

	Histopathological Evaluation		Total
Radiological Evaluation	RSI+	RSI-	
RSI+	2	4	6
RSI-	11	58	69
	13	62	75

Pearson Correlation p=0.282

2.Group: Council of Uroradiology and Pathology Compliance

	Histopathological Evaluation		Total
Council of Uroradiology Evaluation	RSI+	RSI-	
RSI+	8	3	11
RSI-	5	59	64
	13	62	75

Pearson Correlation p=0.0004

Detection of RSI with MRI or CT		
	Group-1	Group-2
Sensitivity	15.4%	61.5%
Specificity	93.9%	95.1%
Positive Predictive Value	33.3%	72.7%
Negative Predictive Value	84.1%	92.2%
RSI: Renal sinus invasion, MRI: Magnetic resonance image, CT: Computer tomography		

Discussion

For the diagnosis of RCC, CT or MRI are the appropriate diagnostic methods. In the interpretation of these images, differences in opinion among radiologists are often encountered. As a result of these differences; follow-up, decision of operation and operation types can change completely. Renal masses are basically divided into two parts as cystic and solid. Diagnosis of cystic complex masses can sometimes be more complicated. Sundi et al. (7) showed in their prospective study that sensitivity of CT was 36% and specificity of CT was 76%, while sensitivity of MRI was 71% and specificity of MRI was 91% in complex cystic masses. The Bosniak classification, first defined in 1986, is also routinely used today for the classification of cystic masses (12). Yonguc et al. (13) showed that 77.6% of Bosniak type 3 and 4 cysts were histopathologically malignant. Similarly, in our study, the histopathology of 87.5% of cystic renal masses in the first group and 86.8% of cystic renal masses in the second group were malignant. On the other hand, differences in opinion in the diagnosis of Bosniak grade 2, 2F and 3 cysts are more often

encountered than Bosniak grade 1 and 4 cysts. In both studies, it was observed that the alignment between radiologists was moderate in Bosniak 2-3 cysts (14,15). In our study, 40 out of 75 patients (53.3%) were evaluated as having cystic renal mass in group 1, while 38 out of 75 patients (50.7%) were evaluated as having cystic renal mass in group 2. Malignant characteristics of cystic masses were also found to be similar in both groups (87.5% vs. 86.8%).

In patients undergoing nephrectomy, detection of RSI is defined as pT3a according to TNM staging. According to many studies, positivity of RSI is associated with poor prognosis. Pre-diagnosis of these patients is possible with preoperative imaging. Thompson et al. (16) indicated that the patients who underwent radical nephrectomy, were shown as having pT1 stage and died in follow-up had more RSI. Of the 577 patients identified as having pT1 stage disease, 49 died in 17-year follow-up. Among these patients, original specimens of 33 were re-examined and 14 (42%) of these patients were found to have RSI. García Marchinena et al. (17) reported that RSI was associated with poor prognosis. Bedke et al. (18) showed that perinephric and renal sinus fat invasion was identified as a poor prognostic marker in their study involving 106 patients with T3a tumors. Five-year cancer-specific survival was indicated as 31% when both were positive. Therefore, prior recognition of RSI is very important in the follow-up of the disease. Bolster et al. (19) showed that tumor size, location, irregular tumor boundaries and invasion of the pelvic system were the most important factors in determining RSI during the preoperative period.

In our study, it was observed that the point at which the two groups diverged was RSI. When only the radiology report was taken; the sensitivity of detection of RSI was 15.4%, specificity was 93.9%, positive predictive value was 33.3%, negative predictive value was 84.1% and there was no correlation between the pathologist and the radiologist in the correlation analysis. On the other hand; sensitivity was 61.5%, specificity was 95.1%, positive predictive value was 72.7% and negative predictive value was 92.2% in group 2 and there was correlation between the pathologist and the radiologist. When the Kappa value was calculated to measure the alignment between the two groups, it was calculated as - 3.1, and this showed that there was a serious disagreement between the two groups. Renard et al. (20) evaluated the detection of T3a renal masses by multidetector CT and showed that the alignment between two radiologists was poor. Bolster et al. (19) observed that there was a moderate level of alignment between two radiologists in determining RSI. Taking this decision in the CoU affected the surgeon's decision of operation and had a primary effect on partial and radical nephrectomy decision in patients with T3a tumor. Radical nephrectomy is also recommended for T3a tumors except for very rare publications in the literature (21).

Many previous studies have indicated that multidisciplinary approach leads the management of patients in a critical way. Kurpad et al. (22) showed that diagnosis or treatment of 38% of 269 patients with urological malignancies changed, especially in bladder and kidney cancer, when they were evaluated multidisciplinarily. Pillay et al. (23) evaluated the effects of decision making following a multidisciplinary approach on diagnosis, staging, patient management and patient survival in oncology patients in the systematic review of 27 studies. This review showed that between 4% and 45% of patients had a change in diagnosis. It was determined that patients who were evaluated as multidisciplinary received treatments more appropriate to the current guidelines, had more appropriate staging, and received neoadjuvant and adjuvant therapy more frequently.

Study Limitations

This study is the first to demonstrate the importance of multidisciplinary approach in predicting RSI. The limitations of the study included that it was retrospective and that it was conducted with relatively few patients. The lack of patients' survival data could be demonstrated among the limitations. The lack of information about which radiologist in the service procurement evaluated CT and the experience of this radiologist, the lack of data on whether there was difference between CT and MRI could be seen as limitations of the study.

Conclusion

The multidisciplinary approach to detecting RSI has higher sensitivity, specificity, positive and negative predictive values than radiology reporting. In terms of RSI, the surgeon's re-evaluation of the imaging with the radiology team during the preoperative period will significanty affect the approach to these patients in terms of decision of radical/partial nephrectomy.

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Ethics

Ethics Committee Approval: The study was approved by İstanbul Medeniyet University, Göztepe Training and Research Hospital Committee (approval no: 2020/0198)

Informed Consent: Informed consent form was taken from all of the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.Ö.K., M.Ç.Ç., A.Y., Design: H.Ö.K., M.Ç.Ç., Data Collection or Processing: H.Ö.K., M.Ç.Ç., A.İ., M.K.A., Analysis or Interpretation: A.Y., R.G.A., N.G., Literature Search: N.G., Writing: H.Ö.K., M.Ç.Ç.

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Original Article

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The Effect of Tumor Localization and Clinicopathological Factors on Intravesical Recurrence and Survival in Primary Upper Urinary Tract Urothelial Tumors

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Abstract

Objective: We aimed to investigate the factors affecting intravesical recurrence and survival in patients undergoing radical nephroureterectomy and bladder cuff excision due to primary upper urinary system urothelial tumor (UUST) in our clinic.

Materials and Methods: The data of 52 patients who were operated for primary UUST between 2008 and 2018 were retrospectively evaluated. All patients underwent preoperative computed tomography and magnetic resonance urography. Tumor localizations were grouped according to the ureteropelvic compound. During the follow-up period after radical surgery, the patients underwent physical examination, routine blood tests and radiological evaluation. The patients were followed up quarterly in the first two years, every six months for the next two years and then yearly with cystoscopy.

Results: Thirteen female and 39 male patients with an average age of 60.5±10.35 years were included in the study. Mean follow-up time was 66.8±38.2 months. Thirty (58%) patients had renal tumors, 13 (25%) patients had ureteral tumors and 9 (17%) patients had multifocal tumors. Intravesical recurrence was detected in 9 (69%) patients with ureteral tumor (p=0.047). Ten-year overall survival of patients with ureteral tumors was 50% (35.4% side effect) (Log rank test=0.012). Recurrent-free survival was significantly worse in ureteral tumors (Hazard ratio:3, p=0.04).

Conclusion: The ureteral tumor group was significantly worse in terms of postoperative intravesical recurrence and overall survival and recurrence-free survival.

Keywords: Urothelial carcinoma, intravesical recurrence, cancer, ureters

Introduction

Urothelial tumors of the upper urinary tract (UUST) are extremely rare tumors, accounting for approximately 5-10% of all urothelial tumors (1). Pyelocaliceal tumors are more than twice as likely as isolated ureteral tumors, and 17% of UUSTs have simultaneous bladder cancer. After treatment, bladder recurrence is observed in 22-47% and contralateral UUST recurrence in 2-6% (1). Preoperative prognostic markers in UUST include tumor diameter, grade, localization, multifocality, hydronephrosis, and gender. Postoperative prognostic markers in UUST are stage, grade, lymph node involvement and histological variant of the tumor (1,2). The disease is approximately 60% invasive at the time of diagnosis and the gold standard treatment method is radical nephroureterectomy (RNU) and lymph node dissection involving bladder cuff excision. Local advanced disease and lymph node metastasis are detected in approximately 20-40% of patients at the time of diagnosis. Although RNU and bladder cuff excision are performed, 5-year disease-specific mortality rates are 15% in pT2N0 disease, 45% in pT3N0 disease and 88% in pT4N0 disease (2).

A new meta-analysis have identified significant determinants of postoperative intravesical recurrence (PIVR) after RNU (3). Patient-specific factors are male gender, previous bladder cancer, smoking, and preoperative chronic renal disease; tumor-specific factors are preoperative positive urine cytology, tumor localization multifocality, pathologic stage, and necrosis; and treatment-specific factors are laparoscopic approach, surgical removal of the bladder cuff by extravesical route and positive surgical boundary (3).

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In this study, we investigated age, genderw, presence of preoperative hydronephrosis, smoking, tumor localization, and the effect of surgical technique and pathological stage on PIVR and survival in patients with primary UUST.

Materials and Methods

Our study included 52 patients who underwent RNU due to primary UUST between 2008 and 2018. The data from the urological cancers database, which were being recorded prospectively in our clinic, were retrospectively evaluated for this study. Computed tomography urography and magnetic resonance urography were used for preoperative imaging of patients. Tumors were divided into three groups according to their localization, according to ureteropelvic junction (UPJ):

I. Tumors above UPJ: Renal tumors.

II. Tumors below UPJ: Ureteral tumors.

III. More than one tumor in both kidneys and ureters, or single tumor that takes up space both below and above UPJ: Multifocal tumors, i.e. tumors placing in kidney and ureter.

All patients' urine was evaluated cytologically during preoperative period. Thirty-three patients underwent ureterorenoscopy (URS) before radical surgery. Sixteen of these underwent biopsy and mass was seen in the collector system in 17 patients and they did not undergo biopsy.

RNU was performed with standard open (4) and laparoscopic methods. In laparoscopic RNU, two different methods were applied for the distal ureter. In 12 of the patients, after the nephrectomy was completed laparoscopically, the bladder cuff excision was performed by the open method. In 20 of the 5 patients, intraoperative distal ureteral and intravesical chemotherapy techniques were applied during laparoscopic RNU and for this, the operation was started in lithotomy position. A ureteral catheter was inserted into the ureter so that the tip remained distal to the tumor, and then it was fixed to urethral catheter. Then, the position was changed to laparoscopic RNU. In the early stage of the operation, after the ureter was found and clamped in the distal part of the tumor level and after the patient's urethral catheter was also clamped; Mitomycin (20 mg) or Epirubicin (50 mg) diluted in 50 mL distilled water was given from the ureteral catheter, while in a small number of patients in whom these were not found, distilled water was slowly administered. When irrigation was completed, the ureteral catheter was removed and the urethral catheter remained closed. Thus, the chemotherapeutic agent was allowed to wash the distal part of ureter and wait in the bladder until the cuff excision. Just prior to the cuff excision, the bladder was emptied and extensively irrigated. Following this, the cuff excision was performed by incising detrusor fibers all the way to the bladder mucosa circumferentially and attaching clips to the bladder mucosa, including the ureteral orifice and the surrounding area.

Paraortic and iliac lymph node dissections were performed in both open and laparoscopic methods and the operation was completed.

There were two patients who underwent radical nephrectomy because urothelial carcinoma (UC) was not considered at the forefront in preoperative examinations. In the histopathological examination of these patients, UC was detected and ureteral stump and bladder cuff excisions were applied.

Statistical Analyses

Statistical analyses were performed in SPSS V23.0 program and $p<0.05$ was considered statistically significant. The chi-square test for categorical variables, Kaplan-Meier test for survival analysis, and single and multivariate Cox regression analyses were used. Ethics committee approval was received for this study from the Ethics Committee of Çukurova University (approval number: December 2018,7).

Results

In our study, 13 of 52 (25%) patients who underwent surgery for UUST were female and 39 (75%) were men and they had an average age of 60.5±10.35 (38-86) years. Forty (76.9%) patients had cigarette use, while 12 (23.1%) patients did not. At the time of diagnosis, 31 (59.6%) patients had hematuria, while 21 (40.4%) patients had no hematuria. The cytology of 17 (32.7%) patients was positive for malignancy and the cytology of 35 (67.3%) patients was negative. In preoperative imaging, 25 (48.1%) patients had hydronephrosis, while 27 (51.9%) patients had no hydronephrosis. The mean tumor diameter of the patients was 4.58±2.18 (1-10) cm. Renal tumor was found in 30 (57.7%) patients, ureteral tumor was found in 13 (25%) patients and both renal and ureteral tumors (multifocal localization) were found in 9 (17.3%) patients.

Thirty-three (63%) patients underwent URS before radical surgery. Sixteen (30%) patients underwent a biopsy, while a mass was found within the collector system in 17 (32%) patients and they did not undergo biopsy. Histopathological examinations of biopsies performed during URS were reported as suspicious UC in 4 patients, UC with unspecified grade in 2 patients, low grade UC in 8 patients and high grade UC in 2 patients.

Twenty (38.5%) patients underwent open RNU and 32 (51.5%) patients underwent laparoscopic RNU and lymph node dissection. In histopathological evaluation, low grade UC was found in 12 (23.1%) patients and high grade UC was found in 40 (76.9%) patients. There was no sign of carcinoma in situ in specimens.

Histopathology of 16 out of 17 patients with positive preoperative urinary cytology and 24 out of 35 patients with negative preoperative urinary cytology was reported as high grade UC ($p>0.05$). The histopathology of 20 out of 25 patients with preoperative hydronephrosis and 20 out of 27 patients without hydronephrosis was reported as high grade UC ($p>0.05$). Histopathological gradings according to tumor localization are given in Table 1. Nineteen of the patients included in our study were older than 66 years and all were reported as having high grade UC histopathology. Of the 33 patients under the age of 66 years, 12 had low grade UC histopathology and 21 had high grade UC histopathology (Table 2) ($p=0.02$).

In postoperative follow-up, PIVR was found in 22 (42.3%) patients. PIVR was found in 7 (41%) of 17 patients with positive preoperative urinary cytology and in 15 (42%) of 35 patients

with negative preoperative urinary cytology (p>0.05). PIVR was observed in 15 (60%) of 25 patients with preoperative hydronephrosis, while PIVR was observed in 12 (44%) of 27 patients without preoperative hydronephrosis (p>0.05). PIVR was not found in 17 (42%) of 40 patients who smoked and PIVR was found in 5 (41%) of 12 patients who did not smoke (p>0.05). PIVR was found in 17 (51.5%) of 33 patients who underwent URS, while PIVR was found in 5 (26.3%) of 19 patients who did not undergo URS (p=0.07). The frequency of PIVR was similar in patients who underwent laparoscopic or open surgery (40.6% and 45%, respectively) (p>0.05). PIVR ratios according to tumor localization are given in Table 3.

The mean duration of follow-up was 66.8±38.2 months in postoperative period and 2 patients died due to cancer-related causes and 4 patients died due to non-disease causes. Ten patients were not included in the survival analyses because they could not be reached.

Five-year overall survival (OS) according to tumor localization was 95% [4.1% side effect (SE)] in renal tumors, 100% in ureteral tumors, 83% (15% SE) in tumors with multifocal localization. Ten-year OS was 76% (17.4% SE) in renal tumor, 50% (35.4% SE) in ureteral tumors, 27% (23.2% SE) in tumors with multifocal localization [95% confidence interval (CI), 61-92], (p=0.012), (Figure 1).

Five-year recurrence-free survival (RFS) according to tumor localization was 63% (8.9% SE) in renal tumors and 28% (13.1% SE) in ureteral tumors (95% CI, 12-23), (p=0.082), (Figure 2).

In Tables 4 and 5, the results of the single and multivariate Cox regression analyses to predict OS and RFS, respectively are given. There was a significant difference between groups in terms of OS in favor of tumors with multifocal localization in single variable regression analysis (p<0.05), (Table 4). Although ureteral tumors had lower RFS, there was no statistically significant difference [p=0.05, hazard ratio (HR)]. The parameters involved in multivariate regression analysis were tumor localization, grade of tumor, pathological stage of tumor, lymph node involvement, preoperative URS and intraoperative Mitomycin/Epirubicin application. There was a significant difference between groups in terms of RFS in favor of ureteral tumors in multivariate regression analysis (p=0.04, HR: 3). Also, N1 stage lymph node involvement was found to be statistically significantly associated with lower RFS in multivariate regression analysis (p=0.01, HR:32).

Discussion

UUST constitutes approximately 5-10% of all urothelial tumors

Table 2. Relationship between patient age and postoperative histopathological grade of tumor

Age (year)	Histopathological grade of tumor		p
	Low n=12, 23%	High n=40, 77%	
≤65	12 (100)	21 (53)	**0.02**
≥65	0 (0)	19 (47)	

Table 1. The relationship of clinical and histopathological data of patients undergoing radical nephroureterectomy due to upper urinary system urothelial tumor with tumor localization

		Tumor localization			
	Patient (%)	Renal n= 30, 58%	Ureteral n= 13, 25%	Multifocal n= 9, 17%	p
Age (med, min-max)	60 (38-86)				0.493
<65	33 (63)	18 (60)	10 (76)	5 (55)	
≥65	19 (37)	12 (40)	3 (24)	4 (45)	
Gender					0.449
Male	39 (75)	24 (80)	8 (61)	7 (77)	
Female	13 (25)	6 (20)	5 (39)	2 (23)	
Technique					0.095
Open	20 (38)	13 (43)	2 (15)	5 (55)	
Laparoscopic	32 (62)	17 (57)	11 (85)	4 (45)	
Stage					0.157
T1	19 (36)	9 (30)	8 (61)	2 (22)	
T2	10 (19)	7 (24)	2 (15)	1 (11)	
T3	13 (25)	8 (26)	3 (24)	2 (22)	
T4	10 (20)	6 (20)	0 (0)	4 (45)	
Pathological grade					**0.01**
Low	12 (23)	4 (13)	7 (53)	1 (11)	
High	40 (77)	26 (87)	6 (47)	8 (89)	
Lymph node involvement					0.485
N0	42 (81)	22 (73)	12 (92)	8 (89)	
N1	1 (2)	1 (3)	0 (0)	0 (0)	
N2	7 (14)	6 (21)	1 (8)	0 (0)	
N3	2 (3)	1 (3)	0 (0)	1 (11)	
Follow-up (med, min-max)	61 (12-169)	53 (13-134)	63 (12-112)	77 (29-169)	0.22

Min: Minimum, Max: Maximum, n: Number

Table 3. The effect of tumor localization and surgical applications on postoperative intravesical recurrence in patients undergoing radical nephroureterectomy due to upper urinary system urothelial tumor

	Patient (%)	Intravesical recurrence		
		Yes (n=22, 42%)	No (n=30, 58%)	p
Tumor localization				
Renal	30 (58)	11 (50)	19 (63)	**0.047**
Ureteral	13 (25)	9 (41)	4 (13)	
Multifocal	9 (17)	2 (9)	7 (24)	
Diagnostic ureterorenoscopy				0.077
Done	33 (63)	17 (77)	16 (53)	
Not done	19 (37)	5 (23)	14 (47)	
Technique				0.756
Open	20 (38)	9 (41)	11 (37)	
Laparoscopic	32 (62)	13 (59)	19 (63)	
Epirubicin				0.756
Done	20 (38)	9 (41)	11 (37)	
Not Done	32 (62)	13 (59)	19 (63)	

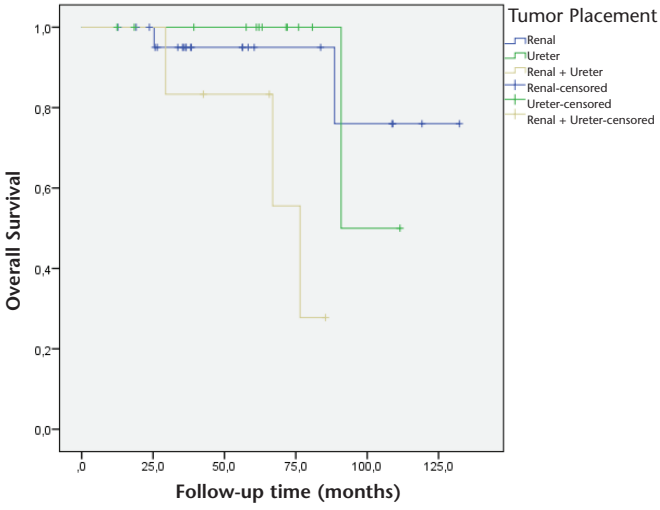


Figure 1. Effect of tumor localization on overall survival. Log- rank test=0.012

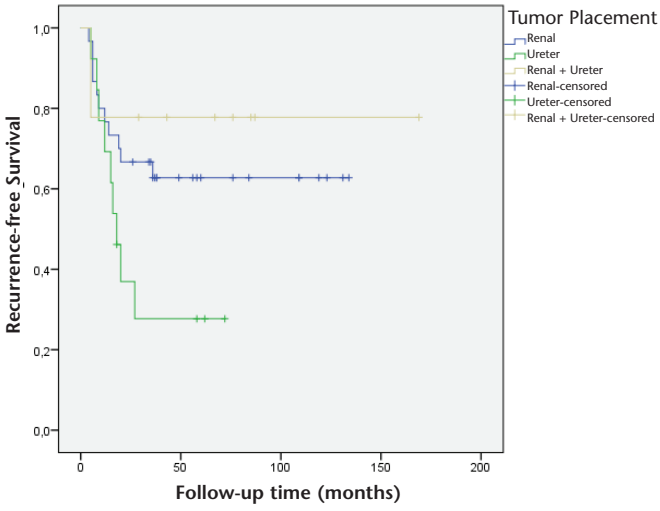


Figure 2. Effect of tumor localization on recurrence-free overall survival. Log-rank test=0.082

(1). Preoperative prognostic markers include tumor diameter, grade, tumor localization, multifocality, hydronephrosis, and gender. Postoperative prognostic markers include stage of the tumor, its grade, histological variant and lymph node involvement (1,2,3,4,5,6). Different approaches can be applied to patients divided into low and high risk groups according to preoperative and postoperative markers. Patients in the high risk group are treated with RNU, which is the gold standard treatment method, while patients in the low risk group may be treated with Nephron-sparing surgery methods.

PIVR is an important problem that should not be overlooked in patients undergoing surgical treatment due to UUST. Therefore, identifying high-risk patients with respect to PIVR can contribute to the quality of monitoring and the survival of patients who develop PIVR by ensuring that follow-up protocols are regulated accordingly. Therefore, the number of various studies examining different risk factors in the literature increases over time.

In the literature, an increase in postoperative mortality and PIVR risk has been reported in patients using tobacco products, especially cigarettes (7). In our study, there was no significant increase in postoperative bladder recurrence in smoking patients (p>0.05). Although there is no threshold value to predict the effect of cigarette consumption on PIVR, it has been thought that this may be related to the amount of cigarette consumption.

There are studies in the literature showing that preoperative hydronephrosis increases the risk of PIVR by indirect means (3). No significant relationship between preoperative hydronephrosis and histopathological grade and IVR was found in our study (p>0.05). The relationship of preoperative hydronephrosis with PIVR was shown in large series and meta-analyses and we thought that we encountered a different result from the literature due to the small number of patients in our study.

Another risk factor for PIVR is the surgical approach. In a meta-analysis of clinicopathological factors effecting PIVR, laparoscopic approach has been reported to increase the risk of PIVR compared to open surgery (2,3,4,5,6,7,8). However, there was no significant relationship between the surgical techniques and PIVR in our study (p>0.05) (Table 3). There was no difference in terms of PIVR between the two different methods used for bladder cuff excision in our clinic, suggesting that both techniques were oncologically safe.

Table 4. Single and multivariate Cox regression analyses showing the effects of prognostic markers on overall survival in patients undergoing radical nephroureterectomy

	Univariate analysis			Multivariate analysis		
Parameter	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Tumor localization						
Renal	1	Ref	-	1	Ref	-
Ureteral	0.9	0.8-10	0.98	1.8	0-86	0.88
Multifocal	13.6	1.1-158	**0.03**	2.23	0-349	0.87
Tumor grade	30	0.6-167	0.4	1.4	0-108	0.98
Tumor Stage						
T1	1	Ref	-	1	Ref	-
T2	0.8	0-3253	0.98	1.01	0-5.81	0.99
T3	21	0-3267	0.61	2.44	0-145	0.97
T4	1060	0-46760	0.36	339	0-1917	0.81
Lymph node involvement						
N0	1	Ref	-	1	Ref	-
N1	3.4	0.3-35	0.3	7.5	0-5423	0.65
N2	0	0	0.9	0.1	0-315	0.67
N3	11.7	0.9-139	0.05	8.8	0-3060	0.59
Ureterorenoscopy	0.7	0.1-4	0.7	1.04	0.9-119	0.98
Epirubicin/Mitomycin	0.8	0.1-4.5	0.8	0.8	0.1-129	0.95

CI: Confidence interval, HR: Hazard ratio

Table 5. Single and multivariate Cox regression analyses showing the effects of prognostic markers on recurrence-free survival in patients undergoing radical nephroureterectomy

	Univariate analysis			Multivariate analysis		
Parameter	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Tumor localization						
Renal	1	Ref	-	1	Ref	-
Ureteral	2.2	0.9-5.4	0.07	3	1.01-8.9	**0.04**
Multifocal	0.6	0.1-2.7	0.5	0.7	0.1-5	0.7
Tumor grade	0.8	0.3-2.1	0.6	1.7	0.4-7	0.4
Tumor Stage						
T1	1	Ref	-	1	Ref	-
T2	1.5	0.5-4.1	0.38	1.5	0.39-5.7	0.54
T3	0.4	0.1-1.4	0.17	0.2	0.03-1.6	0.15
T4	0.5	0.1-2.06	0.38	0.6	0.07-6.7	0.74
Lymph node involvement						
N0	1	Ref	-	1	Ref	-
N1	7.7	0.9-64	0.05	32	2.08-505	**0.01**
N2	0.5	0.1-2.4	0.43	0.9	0.1-5.9	0.93
N3	1.2	0.1-9.4	0.82	2.1	0.1-33	0.59
Ureterorenoscopy	0.4	0.1-1.1	0.1	0.7	0.2-2.3	0.59
Epirubicin/Mitomycin	1.08	0.4-2.5	0.8	0.93	0.3-2.8	0.9

CI: Confidence interval, HR: Hazard ratio

There are studies showing that gender is related to PIVR in UUST. Tanaka et al. (9) reported an increased risk of PIVR in men in the study involving 474 patients. However, Seisen et al. (3) found no significant relationship between gender and PIVR in their meta-analysis including 5376 patients including that study. In our study, there was no correlation between gender and PIVR in line with this meta-analysis ($p>0.05$).

It has been reported that patients' cancer-specific survival may decrease as age increases (10,11,12). There is no clear information in the literature regarding one-to-one relationship between tumor grade and PIVR. In our study, tumor grades were higher in patients in the middle or above age group (≥66 years) (13), ($p<0.05$). Cancer-specific survival rate was not measured in our study, because mortality due to cancer was limited to 2 patients in our patient series.

In our study, when the relationship between tumor localization and postoperative tumor grade was examined, it was determined that the postoperative tumor degree in renal tumors was higher than ureteral tumors ($p<0.05$) (Table 1). In the literature, there was no significant difference in between renal and ureteral tumors in terms of postoperative histopathological grades in large series (14,15).

Baboudjian et al. (14) compared 1041 patients with pre-RNU URS with 2909 patients without URS in terms of PIVR in their

review in 2019 and found that recurrence was higher in the URS group ($p<0.05$). Although there was no significant difference in terms of PIVR between "URS" and "No URS" groups in our study, it was thought that if the number of patients was higher, the data could be compatible with the literature ($p=0.07$) (Table 3) (16).

Pyelocaliceal tumors are more than twice as common as isolated ureteral tumors (1,15). The prognosis of ureteral or multifocal tumors has been shown to be worse than that of renal pelvis tumors, when all UUSTs are taken into account (14,15,17,18). Yafi et al. (12) showed in their study performed in 637 patients who underwent RNU and bladder cuff excision due to UUST, that 5-year survival rate was lower and cancer-specific mortality rate and recurrence were higher in patients with ureteral tumor compared with patients with renal tumor. Our study also showed that the overall survival of patients with ureteral tumor was lower than patients with renal tumor (95% CI, 61-92) ($p=0.012$) (Figure 1).

Seisen T et al. (3) screened 12 publications evaluating the effect of tumor localization on PIVR in their review. It was shown that ureteral tumors were found to be associated with higher PIVR rates ($p<0.01$) in a total of 6017 patients with UUST, including 2229 (37%) patients with ureteral tumor and 3788 (63%) patients with renal tumor. In our study, high rates of PIVR were found in ureteral tumors in line with the literature (HR:3, $p<0.05$) (Table 5) (14,15,18).

Study Limitations

Although the data evaluated in this study were obtained from the uro-oncology database, which was being held prospectively in our clinic, retrospective examination of these data for our study was a significant limitation of our study. The low number of patients compared to the broad series in the literature was another weakness. The reasons for this weakness were that the study was single-centered and actually involved only patients with primary diagnosis, which was also an important feature of the study. There were no patients treated with minimally invasive ablative treatment in our series. Therefore, it was not included in our study.

Conclusion

In our study, it was determined that among the primary UUSTs, ureteral and multifocal tumors had a higher risk for PIVR than renal tumors and 5-year OS rate was lower in ureteral tumors compared with renal tumors

The risk groups of the patients should be determined according to the tumor localization at the diagnosis stage in primary UUST. In particular, it may be useful to make adjustments in the duration and frequency of follow-up of patients with ureteral tumors, taking into account the excess risk of PIVR and the low risk of OS.

We believe that prospective studies with larger number of patients are needed to help tailor post-treatment follow-up of patients with UUST to patient risk groups.

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Ethics

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Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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Case Report
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A Case of Pediatric Paratesticular Rhabdomyosarcoma Misdiagnosed as Epididymitis

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Abstract

Paratesticular embryonal rhabdomyosarcoma (RMS) is a rare tumor arising from the mesenchymal tissues of testis and paratesticular tissue. RMS which usually presents as a painless mass in the scrotum is frequently seen in children, teens and young adults. Accurate diagnosis and early treatment are essential as it is an aggressive tumor with high metastatic potential and poor prognosis. Orchiectomy is the treatment of choice. Chemo-radiotherapy is recommended in case of recurrence and metastasis. We aimed to present an anusual case of a 9-year-old child with paratesticular RMS, who presented with a painful scrotal swelling which was misdiagnosed as epididymitis.
Keywords: Rhabdomyosarcoma, embryonal, epididymitis

Introduction

Paratesticular embryonal rhabdomyosarcoma (RMS) is a rare tumor originated from the mesenchymal tissues of testis and paratesticular tissue frequently seen in children, teens and young adults (1). Among the malignant tumors, the most common histotype is liposarcoma (46.4%), followed by leiomyosarcoma (LMS) (20%), malignant fibrous histiocytoma (MFH) (13%), and embryonal RMS (9%) (2). Paratesticular embryonal RMS constitutes 7% of all RMS (3). Paratesticular embryonal RMS usually presents as a painless mass in the scrotum (4). However, we herein presented an unusual 9-year-old child with a painful scrotal swelling which was misdiagnosed as epididymitis and caused delay in diagnosis of paratesticular RMS.

Case Presentation

A 9-year old boy presented with a painful left testicular mass in the left scrotum. He was admitted to the emergency department. The medical history of the patient was unremarkable. Physical examination revealed a moderate tenderness and erythema of the left hemi-scrotum. Scrotal ultrasound showed a large iso-hypoechoic testicular mass measuring 4 × 3.5 × 3.5 cm in the left scrotum with marked increased vascularity and it was suspicious for severe epididymitis and the boy was discharged with antibiotics and instructions to follow up in case symptoms persisted. Ten days later, he was re-admitted to the urology outpatient clinic with persistent pain and swelling. Repeated ultrasound findings showed a testicular tumor measuring 4 × 4 × 4 cm in the left scrotum. He was hospitalized for further evaluation and an exploratory operation. Abdominopelvic computed tomography (CT) and chest radiography revealed no metastases. Complete blood count, beta-human chorionic gonadotropin (0.1 IU/L), serum alpha-fetoprotein (0.98 ng/mL), and lactate dehydrogenase (110.0 IU/L) were within normal limits. Informed consent form was obtained from the patient's parents. The following day, the patient underwent left high radical orchiectomy. Macroscopic examination showed that the testis was enlarged and there was a yellow myxoid solid tumor (4 × 4.2 × 3.5 cm) (Figure 1). Normal testicular tissue was expelled peripherally. The tunica vaginalis had been invaded by the tumor in a small area but the tunica albuginea and testis had not been invaded by the tumor, and the surgical margin was also negative. Histopathological evaluation of the surgical specimen demonstrated a tumoral proliferation with a mixture of haphazardly arranged rhabdomyoblasts and undifferentiated primitive cells which were small and round with minimal cytoplasm and dark nuclei. Spindle cells, clear cell change and tadpole cells were also seen. The tumor showed a high mitotic activity (Figure 2). Immunohistochemically, the tumor was

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strongly positive for desmin, vimentin, myoglobin and negative for calretinin, CK19, EMA, AFP, HCG, CD30, CD117, and CD99 (Figure 3).

Because there was no evidence of metastasis and the patient was <10 years old, retroperitoneal lymph node dissection (RPLND) was not performed in our case. First, the patient was classified in the group I of the Intergroup RMS study and then 3 cycles of adjuvant chemotherapy (VAC regimen: vincristine 1.5 mg/m^2 on day 8 intravenous (IV); dactinomycin 1.5 mg/m^2 on day 8 IV; and cyclophosphamide 150 mg/m^2 intramuscular on day 1~7) were performed. At 1 year of follow-up, our patient was assessed and demonstrated good clinical improvement and was determined to be cured.

Discussion

Paratesticular RMS accounts for 6% of all non-germinal intrascrotal tumors (2). Primary paratesticular RMS are seen rarely (1). Paratesticular sarcomas are mostly RMS and seen in children (3). There are two frequency peaks for the development of RMS at the age of 4 and 18 years and 70% of the patients develop under the age of 10 years (3). There is no difference between races in terms of frequency (5). Most of the patients typically present with painless unilateral scrotal swelling like a solid testicular tumor. However, our case presented with a painful unilateral scrotal swelling suggesting epididymitis. When evaluating a patient with acute testicular pain and swelling, the diagnosis should be testicular torsion until proven otherwise. Whereas, testicular torsion usually presents as rapid-onset pain, epididymitis and orchitis have a gradual onset of pain. Patients with a testicular tumor usually present with a painless mass found either by the patient or by the physician on routine examination. After completion of a detailed history, the physical examination usually reveals a small nontender palpable lesion on the posterior aspect of the affected testicle. Once a lesion is identified, the scrotum should be transilluminated. A solid mass will not allow light to pass through or give a red glow. A secondary examination of the chest should be performed to evaluate for gynecomastia and abdomen should also be evaluated. Follow-up testing includes diagnostic imaging and laboratory testing. Scrotal ultrasonography will help define suspected lesions revealing a hypoechoic signal. Magnetic resonance imaging can also be employed and will demonstrate a mass that is relatively isointense on T1 imaging and enhancement with IV gadolinium on T2 imaging. Obtaining tumor markers, α fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase also is useful for monitoring progression but cannot be used to screen or to make an initial diagnosis. In all patients with suspected epididymitis, scrotal color Doppler ultrasonography is the preferred test and it should be performed routinely to exclude a scrotal mass. This imaging modality shows a mass with heterogeneous echogenicity and inguinoscrotal extension in 80% of patients. Sonographic characteristics of paratesticular RMS are nonspecific. An associated hydrocele might be present but is more commonly seen with epididymitis like in our patient. Metastases typically develop by hematogenous or

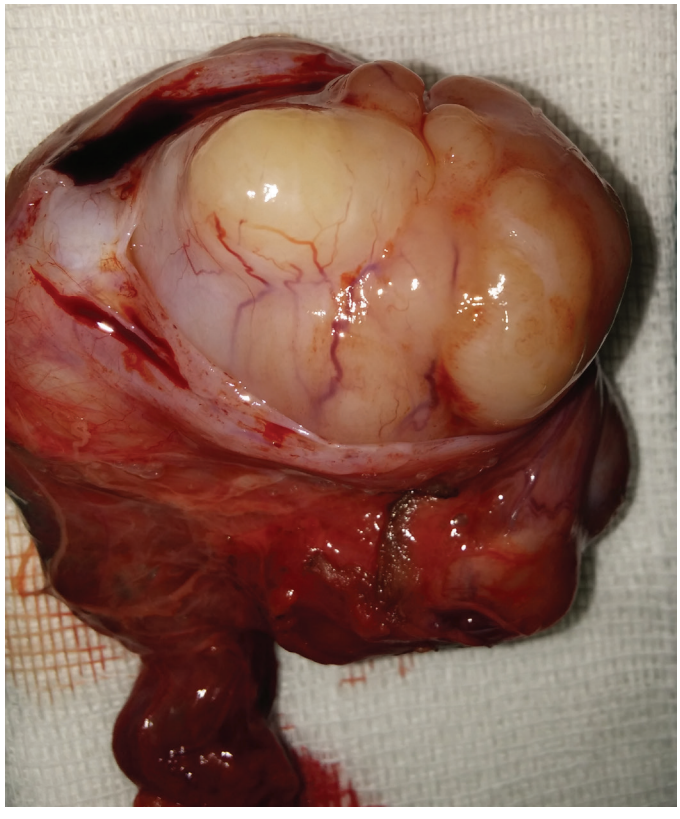


Figure 1. Macroscopic appearance of paratesticular rhabdomyomsarcoma

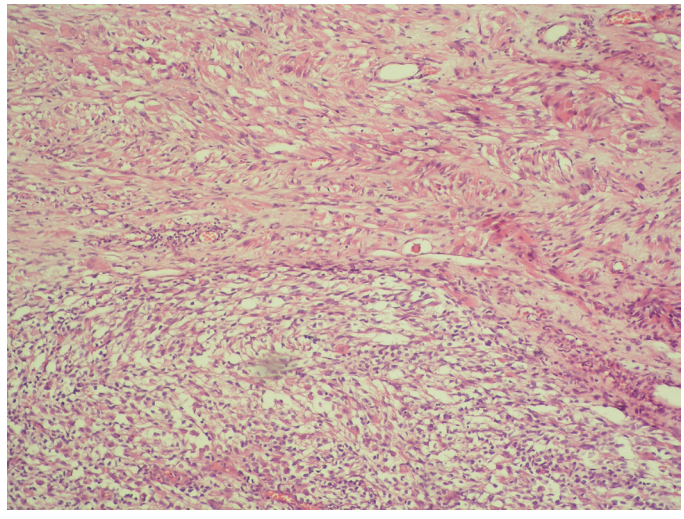


Figure 2. Undifferentiated primitive cells, spindle cells, clear cell change, and rhabdomyoblasts (H&E x100)

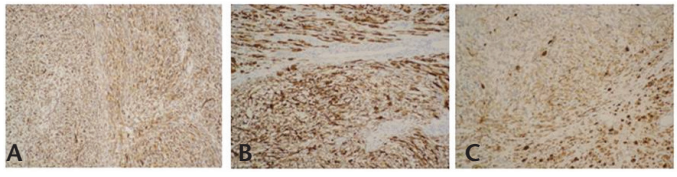


Figure 3. (A) Desmin positivity (x 400),
(B) Vimentin positivity (x 400),
(C) Myoglobin positivity (x 400)

lymphatic routes and direct invasion of the testicular tunica (6). Metastasis of RMS is common to the lung, bone marrow, brain, liver, omentum and lymph nodes (3,6). CT scan of chest, abdomen and pelvis is done to rule out possibility of metastasis and most clinicians prefer the use of thoraco-abdomino-pelvic CT compared to ultrasound for regional lymph nodes. In the international classification of RMS, there are 5 recognized variants: Embryonal, alveolar, botryoid embryonal, spindle cell embryonal, and anaplastic (7). The most common variant is embryonal variant, which is most associated with tumors of the genitourinary tract and the head and neck. In embryonal RMS, small cells with hyperchromatic nuclei, minimal cytoplasm as well as cells with rims of eosinophilic cytoplasm and spindle cells with cytoplasmic tails and variable cross striations in myxoid or collagenous stroma is seen. Immunohistochemistry is helpful to exclude other intratesticular spindle cell sarcomas like fibrosarcoma and LMS. Intratesticular RMS have better prognosis than paratesticular RMS (8). Tumor markers such as alpha feto protein, beta-human chorionic gonadotropin and carcinoembryonic antigen are within normal range in RMS. The tumor markers were also within normal range inour patient.

Multidisciplinary treatment approaches including surgery, chemotherapy and radiation have greatly improved the prognosis of paratesticular RMS (8,9). The initial treatment for a RMS is inguinal orchiectomy. Orchiectomy followed by chemotherapy is the best treatment (9). A retroperitoneal lymphadenectomy should not be performed without first obtaining imaging including a CT scan. Because of RMS is chemosensitive, chemotherapy should be routinely performed. The chemotherapy agents used are vincristine, actinomycin D and cyclophosphamide. Radiotherapy is recommended to treat residual microscopic tumor, local recurrence or metastasis (9).

Paratesticular RMS is a rare and potentially aggressive tumor seen in children and young adults. A multimodality approach in diagnosis as well as in treatment is needed. Localized form has good prognosis whereas metastatic disease has poor prognosis. Paratesticular RMS has a better prognosis than RMS originating in other locations because of its favorable histology and possible early detection (8). There is a relationship between age at diagnosis and likelihood of regional lymph node involvement in boys with non-metastatic paratesticular RMS and nodal relaps rate is lower under 10 years of age (10). RMS study group recommends performing a modified ipsilateral retroperitoneal lymph-node dissection over 10 years of age who have no clinical evidence of regional node involvement (10). Although not routinley performed by many centers there have been important debates about the importance of systemic lymphadenectomy because lymph node involvement may accompany 19-38% of tumors . Abhijith et al. (11) reported that patients over 10 years, with or without radiographic evidence of retroperitoneal disease, should undergo a staging RPLND and receive radiation in addition to chemotherapy if lymph node involvement was positive. The current trend is to avoid dissection if radiological examinations show up no lymph node involvement >1 cm (12). Wiener et al. (13) suggested that adolescents should have ipsilateral RPLND dissection as part of their routine staging, and those with positive lymph nodes require intensified chemotherapy as well as nodal irradiation. In recent years, increased use of minimally invasive surgery has changed to RPLND. Tomaszewski et al. (14) concluded that laparoscopic RPLND for high-risk pediatric patients with paratesticular RMS was a safe diagnostic and therapeutic procedure with the benefit of rapid convalescence, enabling early commencement of adjuvant chemotherapy. Cost et al. (15) reported on two cases of adolescents who were treated using robot-assisted laparoscopic RPLND (R-RPLND), one with paratesticular RMS and one with testicular germ cell tumor with good outcomes and low morbidity. Robotic assistance provides advanced three-dimensional visualization and more precise surgical instrumentation. We hope this procedure will achieve a complete resection and potentially better nerve preservation. Early identification of paratesticular RMS is critical. Radical orchiectomy followed by chemotherapy is the recommended treatment. Radiotherapy is recommended for the control of local recurrence and metastasis. Strict follow up for long term is the rule in all patients.

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Ethics

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Authorship Contributions

Concept: A.A., Design: C.A., Data Collection or Processing: A.Ç., Analysis or Interpretation: C.A., Z.B.A., Literature Search: A.A., A.Ç., Writing: C.A.

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Video Article

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Laparoscopic Partial Nephrectomy: Tips and Tricks

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Introduction

Partial nephrectomy (PN) should be recommended for clinically stage T1 or "resectable" T2 tumors rather than radical nephrectomy if technically feasible. Technical preference for PN depends on the expertise of the surgeon (1). In experienced hands, laparoscopic partial nephrectomy (LPN) indeed works as an effective nephron preserving platform despite a more difficult learning curve (2). In this video article, we aim to present LPN's technical details and tips on all steps.

Approach, Patient Positioning and Trocar Setup

We mostly prefer the transperitoneal approach, as it provides a wider area during operation and easier anatomical orientation. We use a modified lateral decubitus position, which helps in colon medialization by allowing the intestines to fall away from the kidney. We use the closed technique to create pneumoperitoneum. The optic trocar is usually placed into the pararectal line or umbilicus according to the anatomical features of the patient. The location of other trocars is detailed in the video.

Vascular and Perirenal Dissection

First, by cutting the Toldt's line and lienorenal and triangular ligaments, mobilizing the colon, liver, and spleen is a part of this stage. The duodenum is medialized with the Kocher maneuver after mobilization. Following medialization, Gerota's fascia is incised over the gonadal vein and Gerota's fascia is dissected to the inferior border of the renal vein and the lower pole is suspended. The plane between the kidney and adrenal gland may be freed to help facilitate mobilization. The renal vein and artery are dissected separately and secured with silicon tapes. The use of intraoperative ultrasound (IU) may guide to proper parenchymal dissection, prevention of tumor capsule breach and defining margins. We use ultrasonic energy devices such as Thunderbeat® for perirenal dissection and margin of the tumor is scored by hook cautery. The use of IU in endophytic masses is essential to perform PN.

Resection and Renorraphy

After preparations, we insert endo-bulldog clamps separately into the artery and vein. To avoid tumor capsule breach and to develop the crater, the tumor is resected with cold scissors, tips pointing outwards. The surgeon uses the suction to keep the resection field bloodless and the assistant creates space by retracting the kidney. Obvious arteries in tumor bed can be controlled with metal or Hem-o-lok™ clips. The renorraphy is performed in two phases; in the first step, we prefer 2/0 V-loc™ or monocryl sutures with a Hem-o-lok™ clip in the end. In the second step, we use 2/0 absorbable, braided suture with sliding clip technique (3). Bulldog clamps are released after renorraphy, by aligning the clamp's base with the bulldog remover. For hemostasis, visual inspection of the resection site is done by reducing the pressure to 5 mm Hg. The specimen is placed into endobag via the working port. Finally, the Gerota's fascia is closed with a 2/0 absorbable suture, paying attention to the ureter. We remove the specimen from the separate Gibson incision if the patient is not morbidly obese.

Conclusion

Minimally invasive PN is one of the most demanding procedure in urology practice and it can be used even in complex cases safely and efficiently with experience.

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