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

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

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

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

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

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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.

The Bulletin publishes basic and clinical research original articles, reviews, editorials, case reports, 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 international databases and is committed to rigorous peer review.

The Bulletin of Urooncology does not charge any article submission or processing charges, nor do authors receive any remuneration or compensation for their manuscripts.

Manuscripts must be written in Turkish or 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 250 words have been published. In this case, however, the name, date, and place of the meeting in which the paper was presented should be stated. Direct quotations, tables, or illustrations taken from copyrighted material must be accompanied by written permission for their use from the copyright owner and authors.

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

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During the evaluation of the manuscript, the research data and/or ethics committee approval form can be requested from the authors if it's required by the editorial board.

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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:

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

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

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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.

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

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All retrospective, prospective, and experimental research articles must be evaluated in terms of biostatistics 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.

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Accepted articles will be published in English online and in both English and Turkish in hard copy. The translation process will be conducted by the Bulletin. 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).

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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 in Times Roman or Arial font.

Each section of the article should be started on a new page and be organized according to the following sequence:

- 1) Title,
- 2) Abstract and keywords (Turkish and English),
- 3) Main text,
- 4) Acknowledgements (optional),

5) References,

6) Tables/figures (each table should be written with the titles and footnotes in a separate page) and figure legends.

All manuscripts submitted must be accompanied by the "Copyright Transfer and Author Declaration Statement form" (www.uroonkolojibulteni.com). The corresponding author must provide a full correspondence address including telephone, fax number, and e-mail address. Contact information for the corresponding author is published in the Bulletin.

A. Original Research Articles

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Content:

- Title

Abstract (structured abstract limited to 300 words, containing the following sections: Objective, Materials and Methods, Results, Conclusion)

- Keywords (List 3-5 keywords using Medical Subjects Headings [MeSH])

Introduction

- Materials and Methods/Patients and Methods

- Results

- Discussion

- Study Limitations

- Conclusion

- Acknowledgements

- References

- Tables/Figures

Preparation of research articles, systematic reviews, and meta-analyses must comply with study design guidelines: CONSORT statement for randomized controlled trials (Moher D, Schulz 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/>);

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Figure Legends

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Case reports should include cases which are rarely seen and distinctive in diagnosis and treatment. These can include brief descriptions of

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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.

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Abstract (limited to 150 words, unstructured)

- Keywords (List 3-5 key words using Medical Subjects Headings [MeSH])

Introduction

Case Presentation

Discussion

References

Tables/Figures

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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 3.

Content:

- Title

Abstract (maximum 250 words; without structural divisions;

- Keywords (List 3-5 key words using Medical Subjects Headings [MeSH])

Introduction

Main Text

Conclusions

Tables/Figures

Figure Legends

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).

D. Literature Review

These 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 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.

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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 than 500 words with maximum of

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

Any grants or financial support received for the paper

B. Abstract and Keywords

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

C. Main Text

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

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

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

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

Conclusion: The conclusion of the study should be highlighted.

D. Acknowledgements

Acknowledgments are given for contributors who may not be listed as authors, or for grant support of the research. Any technical or financial support or editorial contributions (statistical analysis, English/Turkish evaluation) to the study should appear at the end of the article.

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Books: Greenspan A. *Orthopaedic Radiology a Practical Approach*. 3rd ed. Philadelphia: Lippincott Williams Wilkins; 2000. p. 295-330.

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

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

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Evaluation of the Side Effect Profile of Intracavitary *Bacillus Calmette-Guérin* Treatment in Non-muscle-invasive Bladder Cancer

İ Şenol Tonyalı MD, İ Mustafa Karaaslan MD, İ Mehmet Yılmaz MD, İ Cavit Ceylan MD

Türkiye Yüksek İhtisas Training and Research Hospital, Clinic of Urology, Ankara, Turkey

Abstract

Objective: To reveal the association of side effect profiles seen in patients receiving intravesical bacillus Calmette-Guérin (BCG) immunotherapy for non-muscle-invasive bladder cancer (NMIBC) treatment with patient age and possible changes over time due to the use of different BCG strains.

Materials and Methods: We retrospectively analyzed the medical records of all patients who received BCG for NMIBC in our hospital between January 2013 and December 2017. Investigated parameters included patients' demographics, treatment dates, local and systemic side effects (dysuria, hematuria, cystitis, headache, arthralgia/myalgia, chills, fever, fatigue, epididymo-orchitis, renal abscess, pneumonia, hepatitis, and sepsis), need for hospitalization and antituberculous therapy, discontinuation of therapy, and doses received.

Results: The study included 89 patients (84 male, 5 female) with a mean age of 67.4±10.2 years. The most common side effects were dysuria (41.6%), chills (31.5%), hematuria (30.3%), fever (29.2%), cystitis (24.7%), and fatigue (23.6%). Ten patients (11.2%) were hospitalized due to treatment-related side effects. Ten patients discontinued treatment due to side effects. Sixty-two patients (69.7%) experienced at least 1 local or systemic side effect. There was no significant difference between patients younger and older than 70 years in terms of side effect rates (69.8% vs 69.4%, p=0.576). In addition, a significant difference was not observed in complication rates when we compared treatment before and after 2016 (65.3% vs 75%, p=0.322).

Conclusion: Intracavitary BCG can be the treatment of choice in NMIBC even in patients at an advanced age. The absence of a significant change in complication rates over the years despite changing strains may be evidence that strains have a similar side effect profile.

Keywords: Bladder cancer, bacillus Calmette-Guérin, strain, intracavitary

Introduction

Bladder cancer is the eleventh most common cancer globally and the 7th most common among men. Most bladder cancers are of urothelial cancer histology, and these are categorized as either muscle-invasive bladder cancer (MIBC) or non-muscle-invasive bladder cancer (NMIBC). NMIBC accounts for about 75% of all bladder cancers (1). NMIBC has a recurrence rate of 50-80% and progresses to MIBC in about 30% of cases. NMIBCs are candidates for bladder-sparing treatment approaches (2).

Various intravesical chemotherapy and immunotherapy options are available for patients with intermediate- to high-risk NMIBC. Bacillus Calmette-Guérin (BCG) is a heterogeneous organism, with at least 8 different strains used for intravesical immunotherapy (3). It was first defined in 1976 by Morales et al. (4) and is classically administered based on a 6-week induction schedule. Optimal maintenance dose and interval have not been definitely determined, but durations of 1 to 3 years have been reported (5). BCG therapy is superior to intravesical chemotherapeutics in reducing the risk of both recurrence and progression (3).

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Although BCG immunotherapy is proven effective for NMIBC, it may also cause several local and systemic side effects. These adverse reactions can range from mild malaise and fever to fatal or life-threatening sepsis (6).

In our clinic, BCG Culture SSI (Danish strain 1331, 120 mg) has been used most commonly for intracavitary BCG therapy since mid-2015. Prior to that, the BCG Connaught strain (81 mg) was preferred.

In this study, we evaluated patients who received intravesical BCG immunotherapy for NMIBC to determine whether side effect profiles are associated with patient age and whether they show variation over time due to the use of different strains.

Materials and Methods

The data of patients who received intracavitary BCG treatment in our hospital for intermediate- to high-risk NMIBC between January 2013 and December 2017 were examined retrospectively. Patients who reported any local or systemic side effects during induction or maintenance BCG therapy were noted. Patients who had previously received chemotherapy or radiotherapy for bladder tumor were excluded from the study. Urine analysis and urine culture were conducted prior to BCG therapy in all cases. Treatment was postponed for patients with hematuria and active urinary tract infection. Induction therapy was administered weekly for 6 weeks; maintenance therapy was typically given as 3 weekly doses at 3, 6, 12, 18, 24, 30 and 36 months. Analyzed parameters included the patients' demographic data, dates of treatment, local and systemic side effects (dysuria, hematuria, cystitis, headache, arthralgia/myalgia, chills, high fever, malaise, epididymo-orchitis, renal abscess, pneumonia, hepatitis, sepsis), need for hospitalization, need for antituberculous therapy, treatment discontinuation due to side effects, and dosage received. All patients with available data were included in the study, regardless of gender or age. Patients were divided into 2 groups based on age. Patients under 70 years of age and those older than 70 years of age were compared in terms of side effect profile. In addition, patients treated before and after 2016 were compared to determine whether the change of strains had an influence on the side effect profile over time.

Ethics committee approval was obtained from Türkiye Yüksek İhtisas Training and Research Hospital Board of Education Planning and Coordination. Written informed consent was not obtained because this study is retrospective.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics for Mac v.21.0 (IBM Corp., Armonk, NY). Quantitative values were expressed as mean \pm standard deviation and qualitative values were expressed in numbers and percents. Comparisons between groups were done using Mann-Whitney U test and chi-square test. $P < 0.05$ was considered statistically significant.

Results

A total of 89 patients (84 males and 5 females) were included in the study. Their mean age was 67.4 ± 10.2 years. Mean ages of the males and females in the study were 67.8 ± 10.1 years and 60.8 ± 10.7 years, respectively. There was no significant difference between males and females with regard to age ($p = 0.137$). The

most common side effects were dysuria (41.6%), chills (31.5%), hematuria (30.3%), high fever (29.2%), cystitis (24.7%), and malaise (23.6%). One patient (1.1%) was diagnosed with epididymo-orchitis, 1 (1.1%) with renal abscess, 1 (1.1%) with pneumonia, and 2 (2.2%) with hepatitis related to treatment. A total of 4 patients (3.4%) received antituberculous therapy. Ten patients (11.2%) were hospitalized due to BCG-related side effects. Ten patients (11.2%) had to discontinue intracavitary BCG therapy due to side effects. Of the 10 patients who discontinued treatment, 6 were receiving induction and 4 were receiving maintenance doses. Patients who were unable to complete the induction treatment were switched to intracavitary chemotherapeutic agents. The mean age of the hospitalized patients was 70.2 ± 8.4 years, whereas that of the other patients was 67 ± 10.4 years ($p = 0.366$). Sixty-two patients (69.7%) experienced 1 or more systemic or local side effect. There was no difference between patients over and under the age of 70 in the rate of side effects (69.4% vs 69.8%, $p = 0.576$). There was also no significant difference in rate of side effects between patients treated before and after the year 2016 (65.3% vs 75%, $p = 0.322$) (Table 1).

Discussion

Intracavitary BCG immunotherapy for NMIBC was first described by Morales et al. (4) and it was reported that certain criteria must be met for effective BCG immunotherapy. These include the ability to develop immune response against mycobacterial antigens, sufficient number of live bacilli, close contact between BCG and tumor, relatively low tumor burden, and absence of major systemic side effects (4).

There is no consensus on the optimal BCG preparation, dose, or administration schedule. Although BCG toxicity is commonly reported after intense regimens, very severe side effects may also be seen after only a few instillations. In a study conducted with 2602 patients, fever was reported in 2.9%, pneumonia/hepatitis in 0.7%, gross hematuria in 1%, arthralgia in 0.5% and epididymo-orchitis in 0.4%. No variation was observed in the complication rates of different BCG strains (6). It was shown in another study that decreasing the BCG dose did not reduce the side effect rate (7). Although the rates of hematuria and fever reported in our current study were lower than those obtained in the aforementioned one, the rates of pneumonia, hepatitis, and epididymo-orchitis ratios were similar. There was also no significant change in the complication rates of patients receiving BCG over time. This may be evidence that different strains have similar side effect profiles.

Various solutions have been attempted to minimize the related side effects without compromising the therapeutic efficacy of BCG therapy. These include gradually reducing the dose given in each successive instillation or extending the intervals between instillations. It was reported that common side effects occurred significantly less frequently in patients who received a reduced dose of 75 mg instead of the standard 150 mg dose of BCG (Pasteur strain) [cystitis, 57% to 32%; fever < 38.5 °C, 26% to 12%; gross hematuria 24% to 13% ($p < 0.05$)] (8). In another study by Irie et al. (9), 40 mg BCG (Tokyo 171 strain), which is half the full dose, had similar efficacy to the full dose but resulted in a significant reduction of BCG toxicity.

Side effects		Age (years)			Treatment year		
		<70 (n=53)	>70 (n=36)	p	2016 and later (n=40)	Before 2016 (n=49)	p
Systemic side effects	Malaise	13 (24.5%)	8 (22.2%)	1.000	9 (22.5%)	12 (24.5%)	1.000
	Fever	15 (28.3%)	11 (30.6%)	0.817	14 (35%)	12 (24.5%)	0.350
	Arthralgia/myalgia	4 (7.5%)	6 (16.7%)	0.181	3 (7.5%)	7 (14.3%)	0.313
	Chills	16 (30.2%)	12 (33.3%)	0.818	14 (35%)	14 (28.6%)	0.516
	Headache	5 (9.4%)	6 (16.7%)	0.341	4 (10%)	7 (14.3%)	0.541
	Renal abscess	1 (1.9%)	0	0.407	0	1 (2%)	0.364
	Pneumonia	0	1 (2.8%)	0.222	1 (2.5%)	0	0.266
	Hepatitis	1 (1.9%)	1 (2.8%)	0.781	0	2 (4.1%)	0.196
Local side effects	Dysuria	24 (45.3%)	13 (36.1%)	0.511	18 (45%)	19 (38.8%)	0.666
	Hematuria	18 (34%)	9 (25%)	0.482	13 (32.5%)	14 (28.6%)	0.817
	Cystitis	14 (26.4%)	8 (22.2%)	0.803	11 (27.5%)	11 (22.4%)	0.627
	Epididymo-orchitis	0	1 (2.8%)	0.222	0	1 (2%)	0.364
Hospitalization	-	6 (11.3%)	4 (11.1%)	0.975	7 (17.5%)	3 (6.1%)	0.091
Antituberculous therapy	-	1 (1.9%)	2 (5.6%)	0.347	0	3 (6.1%)	0.111
Treatment discontinuation due to side effects	-	4 (7.5%)	6 (16.7%)	0.181	4 (10%)	6 (12.2%)	0.739

In still another study, Koga et al. (10) reported a 95.9% incidence of side effects with general intracavitary BCG (Tokyo 172 strain). Administration of BCG for treatment purposes instead of prophylaxis and BCG dose were found to be independent risk factors for side effects (10). In another report, instillation of BCG (Connaught strain) doses reduced from 81 mg to 27 mg had similar effects on progression as the standard dose, with less toxicity (11). In a study including 1316 patients, Brausi et al. (5) demonstrated that neither dose nor treatment duration had a significant influence on the side effect profile of intracavitary BCG treatment. Making a similar comparison was not possible in our study since we had patients receiving both induction and maintenance treatment and sufficient data regarding progression were not available.

In a study conducted by Heiner and Terris (12) with 58 patients receiving intracavitary BCG, 22 (37.9%) of the patients had treatment-related complications. Complication rates in patients receiving maintenance treatment were 17.6% for those less than 70 of age and 48.6% for those over 70. The mean age of patients with complications was significantly higher than those without complications (76 years vs 70.3 years, $p < 0.00001$) (12). In our study group there was no significant difference in rates of complications related to intracavitary BCG therapy between patients under and over the age of 70.

Study Limitations

Our study included a relatively small number of patients. Due to lack of patient cooperation and insufficient record-keeping, the data were not clear in terms of which patient received which strain how many times, and after how many doses side effects started or ended. Moreover, although the induction treatment schedule was the same, the maintenance treatment protocol may vary between clinicians.

Conclusion

Intracavitary BCG treatment is a treatment option for NMIBC that can also be used in patients at advanced ages. Despite strain variations, complication rates did not change significantly over the years in our study, suggesting that strains have similar side effect profiles.

Ethics

Ethics Committee Approval: Approval was obtained from Türkiye Yüksek İhtisas Training and Research Hospital Board of Education Planning and Coordination.

Informed Consent: Not obtained because this study is retrospective.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.T., M.K., M.Y., C.C., Concept: Ş.T., C.C., Design: Ş.T., M.K., M.Y., C.C., Data Collection or Processing: Ş.T., M.K., M.Y., C.C., Analysis or Interpretation: Ş.T., M.K., M.Y., C.C., Literature Search: Ş.T., M.K., M.Y., C.C., Writing: Ş.T.

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Kasa İnvaziv Olmayan Mesane Kanserinde İntrakaviter Bacillus Calmette-Guérin Tedavisinin Yan Etki Profilinin Değerlendirilmesi

Evaluation of the Side Effect Profile of Intracavitary Bacillus Calmette-Guérin Treatment in Non-muscle-invasive Bladder Cancer

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Öz

Amaç: Kasa invaziv olmayan mesane kanseri (KİOMK) tedavisi için intravezikal bacillus Calmette-Guérin (BCG) immünoterapisi alan hastalarda görülen yan etki profillerinin hasta yaşı ile ilişkisini ve verilen farklı suşlar nedeni ile yıllar içinde olan olası değişimini ortaya koymaya çalıştık.

Gereç ve Yöntem: Hastanemizde orta ve yüksek riskli KİOMK nedeniyle Ocak 2013-Aralık 2017 tarihleri arasında intrakaviter BCG tedavisi alan hastaların verileri retrospektif olarak incelendi. İncelenen parametreler arasında hastaların demografik bilgileri, tedavi aldığı tarihler, lokal ve sistemik yan etkiler (dizüri, hematüri, sistitizm, baş ağrısı, artralji/miyalji, üşüme/titreme, yüksek ateş, kırgınlık, epididimoorşit, renal apse, pnömoni, hepatit, sepsis), hospitalizasyon ihtiyacı, antitüberküloz tedavi ihtiyacı, yan etki nedeni tedaviyi sonlandırma ve aldığı doz bilgisi var idi.

Bulgular: Çalışmaya 84'ü erkek, 5'i kadın olmak üzere toplam 89 hasta dahil edildi. Hastaların ortalama yaşı 67,4±10,2 yıl idi. En sık görülen yan etkiler sırasıyla dizüri (%41,6), üşüme-titreme (%31,5), hematüri (%30,3), yüksek ateş (%29,2), sistit (%24,7) ve kırgınlık (%23,6) idi. On (%11,2) hasta BCG yan etkilerine bağlı olarak hospitalize edildi. Hastaların 10'u (%11,2) yan etkiler nedeniyle tedaviyi sonlandırdı. Sistemik ya da lokal olmak üzere bir yan etki ile karşılaşan hasta sayısı 62 (%69,7) idi. Yan etki oranları açısından 70 yaş altı ve 70 yaş üstü hastalar arasında fark bulunmamakta idi (%69,8'e karşı %69,4, p=0,576). Ayrıca 2016 yılı öncesi ve sonrasındaki tedavilerin karşılaştırılmasında yan etki oranlarında anlamlı bir farklılık gözlenmemiştir (%65,3'e karşı %75, p=0,322).

Sonuç: İntrakaviter BCG tedavisi KİOMK tedavisinde ileri yaşta hastalarda da kullanılabilecek bir tedavi seçeneğidir. Değişen suşlara rağmen yıllar içerisinde komplikasyon oranlarında anlamlı bir değişiklik olmaması suşların benzer yan etki profiline sahip olduğunun bir kanıtı olabilir.

Anahtar Kelimeler: Mesane kanseri, bacillus Calmette-Guérin, suş, intrakaviter

Abstract

Objective: To reveal the association of side effect profiles seen in patients receiving intravesical bacillus Calmette-Guérin (BCG) immunotherapy for non-muscle-invasive bladder cancer (NMIBC) treatment with patient age and possible changes over time due to the use of different BCG strains.

Materials and Methods: We retrospectively analyzed the medical records of all patients who received BCG for NMIBC in our hospital between January 2013 and December 2017. Investigated parameters included patients' demographics, treatment dates, local and systemic side effects (dysuria, hematuria, cystitis, headache, arthralgia/myalgia, chills, fever, fatigue, epididymo-orchitis, renal abscess, pneumonia, hepatitis, and sepsis), need for hospitalization and antituberculous therapy, discontinuation of therapy, and doses received.

Results: The study included 89 patients (84 male, 5 female) with a mean age of 67.4±10.2 years. The most common side effects were dysuria (41.6%), chills (31.5%), hematuria (30.3%), fever (29.2%), cystitis (24.7%), and fatigue (23.6%). Ten patients (11.2%) were hospitalized due to treatment-related side effects. Ten patients discontinued treatment due to side effects. Sixty-two patients (69.7%) experienced at least 1 local or systemic side effect. There was no significant difference between patients younger and older than 70 years in terms of side effect rates (69.8% vs 69.4%, p=0.576). In addition, a significant difference was not observed in complication rates when we compared treatment before and after 2016 (65.3% vs 75%, p=0.322).

Conclusion: Intracavitary BCG can be the treatment of choice in NMIBC even in patients at an advanced age. The absence of a significant change in complication rates over the years despite changing strains may be evidence that strains have a similar side effect profile.

Keywords: Bladder cancer, bacillus Calmette-Guérin, strain, intracavitary

Giriş

Mesane kanseri dünya genelinde en yaygın 11, erkekler arasında ise en yaygın 7. malignitedir. Mesane kanserlerinin çoğu ürotelyal kanser histolojisindedir ve bunlar kasa invaziv olan mesane kanseri (KIMK) ve kasa invaziv olmayan mesane kanseri (KİOMK) olarak 2 gruba ayrılır. KİOMK tüm mesane kanserlerinin yaklaşık %75'ini oluşturur (1). KİOMK %50-80 rekürrens göstermekle birlikte %30 oranında da KİMK'ye progresyon gösterir. KİOMK'ler mesane koruyucu tedavi yöntemleri için adaydırlar (2).

Orta ve yüksek riskli KİOMK hastaları için çeşitli intravezikal kemoterapi ve immünoterapi seçenekleri bulunmaktadır. Bacillus Calmette-Guérin (BCG), intravezikal immünoterapi için en az 8 farklı suşundan faydalanılmış heterojen bir organizmadır (3). İlk kez 1976 yılında Morales ve ark. (4) tarafından tanımlanmıştır ve klasik olarak 6 haftalık indüksiyon şemasına göre verilir. Optimal idame dozu ve aralığı kesin olmamakla beraber 1 ile 3 yıl arasında idame tedavileri bildirilmiştir (5). BCG tedavisinin intravezikal kemoterapotiklere üstünlüğü rekürrens riskini azaltmanın yanında progresyon riskini de azaltmasıdır (3). BCG immünoterapisinin KİOMK'de etkinliği gösterilmiş olmakla beraber çeşitli lokal ve sistemik yan etkilere de neden olabilir. Bu yan etkiler hafif bir kırgınlık ve ateş ile ölümcül ya da hayatı tehdit eden septik tablo arasında değişebilir (6).

Kliniğimizde 2015 yılı 2. çeyreğinden itibaren en sık uygulanan intrakaviter BCG suşu BCG Culture SSI (120 mg) idi. Öncesinde ise genellikle BCG Connaught suşu (81 mg) kullanılmakta idi. Bu çalışmamızda, KİOMK tedavisi için intravezikal BCG immünoterapisi alan hastalarda görülen yan etki profillerinin hasta yaşı ile ilişkisini ve verilen farklı suşlar nedeni ile yıllar içinde olan olası değişimini ortaya koymaya çalıştık.

Gereç ve Yöntem

Hastanemizde orta ve yüksek riskli KİOMK nedeniyle Ocak 2013-Aralık 2017 tarihleri arasında intrakaviter BCG tedavisi alan hastaların verileri retrospektif olarak incelendi. İndüksiyon ya da idame BCG tedavisi sırasında herhangi bir lokal ya da sistemik yan etki yaşadığını belirten hastalar kaydedildi. Daha önceden mesane tümörü nedeniyle kemoterapi ya da radyoterapi alan hastalar çalışmadan dışlandı. İntrakaviter BCG tedavisi öncesi tüm hastalar idrar tahlili ve kültürü ile değerlendirildi. Hematürisi ve aktif üriner sistem enfeksiyonu olan hastalarda tedavi ertelendi. İndüksiyon tedavisi 6 hafta boyunca her hafta, idame tedavisi ise sıklıkla 3, 6, 12, 18, 24, 30 ve 36. aylarda 3 haftalık dozlarla verildi. İncelenen parametreler arasında hastaların demografik bilgileri, tedavi aldığı tarihler, lokal ve sistemik yan etkiler (dizüri, hematüri, sistitizm, baş ağrısı, artralji/miyalji, üşüme/titrete, yüksek ateş, kırgınlık, epididimoorşit, renal apse, pnömoni, hepatit, sepsis), hospitalizasyon ihtiyacı, antitüberküloz tedavi ihtiyacı, yan etki nedeni tedaviyi sonlandırma ve aldığı doz bilgisi var idi. Cinsiyet ve yaş ayrımı yapılmaksızın verilerine ulaşılabilen tüm hastalar çalışmaya dahil edildi.

Hastalar yaşlarına göre 2 gruba ayrıldı. Yetmiş yaşından küçük olan ve 70 yaşından büyük olan hastalar yan etki profili açısından karşılaştırıldı. Ayrıca değişen suşların zaman içerisinde yan etki profili üzerine bir etkisi olup olmadığını değerlendirmek için 2016 yılı öncesinde ve sonrasında işlem gören hastalar karşılaştırıldı.

Çalışma öncesinde Türkiye Yüksek İhtisas Eğitim ve Araştırma Hastanesi Eğitim Planlama ve Koordinasyon Kurulu onayı alınmıştır. Retrospektif çalışma olduğundan hasta onamı alınmamıştır.

İstatistiksel Analiz

Verilerin analizinde IBM SPSS Statistics for Mac v.21.0 (IBM Corp., Armonk, NY) kullanıldı. Nicel değerler ortalama \pm standart sapma, nitel değerler sayı ve yüzde olarak verildi. Grupların karşılaştırılmasında Mann-Whitney U testi ve ki-kare testleri kullanıldı. $P < 0,05$ istatistiksel olarak anlamlı kabul edildi.

Bulgular

Çalışmaya 84'ü erkek, 5'i kadın olmak üzere toplam 89 hasta dahil edildi. Hastaların ortalama yaşı $67,4 \pm 10,2$ yıl idi. Erkeklerin ortalama yaşı $67,8 \pm 10,1$ yıl iken kadınların ortalama yaşı $60,8 \pm 10,7$ yıl idi. Kadın ve erkekler arasında yaş bakımından anlamlı farklılık yok idi ($p=0,137$). En sık görülen yan etkiler sırasıyla dizüri (%41,6), üşüme-titrete (%31,5), hematüri (%30,3), yüksek ateş (%29,2), sistit (%24,7) ve kırgınlık (%23,6) idi. Tedaviye bağlı olarak 1 (%1,1) hastaya epididimoorşit, 1 (%1,1) hastaya renal apse, 1 (%1,1) hastaya pnömoni ve 2 (%2,2) hastaya hepatit tanısı konmuş idi. Toplamda 4 (%3,4) hasta antitüberküloz tedavisi almıştı. On (%11,2) hastanın BCG yan etkilerine bağlı olarak hospitalizasyonu gerekti. Hastaların 10'u (%11,2) yan etkiler nedeniyle intrakaviter BCG tedavisini sonlandırmak zorunda kaldı. Tedaviyi sonlandıran 10 hastadan 6'sı indüksiyon, 4'ü ise idame dozlarını almakta idi. İndüksiyon tedavisini tamamlayamayan hastalarda intrakaviter kemoterapötik ajanlara geçildi. Hospitalize edilen hastaların yaş ortalaması $70,2 \pm 8,4$ yıl iken diğer hastaların yaş ortalamaları $67 \pm 10,4$ yıl idi ($p=0,366$). Sistemik ya da lokal olmak üzere bir yan etki ile karşılaşan hasta sayısı 62 (%69,7) idi. Yan etki ile karşılaşma açısından 70 yaş altı ve 70 yaş üstü hastalar arasında fark bulunmamakta idi (%69,8'e karşı %69,4, $p=0,576$). Ayrıca 2016 yılı öncesi ve sonrasındaki tedavilerin karşılaştırılmasında yan etki oranlarında anlamlı bir farklılık gözlenmemiştir (%65,3'e karşı %75, $p=0,322$) (Tablo 1).

Tartışma

KİOMK için intrakaviter BCG immünoterapisi ilk kez Morales ve ark. (4) tarafından tanımlanmış ve başarılı bir BCG immünoterapisi için bazı kriterlerin karşılanması gerektiği bildirilmiştir. Bunlar, mikobakteryum antijenine karşı immün cevap geliştirebilme yetisi, yeterli sayıda canlı basil, BCG ve tümörün yakın teması, göreceli düşük tümör yükü ve majör sistemik yan etkilerin olmamasıdır (4).

Optimal BCG preparatı, dozu ve uygulama şeması konusunda kesin bir fikir birliği yoktur. BCG toksisitesi büyük ölçüde yoğun rejimlerden sonra bildirilmiş olsa da birkaç instilasyon sonrası da çok ciddi yan etkiler görülebilir. İki bin altı yüz iki hasta ile yapılan bir çalışmada ateş %2,9, pnömoni/hepatit %0,7, gross hematüri %1, artralji %0,5 ve epididimoorşit %0,4 oranında bildirilmiştir. Farklı BCG suşlarının komplikasyon oranlarında bir değişiklik izlenmemiştir (6). Yapılan bir çalışmada BCG dozunu azaltmanın yan etki oranını azaltmadığı gösterilmiştir (7). Güncel çalışmamızda bildirilen hematüri ve ateş oranları bu çalışmada fazla olmakla birlikte pnömoni, hepatit ve epididimoorşit

Tablo 1. Yan etki profillerinin yaşa ve yıllara göre dağılımı

Yan etkiler		Yaş			Tedavi yılı		
		<70 (n=53)	>70 (n=36)	p	2016 ve sonrası (n=40)	2016 öncesi (n=49)	p
Sistemik yan etkiler	Kırgınlık	13 (%24,5)	8 (%22,2)	1,000	9 (%22,5)	12 (%24,5)	1,000
	Yüksek ateş	15 (%28,3)	11 (%30,6)	0,817	14 (%35)	12 (%24,5)	0,350
	Artralji-miyalji	4 (%7,5)	6 (%16,7)	0,181	3 (%7,5)	7 (%14,3)	0,313
	Üşüme-titreme	16 (%30,2)	12 (%33,3)	0,818	14 (%35)	14 (%28,6)	0,516
	Baş ağrısı	5 (%9,4)	6 (%16,7)	0,341	4 (%10)	7 (%14,3)	0,541
	Renal apse	1 (%1,9)	0	0,407	0	1 (%2)	0,364
	Pnömoni	0	1 (%2,8)	0,222	1 (%2,5)	0	0,266
	Hepatit	1 (%1,9)	1 (%2,8)	0,781	0	2 (%4,1)	0,196
Lokal yan etkiler	Dizüri	24 (%45,3)	13 (%36,1)	0,511	18 (%45)	19 (%38,8)	0,666
	Hematüri	18 (%34)	9 (%25)	0,482	13 (%32,5)	14 (%28,6)	0,817
	Sistit	14 (%26,4)	8 (%22,2)	0,803	11 (%27,5)	11 (%22,4)	0,627
	Epididimoorşit	0	1 (%2,8)	0,222	0	1 (%2)	0,364
Hastanede yatış	-	6 (%11,3)	4 (%11,1)	0,975	7 (%17,5)	3 (%6,1)	0,091
Anti-tüberküloz tedavi	-	1 (%1,9)	2 (%5,6)	0,347	0	3 (%6,1)	0,111
Yan etki nedenli tedavi sonlanması	-	4 (%7,5)	6 (%16,7)	0,181	4 (%10)	6 (%12,2)	0,739

oranları benzer idi. Ayrıca BCG alan hastaların komplikasyon oranlarında yıllar içinde anlamlı bir değişiklik olmamıştır. Bu da farklı suşların yan etki profili üzerinde etkisinin olmadığına bir kanıtı olabilir.

BCG'nin terapötik etkinliğini riske atmadan ilişkili yan etkileri azaltmak için çeşitli formüller denenmiştir. Bunlar her instilasyonda verilen dozu düşürmek ya da instilasyonlar arası zamanı uzatmak olabilir. Yapılan bir çalışmada 150 mg standart BCG (Pasteur şusu) dozu yerine 75 mg azaltılmış doz alan hastalarda sık görülen yan etkilerin anlamlı derecede azaldığı görülmüştür [sistit %57'den %32'ye, ateş <38,5 °C %26'dan %12'ye, gross hematüri %24'ten %13'e (p<0,05)] (8). Irie ve ark. (9) tarafından yapılan bir başka çalışmada tam dozun yarısı olan 40 mg BCG, Tokyo 171 suşu ile, tam doz ile benzer etkinlik saptanmasına karşın BCG toksisitesinde anlamlı azalma bildirilmiştir.

Koga ve ark. (10) tarafından yapılan bir başka çalışmada genel intrakaviter BCG (Tokyo 172 suşu) yan etki insidansı %95,9 olarak bulunmuştur. Profilaksi yerine tedavi amacı ile BCG verilmesi ve BCG dozu yan etki için bağımsız faktörler olarak bulunmuştur (10). Bir başka çalışmada ise 81 mg'dan 27 mg'a azaltılmış BCG (Connaught suşu) dozları ile yapılan instilasyonun progresyonu standart dozla benzer şekilde etkilediği ve toksisitenin daha az olduğu bildirilmiştir (11). Brausi ve ark. (5) tarafından 1316 hasta ile yapılan bir çalışmada ise intrakaviter BCG tedavisinde doz veya tedavi süresinin yan etki profili üzerine anlamlı etkisi olmadığı gösterilmiştir. Bizim çalışmamızda hem indüksiyon hem idame tedavisi alan hastalar bulunduğundan ve progresyona dair yeterli veri bulunmadığından böyle bir karşılaştırma yapmak mümkün değildir.

Heiner ve Terris (12) tarafından intrakaviter BCG alan 58 hasta ile yapılan bir çalışmada hastaların 22 tanesi (%37,9) tedaviye bağlı komplikasyon yaşamıştır. İdame BCG tedavisi alan 70 yaş altı hastalarda komplikasyon oranı %17,6 bulunmuş iken 70 yaşın

üstündeki hastalarda bu oran %48,6 idi. Komplikasyon yaşayan hastaların ortalama yaşı, komplikasyon yaşamayanlara göre anlamlı olarak yüksek bulunmuştur (76 yıla karşın 70,3 yıl, p<0,00001) (12). Bu çalışma grubunda intrakaviter tedaviye bağlı komplikasyon oranı 70 yaşından küçük ve büyük hastalar arasında anlamlı bir fark sergilemiyordu.

Çalışmanın Kısıtlılıkları

Çalışmamızdaki hasta sayısı göreceli olarak azdır. Hangi hastanın hangi suşu kaç kez aldığı ve yan etkilerin kaçınıcı dozdan sonra başladığı ya da sonlandığı bilgisi hasta kooperasyon yetersizliği ve kayıt eksikliğinden tüm hastalarda net olarak belli değildir. Ayrıca, indüksiyon tedavi şeması aynı olmakla birlikte idame tedavi protokolü hekimler arasında farklılık arz edebilir.

Sonuç

Intrakaviter BCG tedavisi KİOMK tedavisinde ileri yaşta hastalarda da kullanılabilir bir tedavi seçeneğidir. Değişen suşlara rağmen yıllar içerisinde komplikasyon oranlarında anlamlı bir değişiklik olmaması suşların benzer yan etki profiline sahip olduğunun bir kanıtı olabilir.

Etik

Etik Kurul Onayı: Çalışma öncesinde Türkiye Yüksek İhtisas Eğitim ve Araştırma Hastanesi Eğitim Planlama ve Koordinasyon Kurulu onayı alınmıştır.

Hasta Onayı: Retrospektif çalışma olduğundan hasta onayı alınmamıştır.

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Vascular Ligation in Laparoscopic Radical Nephrectomy: Comparison of the Endo GIA Stapler and Hem-o-lok Polymer Clips

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Abstract

Objective: Various techniques for vascular ligation are used during laparoscopic surgery. We aimed to compare the Endo GIA stapler and Hem-o-lok polymer clips in laparoscopic radical nephrectomy.

Materials and Methods: The charts and costs were reviewed for all 56 patients who underwent laparoscopic radical nephrectomy at our institution from May 2014 to October 2017. Patients' demographic characteristics, tumor size, blood loss, complications, operative time, and length of hospital stay were evaluated retrospectively. The obtained data were compared statistically.

Results: Forty-six patients eligible for the study were divided into 2 groups according to the use of vascular staples or polymer clips. Amount of blood loss, postoperative drainage volume, and operative time were lower in cases using vascular stapler, while polymer clips were advantageous in terms of cost.

Conclusion: Both techniques have advantages in terms of vascular ligation in laparoscopic radical nephrectomy. These techniques may be chosen based on surgeon preference or patient compatibility; however, it is more appropriate to use the material with which the surgeon is experienced.

Keywords: Nephrectomy, laparoscopic, stapler, clips, ligation

Introduction

Renal tumors are the third most common cancer of the urogenital system and are associated with the highest mortality. They are resistant to chemotherapy and radiotherapy, and the standard treatment method is surgery. Surgery can be open, laparoscopic, or robotic. Laparoscopic nephrectomy was first described by Clayman et al. (1) in 1990 and is currently practiced safely and effectively in many centers. Laparoscopic surgery, which is recommended for stage 1 and 2 renal tumors in current guidelines, can also be performed in cases of larger and more advanced stage tumors (1). These operations can be performed

using retroperitoneal, transperitoneal, and hand-assisted methods, with no differences in terms of their effectiveness or reliability (2,3). Compared to open nephrectomy, laparoscopic surgery has the advantages of being less painful and requiring shorter hospitalization and recovery times, while the high cost, long learning curve, and difficulty of vascular control are considered its disadvantages (4). Starting with the use of metal clips in 1993, various vascular control techniques and materials have been developed to date (2).

In this study, we evaluated differences in vascular control achieved with the Endo GIA stapler and Hem-o-lok polymer clips in laparoscopic nephrectomies performed in our center.

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Materials and Methods

Fifty-six patients who underwent laparoscopic radical nephrectomy (LRN) due to renal tumors between May 2014 and October 2017 were included in the study. The patients' demographic characteristics, tumor size, volume of blood loss, complications, operative time, and length of hospital stay were examined retrospectively. The patients were divided into 2 groups based on the use of Endo GIA stapler (Covidien Endo GIA Universal Articulating Loading Unit 30 mm 2.5 mm) or Hem-o-lok polymer clips (Weck Hem-o-lok Polymer Ligating Clips) for renal pedicle control. Patients in whom both materials were used were excluded from the study. All patients underwent LRN via transperitoneal approach. In patients for whom an Endo GIA stapler was used, the renal artery and vein were ligated without separate dissection. The inferior aspect of the renal vein was dissected until the psoas muscle became visible, and the superior aspect was freed by blunt dissection to enable the upper jaw of the vascular stapler to be positioned in Morison's pouch. The pulse of the renal vein was sensed, and the tip of the Endo GIA stapler was placed so as to rest against the psoas muscle. The stapler was activated to perform ligation. In patients on whom Hem-o-lok clips were used, the artery and vein were dissected separately and 6 clips were placed, 1 distally and 2 proximally on each vessel. After achieving renal pedicle control, the nephrectomy procedure was completed by freeing the kidney from surrounding tissues. Operative time, amount of blood loss, and total drainage volume collected during and after the operation were recorded for each patient. The data were compared between the groups.

Ethical approval was not sought for this retrospective study. Written informed consent was obtained from the patients.

Statistical Analysis

Statistical analyses were conducted using SPSS version 16.0 (SPSS Inc. Chicago, IL, USA), and the Mann-Whitney U test was used for intergroup analysis. A p value below 0.05 was regarded as significant.

Results

Of the 56 patients included in the study, 10 were excluded due to missing data, the use of both ligation methods together, or inability to complete the surgery laparoscopically. Therefore, a total of 46 patients were included in our analysis. The mean age of the patients was 69.8 ± 2.1 years (32-81 years) and the male/female ratio was 26/20. The patients' demographic and tumor characteristics are shown in detail in Table 1. Ligation was done using an Endo GIA stapler in group 1 (n=20) and with Hem-o-lok polymer clips in group 2 (n=26). Extent of bleeding was compared between the groups by evaluating change from pre- to postoperative hemoglobin (Hb) values and calculating intra- and postoperative drainage volumes. The mean decrease in Hb was 1.1 ± 0.3 g/dL (8%) in group 1 and 2.7 ± 0.9 g/dL (18.8%) in group 2. The mean intraoperative drainage volume was similar in both groups (316 ± 45 cc and 354 ± 48 cc, respectively). Postoperative drainage volume indicated significantly less bleeding in group 1 (183 ± 27 cc and 273 ± 29 cc, respectively; $p < 0.02$). Length of hospital stay was similar in both patient groups (4.1 ± 0.4 days and 4.4 ± 0.5 days, respectively). In 1 patient for whom an Endo GIA stapler was used, intraabdominal

Table 1. Demographic characteristics and comparison of patient groups who underwent laparoscopic radical nephrectomy with Endo GIA stapler (group 1) and Hem-o-lok clips (group 2)

	Group 1 (n=20)	Group 2 (n=26)	p
Age (mean, years)	67.2	76.2	-
Gender (M/F)	9/11	17/9	-
Tumor size (mean, mm)	34	47	-
Hemoglobin level			
Preop hemoglobin	13.3	14.3	<0.03
Postop hemoglobin	12.2	11.6	
Change (%)	8	18.8	
Operative time (mean, minutes)	110±10	178±15	<0.05
Intraoperative drainage volume (mean, mL)	316±45	354±48	-
Postoperative drainage volume (mean, mL)	183±27	273±29	<0.02
Hospital stay (mean, days)	4.1±0.4	4.4±0.5	-
Cost (TL)	332	126	-
M: Male, F: Female			

hemorrhage was suspected due to sudden development of hemodynamic instability at postoperative 6 hours. The patient underwent emergency laparotomy during which bleeding from the lumbar vein was detected and repaired. The patient was discharged with no complications on postoperative day 6.

When the groups were compared in terms of operative time, the Endo GIA group had shorter mean operative time (110 ± 10 min vs 178 ± 15 min; $p < 0.05$). In terms of the cost of these materials, the price specified in the Turkish Circular on Healthcare Practices for the Endo GIA stapler used in our center (Covidien Endo GIA Universal Articulating Loading Unit 30 mm 2.5 mm) is 332 TL, while that of a single Hem-o-lok clips (Weck Hem-o-lok Polymer Ligating Clips) is 21 TL. Each pack of Hem-o-lok clips contains 6 clips. The mean cost per patient was calculated as 126 TL for group 2. Therefore, the cost was higher for patients on whom the Endo GIA was used. Statistical analysis showed that the use of Hem-o-lok clips was more advantageous in terms of cost, while the amount of blood loss, postoperative drainage volume, and operative time were lower among patients for whom the Endo GIA vascular stapler was used.

Discussion

LRN, one of the reflections of minimally invasive techniques in urology, has become more common than open nephrectomy in most centers. While vascular control can be achieved by suturing in open radical nephrectomy, suturing difficulties in laparoscopic surgery have led to the development of various new techniques. These include titanium clips, Hem-o-lok clips, staplers, and laparoscopic LigaSure. There are previous studies demonstrating the advantages and disadvantages of the Endo GIA stapler and Hem-o-lok clips (5,6). Chan et al. (7) used the Endo GIA stapler for ligation in LRN and reported instrument-related complications in 10 of 565 patients. They calculated this rate as 1.7% and argued that it is more reliable than other methods (7). Apparent advantages of the Endo GIA stapler are

that it can be angled and is easy to open; however, the two-handed operation is a drawback compared to other methods. In studies evaluating vascular length and the effectiveness of vascular control devices, Hem-o-lok clips were shown to be advantageous in terms of avoiding aortic damage in cases with short renal artery if the trocar is placed properly (5). In addition to vascular length, there are studies showing that vascular pressure also affects the ligation method (6,8). In an experimental study by Kerbl et al. (8), titanium clips were reported to be as safe as 2-0 or 0 silk sutures. Based on their calculations, staples fail in vessels with a pressure over 237 mmHg, leading to leakage after ligation. They concluded that in patients with systolic pressure over 200 mmHg, stapling should only be utilized with the renal vein, and the placement of metal clips was more appropriate for the renal artery (8). While no such measurement was done in our study, hemorrhage was detected in one patient on whom we used a stapler, but no leakage was observed when the stapler line was examined by laparotomy. The hemorrhage was found to originate from the lumbar veins and was considered unrelated to the ligation technique due to its distance from the suture site. Meng et al. (9) used a stapler on 15 of 97 patients, of whom 1 required conversion to open surgery due to hemorrhage, while clips were used for the other 82 patients. The researchers asserted that the clip resulted in fewer complications (9). Studies involving cost analysis have shown that polymer clips are an advantageous material because they are cheaper than vascular staplers and more reliable than titanium. In a cost study by Bernie et al. (5), the average cost per patient to use a vascular stapler was \$258, compared to a cost of \$21 to use clips. However, when the additional \$1395 cost of the clip applicator was taken into account, the total cost per patient was \$49 (5). In a study conducted in Turkey in 2010, the price of an Endo GIA stapler was calculated as 1026.95 TL and that of a single Hem-o-lok clip was calculated as 10.59-15.32 TL depending on size, with an additional cost of 70.63-102.10 TL incurred by the use of 3 clips each for the artery and vein and another for the ureter. The main drawback of Hem-o-lok clips is the cost of the \$950 applicators, which are necessary for every size clip. However, the total calculation showed that using polymer clips is advantageous in terms of cost (10). Guazzoni et al. (11) reported reducing the per patient cost by 805 euros by using Hem-o-lok clips instead of an Endo GIA stapler on patients operated after the year 2003. Therefore, as there are no differences in terms of effectiveness and complications, the general appraisal in the literature is in favor of using clips due to their low cost (5). In our cost analysis, we did not include materials used in both groups, such as trocars, endobags, and camera sleeves, in the calculation. Since 2010, prices for outpatient and inpatient health services in state health institutions are specified in the Circular on Healthcare Practices issued by the Turkish Social Security Institution. According to Circular on Healthcare Practices, the reimbursement value of the polymer clip is 21 TL, while that of the vascular stapler has been updated as 332 TL. While the polymer clip appears to be advantageous in terms of total cost per patient, the benefits of the stapler with regard to operative time and blood loss should not be overlooked. Either technique may be chosen, based on the surgeon's preference and the patient's anatomical structure. We believe that using a stapler is a fast, easy, and reliable method in cases where the pedicle can be easily exposed.

Study Limitations

Because of the small number of cases in our study, we could not perform multiple regression analysis for risk factors affecting cost. Other limitations include the absence of subgroup analysis based on tumor size and location, and the fact that the patients' preoperative blood pressure and vessel width and length were not measured.

Conclusion

Our comparison of these 2 vascular control devices has shown that vascular stapler is advantageous in all respects except cost. Nevertheless, it seems more appropriate for the surgeon to choose the method with which he or she is experienced.

Ethics

Ethics Committee Approval: Not obtained because this study is retrospective.

Informed Consent: Written informed consent was obtained from patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.N.Y., E.Ö., H.B., Concept: T.N.Y., E.Ö., M.D.G., Design: T.N.Y., H.B., Data Collection or Processing: M.D.G., Analysis or Interpretation: T.N.Y., E.Ö., Literature Search: T.N.Y., N.H., Writing: T.N.Y.

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Laparoskopik Radikal Nefrektomide Damar Ligasyonu: Endo GIA Stapler ve Hem-o-lok Polimer Klips Karşılaştırması

Vascular Ligation in Laparoscopic Radical Nephrectomy: Comparison of the Endo GIA Stapler and Hem-o-lok Polymer Clips

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Öz

Amaç: Laparoskopik cerrahide farklı damar ligasyon yöntemleri mevcuttur. Bu çalışmada laparoskopik radikal nefrektomide kullanılan Endo GIA stapler ve Hem-o-lok polimer klips tekniklerinin karşılaştırılması planlandı.

Gereç ve Yöntem: Mayıs 2014 ve Ekim 2017 tarihleri arasında laparoskopik radikal nefrektomi uygulanan 56 hastanın verileri ve hastane faturaları değerlendirildi. Hastaların demografik özellikleri, tümör boyutları, kanama miktarları, komplikasyon durumları, operasyon süreleri, hastanede kalış süreleri ile ilgili veriler retrospektif olarak toplandı. Elde edilen veriler istatistiksel olarak karşılaştırıldı.

Bulgular: Çalışmaya uygun bulunan 46 olgu vasküler stapler ve polimer klips kullanımına göre 2 gruba ayrıldı. Maliyet açısından klips kullanımı avantajlı olarak gözlenirken vasküler stapler kullanılan olguların kanama miktarı, postoperatif dren miktarı ve operasyon süresi düşük bulunmuştur.

Sonuç: Laparoskopik radikal nefrektomide damar ligasyonu açısından her iki tekniğin de birbirinden avantajlı özellikleri bulunmaktadır. Cerrahin tercihi ve hastanın uygunluğu bakımından her iki teknik de tercih edilebilir ancak cerrahın tecrübeli olduğu metodu kullanması daha uygundur.

Anahtar Kelimeler: Nefrektomi, laparoskopi, stapler, klips, ligasyon

Abstract

Objective: Various techniques for vascular ligation are used during laparoscopic surgery. We aimed to compare the Endo GIA stapler and Hem-o-lok polymer clips in laparoscopic radical nephrectomy.

Materials and Methods: The charts and costs were reviewed for all 56 patients who underwent laparoscopic radical nephrectomy at our institution from May 2014 to October 2017. Patients' demographic characteristics, tumor size, blood loss, complications, operative time, and length of hospital stay were evaluated retrospectively. The obtained data were compared statistically.

Results: Forty-six patients eligible for the study were divided into 2 groups according to the use of vascular staples or polymer clips. Amount of blood loss, postoperative drainage volume, and operative time were lower in cases using vascular stapler, while polymer clips were advantageous in terms of cost.

Conclusion: Both techniques have advantages in terms of vascular ligation in laparoscopic radical nephrectomy. These techniques may be chosen based on surgeon preference or patient compatibility; however, it is more appropriate to use the material with which the surgeon is experienced.

Keywords: Nephrectomy, laparoscopic, stapler, clips, ligation

Giriş

Böbrek tümörleri ürogenital sistemin en sık 3. kanseri olup en mortal seyirli tümördür. Kemoterapi ve radyoterapiye dirençli olup standart tedavi yöntemi cerrahidir. Cerrahi yöntem açık, laparoskopik ve robotik tarzda uygulanabilmektedir. Laparoskopik nefrektomi ilk kez 1990 yılında Clayman ve ark. (1) tarafından tanımlanmış olup günümüzde birçok merkezde etkin ve güvenilir şekilde uygulanmaktadır. Güncel kılavuzlarda evre 1 ve 2 böbrek tümörlerinde önerilmekte olan laparoskopik cerrahi daha büyük ve ileri evreli tümörlerde de yapılabilmektedir (1). Retroperitoneal, transperitoneal ve el yardımcı yöntemler eşliğinde bu operasyonlar uygulanabilmektedir ve yaklaşımların etkinliği ve güvenilirliği açısından fark yoktur (2,3). Açık nefrektomi ile karşılaştırıldığında daha az ağrılı olması, hastanede kalış süresinin ve nekahat döneminin daha kısa olması laparoskopik cerrahinin avantajları iken; yüksek maliyet, uzun öğrenme eğrisi ve damar kontrolünün zorluğu da dezavantajları olarak kabul edilmektedir (4). 1993 yılında ilk kez metal klips kullanımıyla başlayan vasküler kontrol tekniği için günümüzde farklı damar kontrol teknikleri ve malzemeleri üretilmiştir (2). Bu çalışmada kliniğimizde yapılan laparoskopik nefrektomi operasyonlarında damar kontrolünü sağlamada Endo GIA stapler ve Hem-o-lok polimer klips kullanımı arasındaki farkları değerlendirdik.

Gereç ve Yöntem

Mayıs 2014 ile Ekim 2017 tarihleri arasında böbrek tümörü nedeniyle laparoskopik radikal nefrektomi (LRN) uygulanan 56 hasta çalışmaya dahil edildi. Çalışmaya alınan olguların demografik özellikleri, tümör boyutları, kanama miktarları, komplikasyon durumları, operasyon süreleri, hastanede kalış süreleri ile ilgili veriler retrospektif olarak incelendi. Hastalar renal pedikül kontrolü amaçlı Endo GIA stapler (Covidien Endo GIA Universal Articulating Loading Unit 30 mm 2,5 mm) veya Hem-o-lok polimer klips (Weck Hem-o-lok Polymer Ligating Clips) kullanımı bakımından 2 gruba ayrıldı. Her 2 malzemenin de kullanıldığı olgular çalışma dışı bırakıldı. Olguların tümüne transperitoneal LRN uygulandı. Endo GIA stapler kullanılan olgularda renal arter ve ven ayrı ayrı diseke edilmeksizin ligasyonu sağlandı. Endo GIA stapler kullanılan olgularda renal venin inferiorunun psoas kası görününceye kadar diseke edilmesini takiben superiordeki Morison boşluğunda vasküler staplerin üst bacağı yerleştirilecek kadar künt diseksiyonla serbestlendi. Renal venin arkasındaki arterin pulsasyonu alınarak Endo GIA staplerin ucu psoas kasına dayanarak yerleştirildi. Stapler aktif hale getirilerek ligasyonu sağlandı. Hem-o-lok klips yerleştirilen olgularda ise arter ve ven ayrı ayrı diseke edilerek distale 1, proksimale 2 adet olmak üzere 6 klips yerleştirildi. Renal pedikül kontrolü sağlandıktan sonra, böbrek çevre dokulardan serbestlenerek nefrektomi işlemi tamamlandı. Retrospektif çalışma olmasından dolayı etik kurul onayı alınmamıştır. Hastalardan yazılı onay alınmıştır.

İstatistiksel Analiz

Olguların operasyon süreleri, kanama miktarları ile operasyon esnasında ve sonrasında toplanan drenaj miktarları kaydedildi. Elde edilen veriler gruplar arasında karşılaştırıldı. İstatistiksel

analizler SPSS 16.0 versiyonu (SPSS Inc. Chicago, IL, USA) kullanılarak gruplar arası Mann-Whitney U testiyle yapıldı. P değeri 0,05'in altındaki değer anlamlı kabul edildi.

Bulgular

Çalışmaya alınan 56 olgunun 10'u veri eksikliği, her 2 ligasyon yönteminin birlikte kullanılması veya cerrahinin laparoskopik metot ile tamamlanamaması nedeni ile çalışma dışı bırakılarak toplam 46 olgu çalışmaya uygun bulundu. Olguların yaş ortalaması 69,8±2,1 yıl (32-81 yıl), erkek/kadın oranı 26/20 olarak görüldü. Olguların tüm demografik özellikleri ve tümörlerin karakteristik özellikleri Tablo 1'de ayrıntılı olarak gösterilmiştir. Grup 1 (20), ligasyon amaçlı Endo GIA stapler kullanılan olgulardan; grup 2 (26) ise Hem-o-lok polimer klips kullanılan olgulardan oluşmaktadır. Gruplar arasındaki kanama miktarının karşılaştırılması amacıyla cerrahi öncesi ve sonrası hemoglobin (Hb) değerleri arasındaki değişim, operasyon esnasındaki drenaj miktarı ve postoperatif drenaj miktarı hesaplandı. Grup 1 olguların Hb miktarındaki düşme ortalama 1,1±0,3 g/dL (%8) iken grup 2'de bu düşüş 2,7±0,9 g/dL (%18,8) seviyesindedir. Operasyon esnasındaki ortalama drenaj miktarı her 2 grupta da benzer olarak izlendi (sırasıyla 316±45 cc, 354±48 cc). Cerrahi sonrası dönemdeki drenaj miktarlarında grup 1'de anlamlı olarak daha az kanama olduğu görüldü (sırasıyla 183±27 cc, 273±29 cc, p<0,02). Hastanede yatış süreleri incelendiğinde her 2 hasta grubunda da benzer süreler gözlemlendi (sırasıyla 4,1±0,4 gün, 4,4±0,5 gün). Endo GIA kullanılan 1 olguda postoperatif 6. saatte ani gelişen hemodinamik instabilite nedeniyle intraabdominal kanama düşünüldü. Acil laparotomi yapılan olgunun lomber venden kanaması olduğu tespit edilip onarım gerçekleştirilerek postoperatif 6. günde sorunsuz taburcu edildi. Operasyon süreleri bakımından gruplar karşılaştırıldığında, Endo GIA kullanılan olguların daha kısa ameliyat süresinde sonuçlandığı istatistiksel olarak gösterilmiştir (sırasıyla 110±10 dakika, 178±15 dakika, p<0,05). Kullanılan malzemelerin maliyetini incelediğimizde kliniğimizde kullanılan Endo GIA

Tablo 1. Olguların demografik özellikleri ve grupların karşılaştırılması

	Grup 1 (n=20)	Grup 2 (n=26)	p
Yaş (ortalama, yıl)	67,2	76,2	-
Cinsiyet (E/K)	9/11	17/9	-
Tümör boyutu (ortalama, mm)	34	47	-
Hemoglobin düzeyi			
Preop hemoglobin	13,3	14,3	
Postop hemoglobin	12,2	11,6	
Değişim (%)	8	18,8	<0,03
Operasyon süresi (ortalama, dakika)	110±10	178±15	<0,05
Operasyon esnasındaki drenaj (ortalama, mL)	316±45	354±48	-
Postop drenaj miktarı (ortalama, mL)	183±27	273±29	<0,02
Yatış süresi (ortalama, gün)	4,1±0,4	4,4±0,5	-
Maliyet (TL)	332	126	-
E: Erkek, K: Kadın			

staplerin (Covidien Endo GIA Universal Articulating Loading Unit 30 mm 2,5 mm) Sağlıkta Uygulama Tebliği fiyatı 332 TL iken tek Hem-o-lok klipsin (Weck Hem-o-lok Polymer Ligating Clips) fiyatı 21 TL olarak belirlenmiştir. Hem-o-lok klipslerin her paketinden 6 adet klips çıkmaktadır. Grup 2 olgularda hasta başı ortalama maliyet 126 TL hesaplanmıştır. Bu açıdan her 2 grubu karşılaştırdığımızda maliyetin Endo GIA kullanılan olgularda daha yüksek olduğu görülmüştür. İstatistiksel olarak incelendiğinde maliyet açısından klips kullanımı avantajlı olarak gözlenirken vasküler stapler kullanılan olguların kanama miktarı, postoperatif dren miktarı ve operasyon süresi düşük bulunmuştur.

Tartışma

Minimal invaziv tekniklerin ürolojideki yansımalarından biri olan LRN çoğu klinikte açık nefrektomiye oranla daha sık yapılmaya başlanmıştır. Açık radikal nefrektomide damar kontrolü sütür ile sağlanırken laparoskopik cerrahideki sütürizasyon zorlukları farklı tekniklerin tanımlanmasına sebep olmuştur. Titanyum klipsler, Hem-o-lok klipsler, stapler ekipmanları ve laparoskopik LigaSure bunlardan bazılarıdır. Bu yöntemlerden Endo GIA stapler ve Hem-o-lok klips kullanımının avantaj ve dezavantajlarını gösteren çalışmalar bulunmaktadır (5,6). Chan ve ark. (7) 565 hastalık LRN serilerinde ligasyon amaçlı Endo GIA stapler kullanmışlardır ve 10 hastada alet bağımlı komplikasyon yaşamışlardır. Bu oranı %1,7 olarak hesaplamışlar ve diğer yöntemlere nazaran daha güvenilir olduğunu savunmaktadırlar (7). Endo GIA stapler ekipmanının açılı olabildiği ve kolay açılması avantajları olarak görünmekteyken, 2 ele ihtiyaç duyması diğer yöntemlere göre negatif bir özelliğidir. Damar uzunluğu ile kullanılan ekipmanların başarısını değerlendiren çalışmalarda trokarın düzgün yerleştirilmesi ile renal arteri kısa kalan olgularda aorta hasarı olmaması açısından Hem-o-lok klipsin avantajlı olduğu gösterilmiştir (5).

Damar uzunluğunun yanı sıra vasküler basıncın da ligasyon yöntemi üzerinde etkisi olduğunu gösteren çalışmalar mevcuttur (6,8). Kerbl ve ark.'nın (8) deneysel çalışmasında titanyum klipslerin 2-0 veya 0 ipek sütür kadar güvenli olduğu belirtilmiştir. Yaptıkları hesaplarda 237 mmHg basıncın üzerindeki damarlarda stapler tekniğinin başarısız olduğunu ve ligasyon sonrası sızdırmaya yol açtığını raporlamışlardır; sonuç olarak 200 mmHg üzeri sistolik basıncı olan olgularda sadece renal ven için stapler, renal arter için ise metal klips yerleştirilmesinin uygun olacağı belirlenmiştir (8). Çalışmamızda bu tarz bir ölçüm yapılmazken stapler uyguladığımız tek olguda kanama görülmüş, bu olguda da laparotomi ile stapler hattı incelendiğinde herhangi bir sızıntı izlenmemiştir. Hastanın kanamasının lomber venlerden kaynaklı olduğu ve kanamanın sütürasyon bölgesinden uzakta olması nedeniyle kullanılan ligasyon tekniğinden bağımsız olduğu belirlenmiştir. Meng ve ark. (9) 97 olgunun 15 tanesinde stapler kullanmışlar; bunlardan 1 tanesinde kanama nedeni açık cerrahiye geçilmiş, diğer 82 olguda ise klips yerleştirmişlerdir. Araştırmacılar klipsin daha az komplikasyona yol açtığını savunmaktadırlar (9).

Maliyet analizinin yapıldığı çalışmalarda polimer klipsin vasküler staplere göre daha ucuz olması ve titanyuma göre daha güvenilir olması bakımından avantajlı bir materyal olduğu gösterilmiştir. Bernie ve ark.'nın (5) maliyet çalışmasında ortalama vasküler stapler kullanımının hasta başı 258 \$, klips kullanımının ise

21 \$'lık bir maliyeti hesaplanmıştır. Ancak klips aplikatörünün 1395 \$'lık ek maliyeti de hesaplandığında hasta başına 49 \$'lık toplam maliyet çıkmıştır (5). 2010 yılında Türkiye'den yapılan bir çalışmada da Endo GIA stapler fiyatının 1026,95 TL olduğu, tek bir Hem-o-lok klips maliyetinin boyutuna göre 10,59-15,32 TL arasında olup 3'er adet arter ile ven ve 1 adet ureter için kullanımının 70,63-102,10 TL ek maliyet getirdiği hesaplanmıştır. Hem-o-lok klipslerin en önemli olumsuzluğu her boyut için gerekli olan 950 \$'lık aplikatör maliyetidir. Yine de total hesapta polimer klips kullanımının maliyet açısından avantajlı olduğu gösterilmiştir (10). Guazzoni ve ark. (11) 2003 yılından sonra yaptıkları olgularda Endo GIA stapler yerine Hem-o-lok klips kullanarak olgu başına 805 EUR maliyeti azalttıklarını bildirmişlerdir. Sonuç olarak genel literatür değerlendirmesi etki ve komplikasyon bakımından herhangi bir fark bulunmaması nedeni ile olgularda ucuz olması bakımından klips kullanımının tercih edilmesi şeklindedir (5). Bizim maliyet analizimizde ise her 2 grupta da ortak kullanılan trokar, endobag, kamera kılıfı gibi malzemeler maliyet analizinde hesaplanmadı. Sağlık kuruluşlarında ayaktan ve yatarak verilen sağlık hizmetlerinin bedeli 2010 yılından beri Sosyal Güvenlik Kurumu Sağlıkta Uygulama Tebliği'ne göre belirlenmektedir. Sağlıkta Uygulama Tebliği'ne göre polimer klipsin ödemesi 21 TL iken vasküler stapler ödemesi 332 TL olarak güncellenmiştir. Hasta başı toplam maliyet açısından polimer klips avantajlı olarak gözükmeyle birlikte staplerin operasyon süresi ve kanama miktarında gözlenen avantajlı tarafları göz ardı edilmemelidir. Cerrahin tercihi ve hastanın anatomik yapısının uygunluğu bakımından her 2 teknik de tercih edilebilir. Biz pedikülün rahatça ortaya konulabildiği olgularda stapler kullanımının hızlı, kolay ve güvenilir bir yöntem olduğuna inanmaktayız.

Çalışmanın Kısıtlılıkları

Çalışmamızda az sayıda olgu bulunması nedeniyle maliyeti etkileyen risk etkenleri için birden çok regresyon analizi yapılamadı. Ayrıca tümör boyutu ve lokalizasyonuna göre alt grup analizi yapılmamış olması, olguların cerrahi öncesi tansiyon bilgileri, vasküler yapıların genişliği ve boyunun hesaplanmamış olması diğer limitasyonlardır.

Sonuç

Çalışmamızda bu 2 ekipmanın karşılaştırması ile vasküler stapler kullanımının maliyet dışında avantajlı olduğu gösterilmiştir. Yine de cerrahin tecrübeli olduğu ekipmanı tercih etmesi daha uygun görünmektedir.

Etik

Etik Kurul Onayı: Retrospektif çalışma olmasından dolayı etik kurul onayı alınmamıştır.

Hasta Onayı: Hastalardan yazılı onay alınmıştır.

Hakem Değerlendirmesi: Editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

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Association Between Postoperative 3rd Month Renal Function After Radical Cystectomy and Preoperative Factors, Oncologic Outcomes, and Complications

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Abstract

Objective: We aimed to investigate the influence of preoperative factors on postoperative renal function and the association between renal function and oncologic outcomes and complications after radical cystectomy (RC).

Materials and Methods: We retrospectively analyzed patients who underwent RC due to muscle-invasive bladder cancer and intravesical treatment-resistant nonmuscle-invasive bladder cancer in our center between January 2006 and March 2017. The patients' age, gender, comorbidities, preoperative estimated glomerular filtration rate (eGFR), presence of hydronephrosis, hydronephrosis grade and laterality, urinary diversion type, preoperative and postoperative pathology findings, eGFR at postoperative 3rd month, oncologic outcomes, and complication rates were evaluated. The patients were divided into 2 groups based on postoperative eGFR: group 1 (<60 mL/min eGFR) and group 2 (≥60 mL/min eGFR), and data were compared between the groups.

Results: The study included 125 patients with urothelial carcinoma of the bladder who underwent RC and had complete records (59 patients in group 1 and 66 patients in group 2). Of the preoperative factors, only presence of hydronephrosis was significantly higher in group 1 (p=0.012). There were no statistically significant differences between the groups in terms of urinary diversion type, pathology findings, oncologic outcomes, or complications.

Conclusion: Preoperative eGFR and hydronephrosis were significantly associated with postoperative 3rd month eGFR. Postoperative eGFR <60 mL/min was not associated with diversion type, pathologic and oncologic outcomes, or complications.

Keywords: Bladder cancer, postoperative renal function, estimated glomerular filtration rate, radical cystectomy, hydronephrosis

Introduction

Radical cystectomy (RC), extended lymph node dissection, and urinary diversion offer the best survival advantage in the treatment of muscle-invasive bladder cancer (MIBC) and high-risk non-muscle-invasive bladder cancer (NMIBC) (1). However, the need for neoadjuvant chemotherapy (NAC) prior to RC or adjuvant chemotherapy (AC) following RC varies depending

on patient characteristics and physician preference (2). For NAC, pre-RC tumor volume (imaging findings consistent with T3 disease and lymph node positivity) and renal function are the important patient-related factors influencing chemotherapy decisions (1,2,3). In contrast, AC is given based on post-RC performance status and renal function (4,5). Although renal functional capacity varies before and after RC, it is important in chemotherapy planning. However, numerous studies have

demonstrated the relationship between renal function and patients' preoperative characteristics, comorbidities, and presence of hydronephrosis (2,4,5). Risk factors for early postoperative acute renal dysfunction have also been identified (6). However, there are no definitive data regarding the effects of postoperative renal function on post-RC complications (6) and oncologic outcomes.

The aim of this study was to investigate the association between postoperative renal function and preoperative factors, post-RC oncologic outcomes, and complications.

Materials and Methods

Patients with bladder cancer who underwent RC in our center between January 2006 and March 2017 were retrospectively analyzed. Histologic type was urothelial carcinoma in all cases included in the study. Patients with bladder cancers other than urothelial carcinoma, patients with upper urinary tract tumors, obstructive urinary tract stone disease, or solitary kidney prior to RC, patients receiving NAC (due to their small number), and patients with missing follow-up data were excluded. The patients' general characteristics and preoperative, peroperative, and postoperative data were screened. The patient group consisted of those with MiBC and NMIBC (Ta, T1, carcinoma *in situ*). The NMIBC group included Ta patients presenting with extensive, refractory, and frequent hematuria and T1 patients resistant to intravesical therapy.

Patients were analyzed in terms of general characteristics (age, gender, presence of diabetes mellitus (DM), hypertension (HT), and other comorbidities); preoperative data [preoperative estimated glomerular filtration rate (eGFR), American Society of Anesthesiologists (ASA) Score, Eastern Cooperative Oncology Group (ECOG) Performance Score, Charlson Comorbidity Index, and presence, grade, and laterality of hydronephrosis]; peroperative data (operation time, type of urinary diversion); pathologic data (pre- and postoperative T stage, grade, and other important pathology findings); postoperative data (eGFR at postoperative 3rd month); oncologic outcomes (upstaging, AC rate, overall mortality and survival time, and cancer-specific mortality and survival time); and complication data (length of hospital stay, rates of early medical and surgical complications, and distribution of complications according to Clavien-Dindo classification). Hydronephrosis was defined as the presence of dilation of the renal pelvis and calyces and renal pelvic anteroposterior diameter of >10 mm in ultrasonography or computed tomography (7). Based on previous studies, the patients were divided into 2 groups according to a postoperative eGFR threshold of 60 mL/min (6,8,9). Patients with eGFR <60 mL/min were in group 1 and those with eGFR ≥60 mL/min were in group 2.

Statistical Analysis

The data were analyzed using Statistical Package for the Social Sciences, version 20.0 (SPSS, Chicago, IL, USA) software. Patients classified into groups 1 and 2 based on postoperative eGFR level were compared. Univariate analysis was done using Mann-Whitney U test and Pearson's chi-square test; multivariate analysis was done using binary logistic regression analysis. In addition, overall survival and cancer-specific survival data were

analyzed using Kaplan-Meier survival analysis and log-rank test. The data in the tables are expressed in median (minimum-maximum) and these values were used for statistical analysis. P value <0.05 was accepted as the level of significance.

Results

A total of 125 patients with urothelial carcinoma of the bladder who underwent RC and had complete records were analyzed. Mean age was 64.1±8.8 (32-83) years and mean follow-up period was 32.4±30.8 (1-113) months; 12 (9.6%) of the patients were female. The mean overall and cancer-specific survival times were 58.7±4.8 and 67.9±5.1 months, respectively. Group 1 included 59 patients and group 2 included 66. Patient characteristics and preoperative data of groups 1 and 2 and the results of comparison between the groups are presented in Table 1. Patient characteristics were similar between the groups. Of the preoperative parameters, preoperative eGFR and hydronephrosis rate were significantly higher in group 1 (p=0.012). Other data affecting eGFR were comparable in the 2 groups. Preoperative, peroperative, and postoperative pathology findings of the groups and their comparative results are given in Table 2. There were no significant differences between the groups in terms of pathology or urinary diversion type. In addition, postoperative pathology results indicated at least stage T1 in all patients who underwent RC due to NMIBC. There were no significant differences in oncologic data or complications between the groups (Table 3). The AC rates of the groups were also similar. The patients showed similar overall survival time (group 1: 57.8±7.0 months and group 2: 54.3±5.7 months, p=0.662) and cancer-specific survival time (group 1: 68.8±7.2 months and group 2: 60.9±6 months, p=0.821) and mortality rates (overall mortality was 49.2% in group 1 and 43.9% in group 2, p=0.560; cancer-specific mortality was 37.3% in group 1 and 34.8% in group 2, p=0.777). The overall and cancer-specific survival curves of the patients are shown in Figures 1 and 2.

Discussion

This study investigated patient characteristics and comorbidities influencing post-RC eGFR at postoperative 3rd month, and ASA Score, ECOG Performance Score, Charlson Comorbidity Index, and the presence of DM, HT, and other comorbidities were found to have no effect on postoperative eGFR. However, we observed a significant correlation between preoperative hydronephrosis and low eGFR (p=0.012). Other than this, the most important factor affecting postoperative eGFR was preoperative eGFR (p<0.001). In a study investigating risk factors for acute renal failure in the early postoperative period (after the withdrawal of ureteral stent on postoperative day 7), acute renal failure was observed in 48 of 145 patients evaluated. In these 48 patients, preoperative eGFR <60, HT, and NAC were identified as independent risk factors for acute renal failure (6). Unlike that study, our study focused on renal function at postoperative month 3 rather than the early postoperative period. In addition, our study did not include patients receiving NAC. In a recent similar study including 164 patients, factors influencing eGFR at postoperative 3rd month were investigated by creating a

Table 1. General characteristics of the patients and the comparison of preoperative data between groups				
		Postoperative eGFR <60 mL/s (Group 1) (n=59)	Postoperative eGFR ≥60 mL/s (Group 2) (n=66)	p
Age (years)		66 (45-83)	64 (32-80)	0.288
Gender	Female	8	4	0.155
	Male	51	62	
Preoperative eGFR		55.1 (17.5-118.4)	75.3 (6.8-141.4)	<0.001
Postoperative 3 rd month eGFR		40.4 (15.7-59.3)	82.5 (60.0-118.4)	-
ASA Score	1	2	3	0.756
	2	37	38	
	3	20	24	
	4	0	1	
ECOG Performance Score	0	15	18	0.88
	1	27	31	
	2	10	11	
	3	4	5	
Charlson Comorbidity Index	0	0	1	0.241
	1	2	1	
	2	15	9	
	3+	42	55	
DM, n (%)		13 (22)	10 (15.2)	0.322
HT, n (%)		21 (35.6)	27 (40.9)	0.542
Other comorbidity, n (%)		45 (76.3)	46 (69.7)	0.410
Preoperative hydronephrosis	(+)	31 (52.5)	20 (30.3)	0.012 *0.012
	(-)	28 (47.5)	46 (69.7)	
Hydronephrosis laterality	Unilateral	22 (71)	15 (75)	0.753
	Bilateral	9 (29)	5 (25)	
Preoperative grade of hydronephrosis	1	0 (0)	4 (20)	0.074
	2	9 (29)	4 (20)	
	3	16 (51.6)	8 (40)	
	4	6 (19.4)	4 (20)	

ASA: American Society of Anesthesiologists, ECOG: Eastern Cooperative Oncology Group, DM: Diabetes mellitus, HT: Hypertension, eGFR: Estimated glomerular filtration rate
*Binary logistic regression analysis
Mann-Whitney U test and Pearson chi-square test

nomogram (2). It was reported that postoperative eGFR was significantly associated with patient age and preoperative eGFR, as well as type of urinary diversion and thickness of abdominal subcutaneous fat tissue. In addition, the authors emphasized that postoperative eGFR may be improved due to removal of the obstruction after surgery in patients with preoperative hydronephrosis, but the difference was statistically nonsignificant (2). They stated that although postoperative eGFR may be improved in cases of hydronephrosis associated with acute obstructions, eGFR may not improve in patients with long-term, slow-growing obstructions (2). Here, the compensatory capacity of the patient's contralateral kidney is also important.

Our results in the present study differ from the aforementioned findings. Firstly, of 51 patients with hydronephrosis, 31 also

had low postoperative eGFR. However, these 51 patients had similar bilateral and unilateral hydronephrosis rates and grade of hydronephrosis in both groups. This may be attributed to the slow progression of hydronephrosis as a chronic process in the bladder, and this leads to permanent renal dysfunction (2). In addition, in the present study, group 1 showed lower postoperative eGFR compared to preoperative values, while an increase was observed in group 2 ($p < 0.001$). Thus it can be said that persistent renal dysfunction due to hydronephrosis in this group does not improve postoperatively. The findings of previous research and our study suggest that comorbidities are not associated with poor postoperative renal function, whereas type of urinary diversion must be evaluated further (2,5,8). In terms of early postoperative acute renal failure, no difference in rate was reported with ileal conduit, neobladder,

Table 2. Comparative results of the patients' preoperative, peroperative, and postoperative findings and pathology data				
		Postoperative eGFR <60 mL/s (Group 1) (n=59)	Postoperative eGFR ≥60 mL/s (Group 2) (n=66)	P
Preoperative T stage	≤T1	6	9	0.835
	T2	51	55	
	T3	2	2	
Preoperative tumor grade	Grade 1	1	2	0.05
	Grade 2	5	0	
	Grade 3	53	64	
CIS	(+)	10	28	0.002
	(-)	49	37	
Squamous differentiation	(+)	9	10	0.984
	(-)	49	55	
Operation time (h)		6 (3-9)	6 (3-8)	0.482
Postoperative T stage	T1	10	16	0.609
	T2	29	26	
	T3	10	10	
	T4	10	14	
Postoperative tumor grade	1	3	5	0.489
	2	1	3	
	3	50	49	
Positive surgical margin	(+)	9	13	0.515
	(-)	50	53	
Number of lymph nodes dissected		12 (1-24)	14 (2-33)	0.197
Number of positive lymph nodes		0 (0-10)	0 (0-8)	0.163
Lymph node positivity	(+)	13	9	0.228
	(-)	44	54	
Percentage of positive lymph nodes		0 (0-70)	0 (0-66.7)	0.154
Prostatic invasion	(+)	7	9	0.831
	(-)	48	55	
Urethral invasion	(+)	3	7	0.258
	(-)	54	57	
Urethral orifice involvement	(+)	13	16	0.770
	(-)	46	50	
Lymphovascular invasion	(+)	11	11	0.799
	(-)	47	53	
Perineural invasion	(+)	7	9	0.745
	(-)	51	55	
Diversion type	Ureterocutaneostomy	25	26	0.735
	Diversion	34	40	

CIS: Carcinoma *in situ*, eGFR: Estimated glomerular filtration rate
Mann-Whitney U test and Pearson chi-square test

and ureterocutaneostomy (6). In the late postoperative period, Thompson et al. (5) reported that advance age, reduced preoperative eGFR, and continent diversion were factors associated with reduced eGFR 3rd month postoperatively. In another study investigating diversion type, 24 patients had ileal neobladder, 12 had ileocecal neobladder, 25 had ileal

conduit, and 9 had ureterocutaneostomy. Although patient age, preoperative eGFR, and HT were significant factors in the choice of diversion, type of diversion was found to have no significant effect on long-term renal functions (9). Postoperative episodes of pyelonephritis and AC were identified as among the factors associated with reduced renal function (9). In

		Postoperative eGFR <60 mL/s (Group 1) (n=59)	Postoperative GFR ≥60 mL/s (Group 2) (n=66)	p
Upstaging	(+)	25	26	0.735
	(-)	34	40	
Stage change	Upstaging	25	26	0.778
	Downstaging	8	12	
	No change	26	28	
Adjuvant chemotherapy, n (%)		17 (28.8)	17 (25.8)	0.701
Overall mortality, n (%)		29 (49.2)	29 (43.9)	0.560
Overall survival (months)		57.8±7.0	54.3±5.7	0.662
Cancer-specific mortality, n (%)		22 (37.3)	23 (34.8)	0.777
Cancer-specific survival (months)		68.8±7.2	60.9±6.0	0.821
Hospital stay (days)		11 (5-29)	11 (5-42)	0.697
Early medical complications	(+)	15	14	0.578
	(-)	44	52	
Early surgical complications	(+)	24	27	0.979
	(-)	35	39	
Clavien-Dindo complication classification	1	3	9	0.172
	2	38	45	
	3a	3	0	
	3b	9	9	
	4a	5	3	
	5	1	0	
eGFR: Estimated glomerular filtration rate Mann-Whitney U test and Pearson chi-square test				

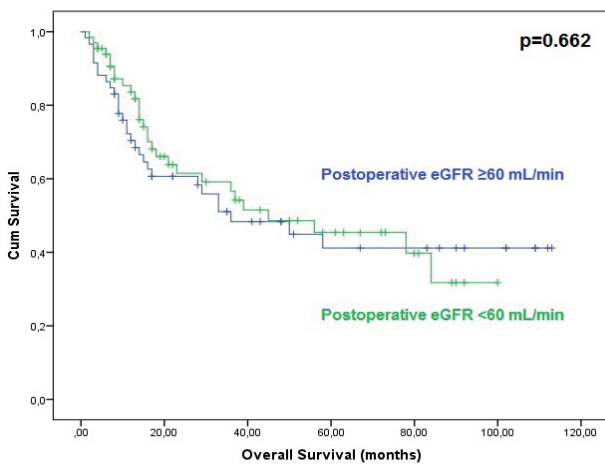


Figure 1. Overall survival analysis curves of patients in groups 1 and 2
eGFR: Estimated glomerular filtration rate

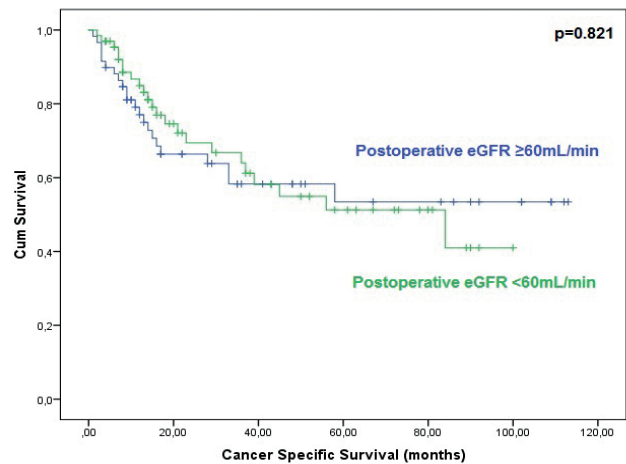


Figure 2. Cancer-specific survival analysis curves of patients in groups 1 and 2
eGFR: Estimated glomerular filtration rate

another study of 68 patients with continent diversion and 47 with incontinent diversion, preoperative eGFR was significantly lower in the incontinent group, while the continent group had a higher proportion of patients with postoperative stage 3B chronic kidney disease (CKD). Significant factors associated with stage 3B CKD at 5 years were advanced age, preoperative eGFR, ureterocutaneostomy, and postoperative hydronephrosis (8). Although our results are consistent with previous studies reporting that comorbidities do not influence renal function, our lack of significant findings regarding diversion type suggests that further investigation into its effect on renal function is warranted. Moreover, while there are some reports that obesity and body mass index (BMI) are associated with postoperative renal function (10,11,12), we were not able to evaluate this in the present study due to incomplete data regarding obesity and BMI.

In our study, preoperative and postoperative pathologic data and operative times of patients were similar at different eGFRs. Analysis of oncologic outcomes showed that upstaging, presence of AC, and overall and cancer-specific survival and mortality rates were also similar at different eGFR. With regard to complication rates, eGFR had similar effects on early medical and surgical complications. Clavien-Dindo complication classification was similar between the groups.

Study Limitations

The most important limitations of this study were the small number of patients, retrospective study design, lack of important data such as BMI, obesity, and preoperative tumor location, and exclusion of patients who received NAC due to their small population.

Conclusion

Our results suggest that postoperative eGFR is significantly associated with preoperative eGFR and hydronephrosis, while the presence of comorbidity is not a significant factor. However, comorbidities may have an effect on preoperative renal function reserve rather than postoperative short-term renal functions. Apart from that, we observed in our study that postoperative eGFR is not associated with type of urinary diversion, pathologic and oncologic outcomes, or complication rates. We believe that larger prospective studies can provide more accurate information.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Radikal Sistektomi Sonrası 3. Ay Renal Fonksiyonun Preoperatif Faktörler, Onkolojik Sonuçlar ve Komplikasyonlarla İlişkisi

Association Between Postoperative 3rd Month Renal Function After Radical Cystectomy and Preoperative Factors, Oncologic Outcomes, and Complications

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Öz

Amaç: Postoperatif renal fonksiyonun preoperatif faktörler ve radikal sistektomi (RS) sonrası onkolojik sonuçlar ve komplikasyonlarla ilişkisini araştırmayı amaçladık.

Gereç ve Yöntem: Ocak 2006 ile Mart 2017 tarihleri arasında kas-invaziv mesane kanseri ve intravezikal tedaviye dirençli kas-invaziv olmayan mesane kanseri nedeniyle kliniğimizde RS uygulanan hastalar retrospektif incelendi. Hastaların yaşı, cinsiyeti, ek komorbidite varlığı, preoperatif tahmini glomerüler filtrasyon hızı (eGFR) düzeyi, hidronefroz varlığı, derecesi ve lateralitesi, üriner diversiyon tipi, RS öncesi ve sonrası patolojik verileri, postoperatif 3. ay eGFR düzeyi, onkolojik sonuçları ve komplikasyon oranları değerlendirildi. Hastalar postoperatif 3. ay eGFR düzeyine göre ikiye ayrıldı. eGFR <60 mL/dakika olan hastalar grup 1 ve eGFR ≥60 mL/dakika olan hastalar grup 2 olarak adlandırıldı. Tüm veriler gruplar arasında karşılaştırıldı.

Bulgular: Ürotelyal karsinom nedeniyle RS uygulanan ve verileri tam olan 125 mesane kanserli hastadan grup 1'de 59, grup 2'de 66 hasta değerlendirildi. Preoperatif faktörlerden sadece hidronefroz varlığı grup 1'de anlamlı yüksek saptandı (p=0,012). Patolojik veriler, üriner diversiyon tercihi, onkolojik veriler ve komplikasyonlar incelendiğinde ise gruplar arası herhangi bir anlamlı farklılık saptanmadı.

Sonuç: Preoperatif eGFR ve hidronefrozun postoperatif 3. ay eGFR düzeyine etkisi olduğu gözlemlendi. Postoperatif <60 mL/dakika eGFR düzeyinin ise diversiyon seçimi, patolojik ve onkolojik sonuçlar ile komplikasyon oranlarına etkisi olmadığı gözlemlendi.

Anahtar Kelimeler: Mesane kanseri, postoperatif renal fonksiyon, tahmini glomerüler filtrasyon hızı, radikal sistektomi, hidronefroz

Abstract

Objective: We aimed to investigate the influence of preoperative factors on postoperative renal function and the association between renal function and oncologic outcomes and complications after radical cystectomy (RC).

Materials and Methods: We retrospectively analyzed patients who underwent RC due to muscle-invasive bladder cancer and intravesical treatment-resistant nonmuscle-invasive bladder cancer in our center between January 2006 and March 2017. The patients' age, gender, comorbidities, preoperative estimated glomerular filtration rate (eGFR), presence of hydronephrosis, hydronephrosis grade and laterality, urinary diversion type, preoperative and postoperative pathology findings, eGFR at postoperative 3rd month, oncologic outcomes, and complication rates were evaluated. The patients were divided into 2 groups based on postoperative eGFR: group 1 (<60 mL/min eGFR) and group 2 (≥60 mL/min eGFR), and data were compared between the groups.

Results: The study included 125 patients with urothelial carcinoma of the bladder who underwent RC and had complete records (59 patients in group 1 and 66 patients in group 2). Of the preoperative factors, only presence of hydronephrosis was significantly higher in group 1 (p=0.012). There were no statistically significant differences between the groups in terms of urinary diversion type, pathology findings, oncologic outcomes, or complications.

Conclusion: Preoperative eGFR and hydronephrosis were significantly associated with postoperative 3rd month eGFR. Postoperative eGFR <60 mL/min was not associated with diversion type, pathologic and oncologic outcomes, or complications.

Keywords: Bladder cancer, postoperative renal function, estimated glomerular filtration rate, radical cystectomy, hydronephrosis

Giriş

Kas-invaziv mesane kanseri (KİMK) ve yüksek riskli kas-invaziv olmayan mesane kanseri (KİOMK) tedavisinde radikal sistektomi (RS), genişletilmiş lenf nodu diseksiyonu ve üriner diversiyon sağkalım avantajına sahip en iyi tedavi yöntemidir (1). Fakat RS öncesi neoadjuvan kemoterapi (NK) ya da RS sonrası adjuvan kemoterapi (AK) gerekliliği hasta özellikleri ve doktor seçimine göre değişmektedir (2). Kemoterapi kararında etkili hasta özelliklerini incelediğimizde, NK için RS öncesi tümör volumü (görüntülemelerde T3 hastalık uyumlu bulgular, lenf nodu pozitifliği) ve renal fonksiyon önem arz etmektedir (1,2,3). AK için ise RS sonrası hastanın performans durumu ve renal fonksiyonu etkili faktörlerdir (4,5). Hastanın renal fonksiyon kapasitesi RS öncesi ve sonrası değişkenlik göstermekle birlikte, kemoterapi planında önem arz etmektedir. Fakat renal fonksiyonun hastanın preoperatif özellikleri, komorbidite varlığı ve hidronefroz varlığı ile ilişkisi birçok çalışmada gösterilmiştir (2,4,5). Postoperatif erken dönem akut renal fonksiyon bozukluğuna etki eden faktörler de tanımlanmıştır (6). Fakat postoperatif renal fonksiyonun RS sonrası komplikasyon (6) ve onkolojik sonuçlar üzerine etkisi net değildir.

Biz bu yazıda postoperatif renal fonksiyonun preoperatif faktörler, RS sonrası onkolojik sonuçlar ve komplikasyonlarla ilişkisini araştırıp sunmayı amaçladık.

Gereç ve Yöntem

Ocak 2006 ile Mart 2017 tarihleri arasında mesane kanseri nedeniyle kliniğimizde RS uygulanan hastalar retrospektif incelendi. Çalışmaya ürotelyal karsinom patolojisi olan mesane kanserli hastalar dahil edildi. Ürotelyal karsinom dışı mesane kanseri saptanan hastalar, üst üriner sistem tümörü olan hastalar, obstrüktif üriner sistem taş hastalığı olan hastalar, RS öncesi soliter böbrekli hastalar, NK gören hastalar (hasta sayısının az olması nedeniyle) ve takip verileri eksik olan hastalar çalışmadan dışlandı. Hastaların genel özellikleri, preoperatif, peroperatif ve postoperatif verileri tarandı. Hasta grubu KİMK ve KİOMK (Ta, T1, karsinoma *in situ*) hastalardan oluşmaktaydı. KİOMK grubunu yaygın, kür edilemeyen ve sık hematüri ile prezente olan Ta hastalar ve intravezikal tedaviye dirençli T1 hastalar oluşturmaktaydı.

Hastaların genel özellikleri [yaş, cinsiyet, diabetes mellitus (DM), hipertansiyon (HT) ve komorbidite varlığı]; preoperatif verileri [preoperatif tahmini glomerüler filtrasyon hızı (eGFR) düzeyi, Amerikan Anestezistler Derneği (ASA) Skoru, Doğu Kooperatif Onkoloji Grubu (ECOG) Performans Skoru, Charlson Komorbidite İndeksi, hidronefroz varlığı, derecesi ve lateralitesi], peroperatif verileri (operasyon süresi, üriner diversiyon tipi), patolojik verileri (preoperatif ve postoperatif T evresi, derecesi ve diğer önemli patolojik bulgular), postoperatif verileri (postoperatif 3. ay eGFR düzeyi), onkolojik sonuçları (evre yükselmesi, AK oranı, genel mortalite ve sağkalım süresi ile kanser spesifik mortalite ve sağkalım süresi) ve komplikasyon verileri (yatış süresi, erken medikal ve cerrahi komplikasyon oranları ve Clavien-Dindo sınıflamasına göre komplikasyon dağılımları) değerlendirildi. Hidronefroz renal pelvis ve kalikslerde dilatasyon varlığı ile ultrasonografi ya da bilgisayarlı tomografi >10 mm renal pelvis anteroposterior çap varlığı olarak tanımlandı (7). Hastalar önceki çalışmalar göz önüne alınarak postoperatif eGFR 60 mL/

dk. düzeyine göre ikiye ayrıldı (6,8,9). eGFR <60 mL/dk. olan hastalar grup 1 ve eGFR ≥60 mL/dk. olan hastalar grup 2 olarak adlandırıldı.

İstatistiksel Analiz

Veriler Statistical Package for Social Sciences, version 20.0 (SPSS, Chicago, IL) programı kullanılarak analiz edildi. Postoperatif eGFR düzeyine göre sınıflandırılan hastalar grup 1 ve grup 2 arasında karşılaştırıldı. Tek değişkenli analizde Mann-Whitney U test ve Pearson ki-kare test, çok değişkenli analizde ise binary logistic regression analizi kullanıldı. Ek olarak, genel sağkalım ve kanser spesifik sağkalım verileri için, Kaplan-Meier survival analizi ve log-rank testi kullanıldı. Tablolardaki veriler ve sonuçları medyan (minimum-maksimum) veri üzerinden analiz edilmiştir. İstatistiksel analizde anlamlılık <0,05 p değeri olarak kabul edilmiştir.

Bulgular

Ürotelyal karsinom nedeniyle RS uygulanan ve verileri tam olan 125 mesane kanserli hasta değerlendirildi. Ortalama yaşı 64,1±8,8 (32-83) yıl ve ortalama takip süresi 32,4±30,8 (1-113) ay olan hastalardan 12'si (%9,6) kadındı. Hastaların ortalama genel ve kanser spesifik sağkalımları 58,7±4,8 ve 67,9±5,1 ay saptandı. Grup 1'de 59, grup 2'de 66 hasta değerlendirildi. Grup 1 ve grup 2 hastaların hasta özellikleri ve preoperatif verileri ve karşılaştırma sonuçları Tablo 1'de verilmiştir. Hasta özellikleri benzer olan 2 grup arasında preoperatif verilerden sadece preoperatif eGFR ve hidronefroz varlığı grup 1'de anlamlı yüksek saptanmıştır (p=0,012). eGFR'ye etkili diğer veriler gruplar arasında benzer saptanmıştır. Grupların preoperatif, peroperatif ve postoperatif patolojik bulguları ve karşılaştırma sonuçları Tablo 2'de verilmiştir. Gruplar arası patolojik verilerde ve üriner diversiyon tipinde anlamlı bir farklılık saptanmadı. Ayrıca KİOMK nedeniyle RS uygulanan hastaların hepsinin postoperatif patolojisi en az T1 evre olarak geldi. Onkolojik veriler ve komplikasyonlar incelendiğinde de yine gruplar arasında herhangi bir farklılık saptanmadı (Tablo 3). Gruplar arası AK oranları da benzer saptandı. Hastaların genel sağkalımı (grup 1: 57,8±7 ay ve grup 2: 54,3±5,7 ay, p=0,662) ve kanser spesifik sağkalımı (grup 1: 68,8±7,2 ay ve grup 2: 60,9±6 ay, p=0,821) ve mortalite oranları (mortalite grup 1'de %49,2 iken grup 2'de %43,9, p=0,560; kanser spesifik mortalite grup 1'de %37,3 iken grup 2'de %34,8, p=0,777) benzerdi. Hastaların genel ve kanser spesifik sağkalım eğrileri Şekil 1 ve Şekil 2'de verilmiştir.

Tartışma

Çalışmamızda postoperatif 3. ay eGFR düzeyine etki eden hasta özellikleri ve komorbiditeleri incelendiğinde, ASA Skoru, ECOG Performans Skoru, Charlson Komorbidite İndeksi, DM, HT ve ek herhangi bir komorbidite varlığının postoperatif eGFR'ye etkisi gösterilememiştir. Fakat preoperatif hidronefroz varlığı ile eGFR düşüklüğü arasında anlamlı ilişki saptanmıştır (p=0,012). Bunun dışında postoperatif eGFR'ye etki eden en önemli etkenin preoperatif eGFR olduğu gözlenmiştir (p<0,001). Postoperatif erken dönem (postoperatif 7. gün üreteral stent çekilmesi sonrası) akut böbrek yetmezliğine etki eden faktörlerin değerlendirildiği bir çalışmada, 145 hasta değerlendirilmiş olup bunların 48'inde akut böbrek yetmezliği tablosu gözlenmiştir.

Tablo 1. Hastaların genel özellikleri ve preoperatif verilerinin gruplar arası karşılaştırmalı sonuçları

		Postoperatif eGFR <60 mL/sn (Grup 1) (n=59)	Postoperatif eGFR ≥60 mL/sn (Grup 2) (n=66)	p
Yaş (yıl)		66 (45-83)	64 (32-80)	0,288
Cinsiyet	Kadın	8	4	0,155
	Erkek	51	62	
Preoperatif eGFR		55,1 (17,5-118,4)	75,3 (6,8-141,4)	<0,001
Postoperatif 3. ay eGFR		40,4 (15,7-59,3)	82,5 (60-118,4)	-
ASA Skoru	1	2	3	0,756
	2	37	38	
	3	20	24	
	4	0	1	
ECOG Performans Skoru	0	15	18	0,88
	1	27	31	
	2	10	11	
	3	4	5	
Charlson Komorbidite İndeksi	0	0	1	0,241
	1	2	1	
	2	15	9	
	3+	42	55	
DM pozitifliği, n (%)		13 (22)	10 (15,2)	0,322
HT pozitifliği, n (%)		21 (35,6)	27 (40,9)	0,542
Herhangi bir komorbidite varlığı, n (%)		45 (76,3)	46 (69,7)	0,410
Preoperatif hidronefroz	Pozitif	31 (52,5)	20 (30,3)	0,012 *0,012
	Negatif	28 (47,5)	46 (69,7)	
Hidronefroz lateralitesi	Unilateral	22 (71)	15 (75)	0,753
	Bilateral	9 (29)	5 (25)	
Preoperatif hidronefroz derecesi	1	0 (0)	4 (20)	0,074
	2	9 (29)	4 (20)	
	3	16 (51,6)	8 (40)	
	4	6 (19,4)	4 (20)	

ASA: Amerikan Anestezistler Derneği, ECOG: Doğu Kooperatif Onkoloji Grubu, DM: Diabetes mellitus, HT: Hipertansiyon, eGFR: Tahmini glomerüler filtrasyon hızı
*Binary logistic regression analizi
Mann-Whitney U testi ve Pearson ki-kare testi

Bu 48 hastada eGFR'nin <60 olmasında, HT ve NK'nin akut böbrek yetmezliği ile ilişkili bağımsız risk faktörleri olduğu gösterilmiştir (6). Çalışmamızda bu çalışmadan farklı olarak postoperatif erken dönem değil postoperatif 3. ay renal fonksiyon değerleri incelenmiştir. Ayrıca çalışmamızda NK gören hastalar değerlendirilmemiştir. Bu konuda son dönemde 164 hastanın değerlendirildiği bir çalışmada postoperatif 3. ay eGFR düzeyine etki eden faktörler araştırılarak bir nomogram oluşturulmuştur (2). Postoperatif eGFR düzeyine, hasta yaşının ve preoperatif eGFR düzeyinin önemli etkileri olduğu, bunun dışında diversiyon tipinin ve subkutan yağ doku kalınlığının da etkili faktörler olduğu belirtilmiştir. Bunun dışında preoperatif hidronefrozlu hastalarda cerrahi sonrası obstrüksiyonun ortadan kalkması ile postoperatif eGFR'de düzelme olabileceği vurgulansa da

istatistiksel fark saptanmamıştır (2). Akut obstrüksiyonlara bağlı hidronefrozda cerrahi sonrası eGFR'de düzelme olabileceken, uzun süreli yavaş gelişen obstrüksiyonlarda eGFR'de düzelme olmayabileceği belirtilmektedir (2). Bunda hastanın kontrateral böbreğinin kompanseasyon yeteneği de önem arz etmektedir. Çalışmamızda bu bulgulara kıyasla farklı sonuçlar saptanmıştır. Birincisi, hidronefroz saptanan 51 hastanın 31'inin düşük postoperatif eGFR ile ilişkili olduğu saptanmıştır. Fakat bu 51 hastanın bilateral ve unilateral hidronefroz oranları ile hidronefroz derecesi gruplar arası benzer bulunmuştur. Bunun nedeni olarak mesane tümörlerinde hidronefroz gelişiminin uzun sürede kronik bir süreç olarak ilerlemesi ve bunun da kalıcı renal fonksiyon bozukluğuna neden olması söylenebilir (2). Ayrıca grup 1'de hastaların böbrek fonksiyonlarında preoperatif eGFR

Tablo 2. Hastaların preoperatif, peroperatif ve postoperatif bulguları ile patolojik verilerinin gruplar arası karşılaştırmalı sonuçları

		Postoperatif eGFR <60 mL/sn (Grup 1) (n=59)	Postoperatif eGFR ≥60 mL/sn (Grup 2) (n=66)	p
Preoperatif T evresi	≤T1	6	9	0,835
	T2	51	55	
	T3	2	2	
Preoperatif tümör derecesi	Grade 1	1	2	0,05
	Grade 2	5	0	
	Grade 3	53	64	
CIS varlığı	Pozitif	10	28	0,002
	Negatif	49	37	
Skvamöz diferansiyasyon	Pozitif	9	10	0,984
	Negatif	49	55	
Operasyon süresi (saat)		6 (3-9)	6 (3-8)	0,482
Postoperatif T evresi	T1	10	16	0,609
	T2	29	26	
	T3	10	10	
	T4	10	14	
Postoperatif tümör derecesi	1	3	5	0,489
	2	1	3	
	3	50	49	
Cerrahi sınır pozitifliği	Pozitif	9	13	0,515
	Negatif	50	53	
Diseke edilen lenf nodu sayısı		12 (1-24)	14 (2-33)	0,197
Pozitif lenf nodu sayısı		0 (0-10)	0 (0-8)	0,163
Lenf nodu pozitifliği	Pozitif	13	9	0,228
	Negatif	44	54	
Pozitif lenf nodu yüzdesi		0 (0-70)	0 (0-66,7)	0,154
Prostat invazyonu	Pozitif	7	9	0,831
	Negatif	48	55	
Üretra invazyonu	Pozitif	3	7	0,258
	Negatif	54	57	
Üreteral orifis tutulumu	Pozitif	13	16	0,770
	Negatif	46	50	
Lenfovasküler invazyon	Pozitif	11	11	0,799
	Negatif	47	53	
Perinöral invazyon	Pozitif	7	9	0,745
	Negatif	51	55	
Diversiyon tipi	Üreterokutaneostomi	25	26	0,735
	Diversiyon	34	40	

CIS: Karsinoma *in situ*, eGFR: Tahmini glomerüler filtrasyon hızı
Mann-Whitney U testi ve Pearson ki-kare testi

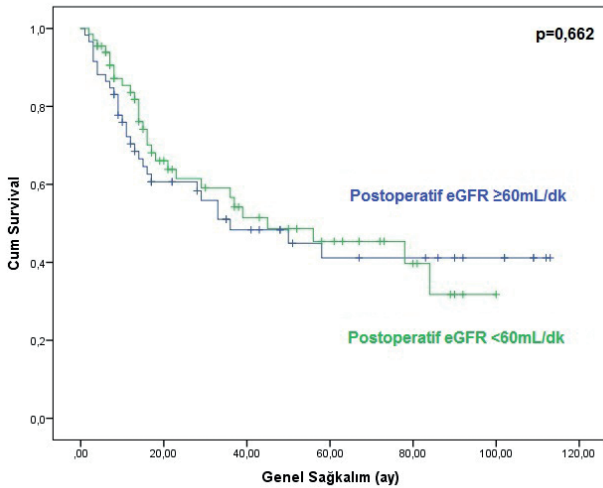
düzelelerine göre postoperatif eGFR düzeylerinde daha da azalma varken, grup 2'de artış gözlenmektedir (p<0,001). Bu durum grup 1'deki hidronefrozun kalıcı renal fonksiyon bozukluğuna neden olması ile açıklanabilir. Önceki çalışmalara ve çalışmamıza baktığımızda hastadaki ek komorbiditelerin postoperatif renal fonksiyon düşüklüğü ile ilişkili olmadığı fakat diversiyon tipinin

değerlendirilmesi gerektiği söylenebilir (2,5,8). Postoperatif erken dönem akut böbrek yetmezliğine baktığımızda ileal konduit, neobladder ve üreterokutaneostomi oranları arasında fark raporlanmamıştır (6). Geç dönemde, Thompson ve ark.'nın (5) yapmış olduğu bir çalışmada ileri yaş, preoperatif eGFR düşüklüğü ve kontinen diversiyonun postoperatif 3. ay eGFR

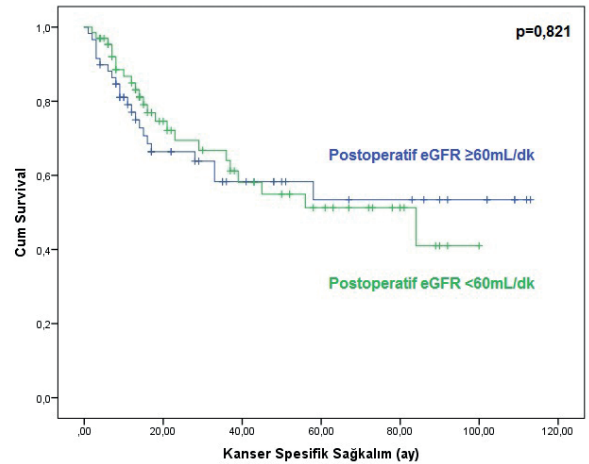
Tablo 3. Hastaların postoperatif verileri, onkolojik sonuçları ve komplikasyon durumlarının gruplar arası karşılaştırmalı sonuçları

		Postoperatif eGFR <60 mL/sn (Grup 1) (n=59)	Postoperatif eGFR ≥60 mL/sn (Grup 2) (n=66)	p
Evre yükselmesi	Pozitif	25	26	0,735
	Negatif	34	40	
Evre değişim durumu	Evre yükselmesi	25	26	0,778
	Evre düşmesi	8	12	
	Aynı evre	26	28	
Adjuvan kemoterapi, n (%)		17 (28,8)	17 (25,8)	0,701
Genel mortalite, n (%)		29 (49,2)	29 (43,9)	0,560
Genel sağkalım (ay)		57,8±7	54,3±5,7	0,662
Kanser spesifik mortalite, n (%)		22 (37,3)	23 (34,8)	0,777
Kanser spesifik sağkalım (ay)		68,8±7,2	60,9±6	0,821
Hospitalizasyon süresi		11 (5-29)	11 (5-42)	0,697
Erken medikal komplikasyon	Pozitif	15	14	0,578
	Negatif	44	52	
Erken cerrahi komplikasyon	Pozitif	24	27	0,979
	Negatif	35	39	
Clavien-Dindo komplikasyon sınıflaması	1	3	9	0,172
	2	38	45	
	3a	3	0	
	3b	9	9	
	4a	5	3	
	5	1	0	

eGFR: Tahmini glomerüler filtrasyon hızı
Mann-Whitney U testi ve Pearson ki-kare testi



eGFR: Tahmini glomerüler filtrasyon hızı



eGFR: Tahmini glomerüler filtrasyon hızı

düşüklüğü ile ilişkili faktörler olduğu belirtilmiştir. Hastaların diversiyon tipinin incelendiği başka bir çalışmada, 24 hastada ileal neobladder, 12 hastada ileoçekal neobladder, 25 hastada ileal konduit ve 9 hastada üreterokutaneostomi uygulanmış olup, diversiyon seçiminde hastaların yaşı, preoperatif eGFR düzeyi ve HT varlığı anlamlı iken, diversiyon tipinin uzun dönem böbrek fonksiyonları üzerine etkisi anlamlı saptanmamıştır (9). Çalışmada renal fonksiyon azalması gözlenen hastalarda buna etki eden faktörler arasında postoperatif piyelonefrit ataklarının ve AK'nin anlamlı olduğu gösterilmiştir (9). Bir diğer çalışmada ise, 68 hastaya kontinen 47 hastaya inkontinen diversiyon uygulanmış olup, preoperatif eGFR inkontinen grupta anlamlı düşük iken kontinen grupta postoperatif kronik böbrek hastalığı (CKD) evre 3B hasta oranı daha yüksek saptanmıştır. Çalışmada 5 yıllık CKD evre 3B böbrek yetmezliği ile ilişkili faktörler incelendiğinde ise, ileri yaş, preoperatif eGFR, üreterokutaneostomi ve postoperatif hidronefrozun anlamlı olduğu raporlanmıştır (8). Tıpkı çalışmamızda olduğu gibi önceki çalışmalarda da komorbiditelerin renal fonksiyon üzerine etkisinin olmadığı belirtilmiş olsa da çalışmamızda anlamlı ilişki saptamadığımız diversiyon tipinin hala renal fonksiyon üzerine etkisinin araştırılması gerektiği sonucu çıkarılabilir. Bunun dışında hastaların obezite ve vücut kitle indeksi (BMI) durumlarının da postoperatif renal fonksiyon üzerine etkisinin olduğunu belirten çalışmalar mevcut olmakla birlikte (10,11,12), çalışmamızda hastaların obezite ve BMI verileri eksik olduğundan dolayı değerlendirme yapılamamıştır.

Çalışmamızda eGFR düzeyine göre hastaların preoperatif ve postoperatif patolojik verileri ve operasyon süresi benzer saptandı. Onkolojik sonuçlara baktığımızda ise, evre yükselmesi, AK oranı, genel ve kanser spesifik sağkalım ve mortalite düzeyleri de eGFR düzeyine göre benzer saptandı. Komplikasyon oranlarına baktığımızda eGFR düzeyinin erken medikal ve erken cerrahi komplikasyonlara etkisi benzer gözlemlendi. Ayrıca Clavien-Dindo komplikasyon sınıflaması da gruplar arası benzer saptandı.

Çalışmanın Kısıtlılıkları

Çalışmamızdaki en önemli kısıtlılıklar, düşük hasta sayısı, retrospektif analiz, BMI, obezite ve preoperatif tümör lokalizasyonu gibi önemli verilerin eksikliği ile NK gören hasta sayısının az olması nedeniyle çalışmaya dahil edilmemesi şeklinde sıralanabilir.

Sonuç

Postoperatif eGFR düzeyine etki eden en önemli bulgunun preoperatif eGFR ile hidronefroz olduğu, ek komorbiditelerin ise postoperatif eGFR düzeyini etkilemediği söylenebilir. Fakat ek komorbiditelerin postoperatif kısa dönem renal fonksiyonlardan ziyade operasyon öncesi renal fonksiyon rezervini etkileyebileceği söylenebilir. Bunun dışında çalışmamızda postoperatif eGFR'nin diversiyon tipi, patolojik ve onkolojik sonuçlar ile komplikasyon oranlarına etkisinin olmadığı gözlemlendi. Fakat geniş serili prospektif çalışmalar ile daha net bilgiler edinilebileceği görüşündeyiz.

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Hasta Onayı: Retrospektif çalışma.

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Impact of Delay from Biopsy to Surgery on the Rate of Adverse Pathologic and Oncologic Outcomes for Clinically Localized Prostate Cancer

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Abstract

Objective: Due to the widespread usage of prostate-specific antigen screening, the number of patients diagnosed with prostate cancer is steadily increasing. Many factors such as high operating room demand, insurance reimbursement, patients' desire to assess multiple treatment options, and anxiety can cause delays in radical treatment. In this study, we examined the effect of delay from prostate biopsy to surgery on outcomes of men with localized prostate cancer.

Materials and Methods: The data of 359 patients who underwent radical prostatectomy (RP) in our clinic between 2008 and 2017 were analyzed retrospectively. Surgical delay was defined as the time from transrectal ultrasound-guided prostate biopsy to surgery. Patients were divided into 3 groups according to the interval between prostate biopsy and RP (≤ 60 , 61-120, ≥ 120 days) and classified according to the D'Amico risk classification.

Results: A total of 248 patients were included in the study. Of these patients, 107 (43.1%) were operated within 60 days of biopsy, 113 (45.6%) 61-120 days after biopsy, and 28 (11.3%) over 120 days after biopsy. Statistical analysis of patients with follow-up of at least 12 months did not reveal a significant difference between the groups in terms of biochemical recurrence ($p=0.06$). A delay of over 120 days was not associated with adverse pathological or oncological findings at surgery for the low-risk group. Extraprostatic invasion increased significantly in the intermediate-risk group with longer surgical delay ($p=0.044$).

Conclusion: Our data demonstrated that a delay of more than 120 days was not associated with adverse pathological outcomes in men with low-risk localized prostate cancer. For men with intermediate-risk disease, delays over 60 days were significantly associated with risk of extraprostatic invasion. Our findings indicate that RP should be performed within 60 days of biopsy for intermediate-risk patients.

Keywords: Delay surgery, localized prostate cancer, prostate biopsy, radical prostatectomy

Introduction

Prostate cancer is the most common cancer diagnosed and the second leading cause of cancer-related deaths in men (1). The number of patients diagnosed with prostate cancer has increased due to the growing popularity of prostate-specific antigen (PSA) screening in the last 20 years (2). As a result, different treatment

modalities have been discovered and side effects related to these new modalities have also increased. Due to these side effects, most patients dealing with prostate cancer should consider several treatment options and seek multiple opinions. In addition, unavailability of operating rooms due to high demand, insurance reimbursement, and the anxiety experienced by patients may delay radical treatment.

Due to side effects of radical treatment and the slow progression of low-grade prostate cancer, active surveillance has become an acceptable approach in this low-risk group (3,4). However, upgrading of Gleason scores in surgical specimens is observed in nearly 30% of patients with low-risk prostate cancer. This indicates that patients may skip to the intermediate- or high-risk groups (5,6,7). Therefore, the issues of delaying surgery and active surveillance are controversial.

The effect of delayed radical treatment on pathologic and clinical results is not clear. In spite of many studies in this area, there is no consensus on what is an acceptable delay. It has been shown that delays of up to 180 days do not affect biochemical recurrence (BCR) and pathologic results in localized-low risk prostate cancers (according to D'Amico risk classification) (8). Because active surveillance is not an option for intermediate- and high-risk prostate cancer, there are very few studies regarding these groups.

In this study, we assessed the effect of the time from prostate cancer diagnosis to surgery on pathologic and oncologic outcomes for different risk groups.

Materials and Methods

Between 2008 and 2017, the data of 359 patients who underwent retropubic radical prostatectomy or robot-assisted radical prostatectomy in our clinic were retrospectively analyzed. We excluded patients who underwent prostate biopsy in an external center (n=104) and patients died with non-cancer specific reasons during follow-up (n=7) from the study. The patients' age, preoperative PSA, preoperative Gleason score, D'Amico risk group stage, surgery type, time from biopsy to surgery, pathologic specimen results, follow-up duration, and PSA values during follow-up were recorded. BCR was defined as serum PSA value ≥ 0.2 ng/mL measured at least 21 days after radical prostatectomy (9). Patients were divided into 3 groups according to duration of surgical delay. Surgical delay was defined as the time (in days) from transrectal ultrasound-guided prostate biopsy until radical prostatectomy. Surgical delay duration was ≤ 60 days in group 1, 61-120 days in group 2, and ≥ 120 days in group 3. Patients were divided into 3 risk groups according to D'Amico risk classification: low (Gleason scores: ≤ 6 , PSA: ≤ 10 ng/mL, and clinical stage: $\leq cT2a$), intermediate (Gleason score: 7 or clinical stage: $cT2b$ or PSA: >10 ng/mL and ≤ 20 ng/mL), and high (Gleason scores: ≥ 8 , PSA: >20 ng/mL, clinical stage: $\geq cT2c$).

Statistical Analysis

Fisher's exact test and Pearson chi-square analysis were performed for categorical variables. The normality assumptions were checked with Shapiro-Wilk test. ANOVA with Tukey honestly significant difference post-hoc test was used to analyze the differences between time intervals for normally distributed data. Differences between groups were evaluated with the Kruskal-Wallis test for analysis of non-normally distributed numerical data; in presence of statistical significance, the post-hoc Bonferroni-Dunn test was applied. The odds ratios of pathological findings at surgery were calculated for all time intervals using logistic regression. Data are expressed as n (%), mean \pm standard deviation or median (minimum-maximum),

as appropriate. P values <0.05 were considered statistically significant. Statistical analysis was completed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY).

Results

A total of 248 patients were included in the study. The mean age of patients was 64.2 years. The mean PSA value was 9.96 ng/mL. Surgical delay was ≤ 60 days for 107 patients (43.1%), 61-120 days for 113 patients (45.6%), and ≥ 120 days for 28 patients (11.3%). According to D'Amico classification, 122 patients (49.2%) were low-risk, 63 (25.4%) were intermediate-risk, and 63 (25.4%) were high-risk. Surgery was open in 97 cases (30.9%) and robot-assisted in 151 (60.1%); patients who underwent open radical prostatectomy had significantly shorter surgical delay compared to robot-assisted cases ($p < 0.001$). Ninety-eight patients were $cT1$ and 150 patients were $cT2$, with surgical delay decreasing significantly with more advanced clinical stage ($p = 0.006$) (Table 1).

When groups were investigated according to D'Amico risk classification, there were no differences in any of the investigated pathologic and oncologic outcomes according to surgical delay in the low- and high-risk groups. In the high-risk group, seminal vesicle invasion was observed in 21 patients (33.3%), positive surgical margin in 39 patients (61.9%), and 36 patients required adjuvant treatment. In the intermediate-risk group, the rate of extraprostatic invasion was significantly higher as surgical delay increased ($p = 0.044$). When pathologic results were examined with logistic regression test for intermediate-risk patients, as the surgical delay increased, the rate of extracapsular prostatic extension was significantly higher ($p = 0.042$) (Table 2).

Mean follow-up duration was 16.1 months (minimum-maximum: 2-72 months), with 55 patients (20.2%) developing BCR during follow-up. However, as surgical delay increased there was no significant difference in terms of BCR between the groups ($p = 0.189$). Statistical analysis of patients with follow-up of at least 12 months did not reveal a significant difference between the groups in terms of BCR ($p = 0.06$) (Table 3).

When we examined the pathologic results, 100 patients (40.2%) had upgrading, 55 patients (22%) had positive surgical margin, 57 patients (23%) had extraprostatic invasion, 34 (13.7%) patients had seminal vesicle invasion, and 14 patients (5.6%) had lymph node positivity. Sixty-one patients required adjuvant radiotherapy or hormonal therapy after radical prostatectomy. However, there was no statistically significant correlation between the duration of surgical delay and the need for additional treatment ($p = 0.394$).

Discussion

With the growing popularity of PSA screening, the number of men diagnosed with low-risk prostate cancer in particular is increasing (9). In other cancer types such as breast and colon cancer, it has been shown that delays in treatment did not affect survival (10,11). For prostate cancer, the effect of treatment delays on long-term survival is uncertain (12).

Active surveillance is an acceptable approach for certain patients in the low-risk group. This protocol protects patients from side effects such as erectile dysfunction and urinary incontinence that can result from surgical treatment. A study by Iremashvili

Table 1. Patient demographics and clinical characteristics

	Time intervals (n=248)			p value
	0-60	60-120	≥120	
Age, mean ± SD	64.2±6.5	64.1±6.7	65.3±5.6	0.677
PSA, median (minimum-maximum)	7.3 (3.5-52.59)	7.7 (3.2-55.01)	7.2 (2.34-38)	0.388
PSA range, n (%)	-	-	-	0.552
<10	77 (72)	73 (64.6)	19 (67.9)	-
10-20	20 (18.7)	29 (25.7)	8 (28.6)	-
>20	10 (9.3)	11(9.7)	1 (3.6)	-
Biopsy Gleason score, n (%)	-	-	-	0.532
6	79 (73.8)	75 (66.4)	22 (78.6)	-
7	23 (21.5)	28 (24.8)	5 (17.9)	-
≥8	5 (4.7)	10 (8.8)	1 (3.6)	-
Clinical stage, n (%)	-	-	-	0.009
T1c	44 (41.1)	36 (31.9)	18 (64.3)	-
T2a	35 (32.7)	36 (31.9)	5 (17.9)	-
T2b	6 (5.6)	20 (17.7)	1 (3.6)	-
T2c	22 (20.6)	21 (18.6)	4 (14.3)	-
Clinical stage, n (%)	-	-	-	0.006
T1	44 (41.1)	36 (31.9)	18 (64.3)	-
T2	63 (58.9)	77 (68.1)	10 (35.7)	-
D'Amico, n (%)	-	-	-	0.463
LR	57 (53.3)	49 (43.4)	16 (57.1)	-
IR	23 (21.5)	33 (29.2)	7 (25)	-
HR	27 (25.2)	31 (27.4)	5 (17.9)	-
Operation type, n (%)	-	-	-	<0.001
Open	57 (53.3)	31 (27.4)	9 (32.1)	-
Robotic	50 (46.7)	82 (72.6)	19 (67.9)	-
Follow-up time, median (minimum-maximum)	13 (2-72)	10 (2-76)	11.5 (3-75)	0.095

PSA: Prostate-specific antigen, SD: Standard deviation, LR: Low-risk, IR: Intermediate-risk, HR: High-risk

Table 2. Odds ratio of adverse pathological findings during surgery for intermediate risk group

	≤60 days	61-120 days OR (95% CI)	>120 days OR (95% CI)	p value
Extraprostatic invasion	Reference	2.250 (1.029-4.918)	0.694 (0.206-2.341)	0.042 , 0.556
Seminal vesicle invasion	Reference	0.396 (0.143-1.092)	0.162 (0.024-1.111)	0.073, 0.064
Surgical margin	Reference	1.569 (0.735-3.351)	1.674 (0.509-5.513)	0.244, 0.397
Lymph node	Reference	1.500 (0.362-6.213)	1.640 (0.110-24.540)	0.576, 0.720

OR: Odds ratio, CI: Confidence interval

Table 3. Comparison of biochemical recurrence and additional treatment data according to time intervals with at least 12 months follow-up

	Time intervals (n=121)			p value
	0-60 days	60-120 days	≥120 days	
Oncological results				
Biochemical recurrence, n (%)	-	-	-	0.061
Negative	42 (72.4)	34 (69.4)	14 (100)	-
Positive	16 (27.6)	15 (30.6)	0 (0)	-
Additional treatment, n (%)	-	-	-	0.102
Negative	41 (70.7)	31 (63.3)	13 (92.9)	-
Positive	17 (29.3)	18 (36.7)	1 (7.1)	-

et al. (9) compared the outcomes of low-risk patients who underwent surgery after a duration of active surveillance and patients underwent surgery immediately, and found that tumor grade and volume were significantly higher in the patients who group who had surgery after active surveillance ($p=0.009$). Additionally, there was no significant difference between the 2 groups for parameters like BCR, Gleason score, surgical margin positivity, or extracapsular extension (9). Van den Bergh et al. (13) divided 158 patients with low-risk prostate cancer into 2 groups. The first group underwent surgery after a mean active surveillance period of 6 months and second group underwent surgery after a mean active surveillance period of 2.6 years. They found that the duration between diagnosis and radical prostatectomy did not correlate with poor outcomes (13). Our results are consistent with the literature, with no significant difference identified with delays of over 4 months in 122 patients with low-risk prostate cancer.

Many reports concluding that delays are safe for low-risk prostate cancer note that the same cannot be said for the intermediate-risk group (14,15,16,17). A study including 748 intermediate-risk patients reported that delays longer than 9 months were associated with significantly higher BCR and surgical margin positivity ($p<0.01$). The same study investigated a subgroup of intermediate-risk patients with low tumor volume in prostate biopsy and found that delays longer than 9 months resulted in significantly higher extracapsular extension rates. However, the same significance was not identified for BCR and surgical margin positivity (18). In a study of 1568 patients in different risk groups, Korets et al. (19) reported that time to surgery did not affect BCR and pathologic results even in the high-risk group. In our study, we found that longer time to surgery was associated with a significant increase in the risk of extraprostatic invasion in intermediate-risk patients.

Surgical specimen reports after radical prostatectomy and PSA screening at certain intervals are the basic parameters used to assess oncologic outcomes. Pathologic specimen reports of radical prostatectomy with extracapsular extension indicate that the patient is pathologically and clinically in T3a stage. The BCR rate after radical prostatectomy varies from 15-40% (20). Of patients with BCR, 52% have an extracapsular extension (21). A large-series study of 2907 T3a stage patients indicated that tumors with focal invasion of the extraprostatic region did not cause a significant difference in terms of BCR. The same study

investigated patients with non-focal extraprostatic invasion and reported that BCR was significantly higher in these patients. The authors emphasized that invasion should be separated into focal and non-focal types, and it was necessary to discuss adjuvant therapy for the non-focal group (22).

Studies in the high-risk group are very limited. Zanaty et al. (23) showed in a recent study that delaying surgery did not affect pathologic and oncologic outcomes. The average delay in this study was reported as 138 days. In our study, we found no significant difference between delay groups in pathologic and oncologic outcomes for the high-risk group.

Robot-assisted radical prostatectomy was first performed in 2000. Its popularity continues to increase due to surgeon comfort and early postoperative recovery for the patient (24). In our study, patients who underwent open radical prostatectomy had significantly shorter surgical delays compared to patients who underwent robot-assisted radical prostatectomy. The reason for this is that most patients preferred robot-assisted surgery and this resulted in later appointment dates for surgery.

Study Limitations

This study has several limitations. Firstly, it was a retrospective study with the bias specific to retrospective studies. Radical prostatectomy was performed by 5 different surgeons. Additionally, the postoperative follow-up duration of patients was short and survival outcomes were not included. Our center is a tertiary hospital with large patient population referred from surrounding provinces and counties. This caused loss of patient data such as preoperative PSA and prostate biopsy results.

Conclusion

The results of our study including 248 patients in different risk groups showed that surgical delays longer than 120 days did not affect pathologic and oncologic outcomes in low-risk patients. As surgical delay increased in intermediate-risk group patients, there was a significant increase in extracapsular extension. We believe that surgery should be performed in the first 60 days for the intermediate-risk group due to the high risk of BCR shown in the literature for these patients.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.S., M.A., Concept: H.A., K.K., M.Y., Design: H.A., E.I., S.T., Data Collection or Processing: Ç.Ö., M.Y., Analysis or Interpretation: S.T., E.I., Literature Search: H.A., K.K., Writing: H.A.

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Genomic Evaluation of Testicular Germ Cell Tumors and its Role in Treatment Planning

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Abstract

The incidence of testicular germ cell tumors (TGCT) has significantly increased over the last 40 years and continues to increase among the young male population. The geographical differences show that a combination of genetic and environmental factors play a role in the pathogenesis of TGCT. However, since the actual mechanisms involved in the development of this disease have still not been fully explained, studies at the genomic level have gained importance. Although TGCTs respond well to chemotherapy, 20-30% of patients display classical chemotherapy resistance. There exists a need for detailed investigation of the molecular mechanisms responsible for such resistance. In this review, we briefly discussed the current information on some risk factors and genomic factors involved in the development of TGCTs.

Keywords: Testicular germ cell tumors, genomics, epigenomics, risk factors

Introduction

Testicular germ cell tumors (TGCTs) have an incidence of up to 10.5 in 100,000 men and are the most common solid tumors affecting the young male population (1). In fact, although testicular cancers are a rare cancer type, it is worrying that the incidence of testicular cancer has doubled in the past 30 years according to statistical analyses in countries such as the USA and UK (1,2).

Almost all primary testicular tumors (95%) are TGCT, while the remaining minority includes nongermlinal neoplasms such as Leydig cell tumors, Sertoli cell tumors, or lymphomas. These tumors are comprised of seminomas, which account for approximately 50% of cases and are derived from undifferentiated primordial germ cells, and nonseminomas, which constitute approximately 40% of cases and exhibit different stages of differentiation. The other 10% of cases show mixed histology (3). Seminomas and nonseminomas are derived from both gonadal and extragonadal anatomic sites and have distinct biological and metastatic properties. Nonseminoma germ cell tumors include embryonic and extraembryonic components and are classified as embryonal cell carcinoma, choriocarcinoma, yolk sac tumor, and teratoma (3,4).

Mortality due to testicular cancer is very low. The main reason for this is the high success rates in the treatment of low- and moderate-risk testicular cancer. Treatment success depends on careful grading during diagnosis, initiation of chemotherapy, as well as effective early treatment with radiotherapy and surgery if necessary, followed by fairly good follow-up. TGCT patients are treated with radiotherapy or chemotherapy depending on histological type and tumor stage after surgery. Nonseminoma germ cell tumors are more aggressive in terms of early spread, have poorer prognosis in advanced stage disease, and are sensitive to platinum-based combination chemotherapy but less responsive to radiation, except for teratomas. In contrast, seminomas have a good prognosis and are highly sensitive to both chemotherapy and radiation (5).

Despite their differences in morphology and time of appearance, recent genome-wide association studies (GWAS) have shown that seminomas and nonseminomas share a common molecular pathogenetic process. Both seminoma and nonseminoma tumors are believed to be derived from carcinoma in situ (CIS), also known as intratubular germ cell neoplasia (ITGCN), where the generation and expansion of tumor cells is restricted in the seminiferous tubules. ITGCN is a precursor lesion often visualized close to invasive TGCT (6,7).

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Epidemiology, Etiology, and Risk Factors

The incidence of TGCT displays marked variation between different countries and ethnic groups, with significantly more cases in Scandinavia than in Africa, Asia, and Latin America, where a very low incidence has been reported. The higher incidence of this disease in Western countries has been attributed to greater exposure to disease-causing factors such as intrauterine exposure to endocrine disruptors like hormone use during pregnancy and fetal development. Since TGCT is a hormone-dependent cancer, variable estrogen levels increase the risk of disease during fetal development. Numerous studies on TGCT have associated disease development with a variety of factors such as cryptorchidism, family history of testicular cancer, maternal lifestyle, genetic factors, hypospadias, and low fertility (4,8).

Family history is an important risk factor for the development of TGCT. Studies performed in large populations showed that sons of men with TGCT have a 4-6 times higher risk of developing TGCT, while brothers have a 8-10 times higher risk (9).

Patients with Klinefelter syndrome (47, XXY), which is a germline chromosomal abnormality, rarely develop TGCT. However, approximately one-third of patients with extragonadal germ cell tumors have an increased risk of testicular CIS. In addition, a 1.6-Mb deletion in the azoospermia factor region of the Y chromosome in patients with infertility doubles the risk of developing TGCT (10,11).

Age is another important risk factor in TGCT development. The most common histological type, seminoma, is seen most commonly in men between 30 and 35 years of age. Embryonal carcinoma and teratocarcinoma are common between the ages of 25 and 35, and choriocarcinoma is common in the ages of 20-30. Although yolk sac tumors and benign teratomas are common in early childhood, these 2 histologic types appear in combination with other histologic types in older ages (12,13).

Although the results of some studies are variable due to small sample sizes, additional risk factors such as low maternal parity, twin birth, birth order, and young maternal age are all considered TGCT risk factors (14).

Genetic and Epigenetic Anomalies in TGCT Development and Their Relevance to Clinical Presentation

Different genetic abnormalities play an important role in the development of TGCTs. In recent years, studies on TGCT have taken important steps toward elucidating the mechanism of this disease when genetic and epigenetic factors are considered together. ITGCN, a noninvasive lesion believed to occur during fetal development, is a precursor for the development of TGCT. ITGCN precursor cells, which are inactive until adolescence, reproduce with hormonal effects. After that, isochromosome 12p [i(12p)] formation causes invasive growth as a possible trigger event and turns into ITGCN, seminoma or nonseminoma TGCT histology (15). The association between TGCT and various anomalies (polyploidization, amplification, etc.) in chromosome 12 has been known for many years. Gains in chromosome 12 and formation of i(12p) on karyotype analysis in many TGCT specimens (nearly 80%) was the first genetic marker discovered in TGCT. The remaining 20% also have 12p gains,

but these occur through chromosomal rearrangements such as amplification of small chromosomal regions (16,17).

Other genes in the 12p region include *NANOG*, *STELLA*, and *GDF3*, which are stem-cell associated genes that play an important role in the embryonic stem cell self-renewal and pluripotent character. *CCND2* controls the cell cycle and is known to maintain the proliferative advantage in early transformed cells. The *KRAS* oncogene is responsible for malignant transformation, while the *GLUT3*, *GAPDH*, and *TP11* genes play a role in energy metabolism and give tumor cells proliferative advantage. DNA repair genes *MGST1* and *RAD52* may also contribute to the development of TGCT (18).

In TGCTs it is often possible to encounter aneuploidic chromosomal gains. In other studies investigating chromosomal anomalies, it has been shown that copy numbers of chromosomes 7, 8, 17, and X are increased and copy numbers of chromosomes 4, 11, 13, and 18 are decreased. Gains in chromosomes 7, 8, 21, and X are common in both seminomas and nonseminomas (16,17,19).

The only locus identified in a linkage analysis study by Rapley et al. (6) was Xq27. In addition, there was an X-linked inheritance pattern in the history of the investigated families. However, this relationship was not confirmed in a comprehensive independent analysis (9). In another study, Lutke Holzik et al. (20) detected a gene on Xq27 that moderately increased the risk of developing sporadic TGCT but not familial TGCT.

The *KIT* gene is located at the 4q12 chromosomal region and belongs to the receptor tyrosine kinase family. It plays crucial roles in cell survival and proliferation and is well characterized in TGCT. This gene encodes the human homolog of the proto-oncogene *c-KIT* (4). According to current data in the Catalogue of Somatic Mutations in Cancer (COSMIC) database, approximately 22% (80/366) of the *KIT* mutations are identified in seminomas and approximately 3% (3/104) are identified in nonseminomas.

Single nucleotide polymorphisms (SNPs) in the *KITLG* gene, which is the ligand for the *KIT* receptor tyrosine kinase, are associated with a 2.5-fold increased TGCT risk. Seven SNPs showing the strongest linkage to TGCT susceptibility, according to the data obtained in GWAS, have been identified for the *KITLG* gene and adjacent areas. This gene is located in the 12q21.3.2 chromosomal region and is responsible for primordial germ cell development, survival, and migration. *KITLG* is involved in proliferation and survival by performing c-KIT dimerization and autophosphorylation in the c-KIT-*KITLG* signaling pathway. These results indicate that *KITLG* plays a critical role in TGCT tumorigenesis. Interestingly, variations in *KITLG* sequence are more common in European populations than in African populations. Moreover, *KITLG* has been associated with pigmentation level. This may explain the significant differences in TGCT incidence between ethnic groups (4,6).

The 4 major GWAS performed to date have demonstrated the association of testicular cancers with genes such as *KITLG*, *SPRY4*, *BAK1*, *TERT*, *ATF1IP*, and *DMRT1*, which are generally recognized as important in cancer pathogenesis (6,7,21,22). Susceptibility locus studies in GWAS revealed over 40 risk loci associated with TGCT, and *KITLG* was found to be the strongest genetic risk factor for TGCT in these studies. *SPRY4* and *BAK1*,

involved in *KITLG-KIT* signaling, are other susceptibility genes for TGCT. While *SPRY4* inhibits *KITLG-KIT* signaling, *KITLG* *KIT* signaling suppresses *BAK1*, which encodes pro-apoptotic proteins and promotes apoptosis by inhibiting the function of anti-apoptotic proteins. For these reasons, *KIT* signaling is very important for TGCT (23,24).

GWAS for TGCT have revealed high telomerase activity in seminoma due to reactivation of *TERT* gene, which encodes the catalytic subunit of telomerase reverse transcriptase and protects from shorten the chromosomal ends in somatic cells, while this activity was low in teratomas. It is especially noteworthy that *TERT* is associated with TGCT because testicular germ cells are one of the rare cell types with high levels of telomerase expression in adults. It is also known that *TERT* is frequently reactive in cancer cells and in this way increases capacity to divide relative to normal healthy cells. The amplification of the 5q15 region observed in many cancer types also supports this (23,25).

In the COSMIC database for the *KRAS* and *NRAS* proto-oncogene receptor tyrosine kinase proteins activating *Raf/MEK/ERK* and *PI3* kinase pathways, mutation rates in seminoma cases are 9% and 5%, respectively, while there are no mutations in nonseminoma cases. Hacıoğlu et al. (26) demonstrated that both *K-RAS* and *N-RAS* mutations coexist in 2 patients with seminomatous tumors and another with nonseminomatous tumors. They also suggested that the analysis of *K-RAS* and *N-RAS* mutations in TGCTs may provide more treatment options, especially in platinum-resistant tumors (26).

Other studies in patients with impaired sexual development have shown that mutations in genes such as *SRY*, *SOX9*, *NR5A1*, *GATA4*, and *DMRT1*, which are involved in processes related to sex differentiation, can pose a risk for TGCT development (23,27).

The *p53* protein plays an important role in cell cycle regulation, cellular stress response, apoptosis induction, and maintenance of genomic integrity by DNA repair. Loss of *p53* function results in impaired cell cycle regulation and increased tumor aggressiveness and chemotherapy resistance. Although *p53* mutations are common in somatic tumors, the COSMIC database shows that these mutations are very rare in TGCT cases. Moreover, wild-type *p53* is frequently overexpressed in TGCTs. However, *p53* overexpression occurs in association with overexpression of murine double minute-2 (*MDM-2*), the oncoprotein that inhibits *p53* through ubiquitination, and *MDM-2* amplification has been reported at a rate of about 25% in cisplatin-resistant patients (4,28,29).

In addition to genetic factors, epigenetic mechanisms play an important role in the etiopathogenesis of TGCT. All epigenetic regulatory processes are responsible for the initiation and maintenance of pluripotency in embryonic stem cells and the continuity of the characteristics of differentiated cell types. The best known regulatory epigenetic mechanism is DNA methylation. Changes in gene methylation known as important contributors to tumorigenesis include hypomethylation and increased expression of oncogenes, and hypermethylation of CpG islands in the promoter and decreased expression of tumor suppressor genes. In terms of the DNA methylation status of different TGCT types, seminoma cases have very low DNA methylation levels, whereas nonseminomatous teratomas, yolk

sac tumors, and choriocarcinomas show hypermethylation due to overexpression of DNA methyltransferases (*DNMT*) (4). In studies to clarify epigenetic mechanisms in TGCTs, promoter methylation was shown in genes such as tumor suppressors *APC*, *ARF*, *TP53*, *RARB2*, *BRCA1*, *RASSF1A*, cell cycle regulator *CCNA1*, DNA repair genes such as *MGMT* and *hMLH1*, transcription factor *HOXA9*, and *PRSS21*, which encodes the protein testisin in testis cell maturation (30).

Although TGCT is generally curable, resistance to cisplatin is observed in a considerable proportion of patients. Unfortunately, there is currently no effective treatment method for this subset of patients. Therefore, it is important to investigate the molecular mechanisms causing cisplatin resistance. Cisplatin-based chemotherapy has an important role in the treatment of TGCT (31). Cisplatin therapy induces apoptosis induction by creating DNA damage in tumor cells. In TGCT, apoptosis is induced by proapoptotic proteins such as *Noxa* and *Puma* because of the low mutation rates of tumor suppressors such as *p53* and *Rb*. These *p53*-mediated cellular responses also occur with *OCT4*, a regulator of pluripotency which is highly expressed in seminomas and embryonal cell carcinomas. Studies have shown that depletion of *OCT-4* causes a significant decrease in cisplatin hypersensitivity and may account for acquired cisplatin resistance in refractory tumors. *OCT4* is a transcription factor that regulates the expression of *Noxa*. In an *in vitro* study by Gutekunst et al. (32), RNA interference-mediated *OCT4* suppression was associated with reduced *Noxa* expression as well as decreased cisplatin sensitivity. These findings indicate that the sensitivity of *OCT4* to chemotherapy depends on the control of *Noxa* expression (4,32).

Loss of the mismatch repair system, which is required to recognize base pairing errors in DNA, is related to the chromosomal anomaly known as microsatellite instability. Studies have shown that microsatellite instability is associated with *BRAF V600E* mutation and this mutation is associated with treatment failure in TGCT patients. Honecker et al. (33) showed that mutated *BRAF* is associated with a decrease in *hMLH1* protein, which plays an important role in DNA repair and promoter hypermethylation, in chemoresistant GCT samples. Therefore, these results indicate that genetic testing may be useful for estimating resistance in TGCT (33).

Albany et al. (34) showed that the second generation DNA methylation inhibitor guadecitabine reduced cisplatin resistance even at low doses in embryonic carcinoma (EC) cell lines and the cisplatin-resistant EC xenograft mouse model. These investigators indicated that these preclinical results are promising for treating refractory TGCT patients with guadecitabine alone or with cisplatin, because the sensitivity of EC cells to guadecitabine depends on the high level of *DNMT3B* expression in EC cells (34).

Aurora B, a serine/threonine protein kinase, is a regulatory protein with important roles in the cell cycle. *Aurora B* overexpression has been observed in a variety of tumor types, including TGCT, and is associated with poor prognosis in cancer patients. Some studies have shown that inhibition of *Aurora* kinases led to significantly reduced proliferation. Therefore, therapeutic *Aurora* kinase inhibition is thought to be important as a possible anticancer regimen due to its important role in cell division (17,35,36).

In an *in vitro* study, Schaffrath et al. (37) tested the effect of kinase inhibitors such as the mammalian target of rapamycin inhibitor RAD001, the endothelial growth factor receptor and vascular endothelial growth factor receptor inhibitor AEE788, and IGF-1R inhibitor AEW541 alone or in combination with cisplatin in cisplatin-sensitive and resistant TGCT cell lines. The researchers demonstrated the inhibitory activity of these kinase inhibitors on cell proliferation at single doses in cisplatin-sensitive and resistant TGCT cell lines. However, when these agents were combined with cisplatin, no promising results were observed in the cisplatin-resistant cell lines. For this reason, they indicated that these targeted drugs have no potential for the treatment of cisplatin-resistant nonseminomatous germ cell tumors (37).

As discussed above, although there are many known molecular characteristics of TCGT, they are not currently used for clinical prediction. However, elucidation of the genetic and epigenetic properties of TGCT has important clinical implications in terms of prevention, treatment strategy, and prognosis in early disease stages.

Conclusion

Much research has been conducted and is still being done to define the molecular mechanisms that can lead to the development of TGCT, which is a complex and multistage disease. In the process of TGCT development, presence of ITGCN, which is known as a precursor lesion with high KIT/KITLG signaling, and chromosomal gains in 12p are the generally known basic profile. However, several advanced genetic analyses aiming to explain TGCT biology and provide insight into treatment response have demonstrated significant differences between tumor subtypes. Therefore, genomic approaches are not currently being used to predict clinical behavior or treatment response in patients with TCGT, which is a heterogeneous tumor group. However, elucidation of the genetic and epigenetic properties of TGCT, while still in early stages, is thought to have significant clinical benefits in terms of disease prevention in the young male population, chemotherapy response, survival after chemotherapy, and mortality reduction in treatment-resistant disease. In addition, especially nonseminoma patients may be classified as having low-, moderate-, and high-risk of treatment resistance according to clinically demonstrated molecular differences. This would allow treatment to be individualized based on predicted chemotherapeutic response according to patients' genomic characteristics. In terms of TGCT detection, since testicular biopsy is an invasive procedure, identifying the precursor lesion ITGCN together with the aforementioned signaling pathways via noninvasive semen testing may facilitate TGCT screening.

Cytotoxic chemotherapy is the mainstay of treatment for advanced disease. Unfortunately, initial therapeutic trials for molecular targets such as receptor tyrosine kinases have been disappointing. TGCT is a relatively low-frequency cancer that is generally susceptible to platinum-based therapies. However, the molecular mechanisms of cisplatin resistance, which is an important clinical issue, have not been well defined. Understanding the molecular mechanisms of cisplatin resistance in TGCT and considering how new therapeutic targets can be

discovered in chemoresistant TGCT are necessary to further improve clinical care for this patient group.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.K., E.K., S.S., **Design:** İ.K., E.K., S.S., **Data Collection or Processing:** İ.K., E.K., S.S., **Analysis or Interpretation:** İ.K., E.K., S.S., **Literature Search:** İ.K., E.K., S.S., **Writing:** İ.K., E.K., S.S.

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Current Status in the Surgery and Conservative Management of Upper Urinary System Tumors

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Abstract

Upper urinary tract urothelial cancers constitute 5% of all urothelial cancers and standard therapy is bladder cuff excision with nephroureterectomy. This treatment is performed as open or technologically assisted (laparoscopic and robotic) surgery. Conservative treatment approaches include endoscopic treatments, segmental resection, and upper urinary tract immunotherapy. Upper urinary tract immunotherapy is considered effective in patients with carcinoma in situ. In addition, the development of targeted molecules and gene therapies is also anticipated. In selected patient groups, endoscopic (antegrade percutaneous and retrograde ureteroscopic) procedures are being implemented as an alternative to nephroureterectomy in order to prevent unnecessary organ loss and to preserve the nephrons. Oncological survival and tumor control with the endoscopic approach are similar to the outcomes of radical surgery in cases with low-stage and grade tumors. Advantages of the endoscopic approach include minimal morbidity and preservation of kidney function, while disadvantages include life-long follow-up and the need for a large number of endoscopies. In cases with a large tumor burden, the retrograde ureteroscopic approach is generally preferred instead of percutaneous treatment.

Keywords: Upper urinary system urothelial cancers, conservative treatment, alternative surgical approaches, oncologic survival, tumor control

Introduction

Urothelial carcinoma is the 4th most common cancer after breast (or prostate), lung, and colorectal cancers (1). Approximately 90-95% of urothelial carcinomas originate in the bladder and 5-10% in the upper urinary tract (UUT) (2). Seventeen percent of patients with UUT tumors (UUTTs) have concomitant bladder tumors (3). According to the European Association of Urology (EAU) guidelines, standard methods for the diagnosis of UUTTs include:

- Urine cytology,
- Cystoscopy,
- Computed tomography (CT),
- Urography,
- Ureteroscopy and biopsy (3).

Recent reports have cited CT urography as the best noninvasive method for evaluating the UUT for urothelial malignancies. There has been debate regarding the timing and method of contrast media administration, as well as imaging criteria used to identify suspected malignancy (4).

Other than these standard diagnostic methods, there are additional diagnostic methods to increase diagnostic potential

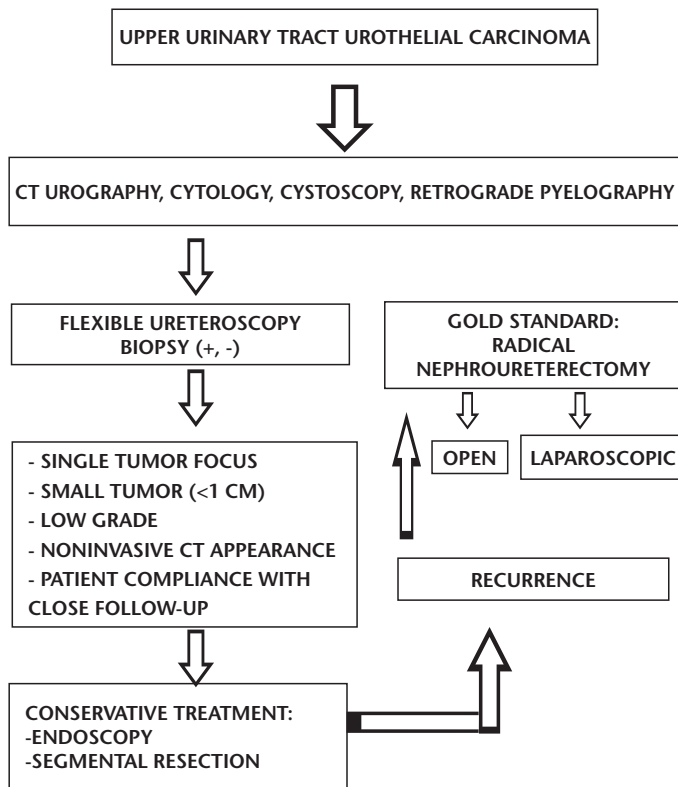
in cases of carcinoma *in situ* (CIS) and small flat lesions, although their effectiveness has not been established. Narrow band imaging (NBI) and photodynamic diagnosis (PDD) are used. NBI is based on the principle of increasing contrast between the mucosa and tumor tissues using light at 2 different wavelengths (blue and green) (5). The method was reported in 1 study to increase the diagnosis rate by 23% (6). Similarly, PDD works on the principle that when a fluorochrome (5-aminolevulinic acid) accumulates in tissue, the pink pathological tissues appear on a blue background when viewed under a light source with a specific wavelength. Two studies on this subject reported that more tumors were detected (7,8). Although further validation of their effectiveness is necessary, these modalities are promising for the future.

The prevalence of invasive tumors at initial diagnosis is 15-25% for the bladder and 60% in the UUT (9). In recurrences of UUTTs, 22-47% of tumors are detected in the bladder, and 26% in the UUT (10). The prevalence of UUTT is 3 times greater in males and peaks in the 70-90 year age group (11). Similarly, tumor grade can be determined with 90% accuracy with ureterorenoscopic biopsy, independent of tumor size (12).

Examination of resection (nephroureterectomy) material from patients with pelvic tumors in the UUT showed that CIS and dysplasia in different locations were present in 60-95% of cases, and recurrences were ultimately the result of a tendency toward multifocal localization (13). Due to this localization pattern, the standard treatment for UUTT is radical nephroureterectomy (RNU). The treatment algorithm is shown in Table 1. The most important parameter affecting treatment outcomes of UUTT is tumor stage and grade. As with bladder cancers, spread occurs via hematogenous and lymphatic route or direct invasion. Muscle invasion has a direct impact on 5-year survival ($\leq 50\%$ among patients with T2-T3 tumors versus $<10\%$ for those with T4 tumors) (14). The classification of patients into low- and high-risk groups is crucial when deciding between conservative and radical surgery in cases of UUTT (15). The determination of low- and high-risk factors is presented in Table 2. The presence of any of the

high-risk factors is sufficient for the patient to be classified in the high-risk group. The gold standard treatment for high-risk tumors is RNU with cuff excision. Conservative treatment of UUTTs is an option for low-risk patients and special indications (such as solitary kidney and renal failure) (3,15). According to version 4.2018 of the National Comprehensive Cancer Network guidelines for bladder cancer, nephron-sparing endoscopic (ureteroscopic and percutaneous approaches) interventions can be recommended alone or in combination with postoperative intrapelvic adjuvant therapies or bacillus Calmette-Guérin (BCG) for low-risk patients. Ureteroscopic methods or resection and anastomosis of the upper/middle/lower ureter can be performed when selecting endoscopic interventions for the renal pelvis and upper ureter (16). However, the risk of tumor spread along the access path should be kept in mind when using percutaneous approaches. In terms of postoperative follow-up, EAU guidelines recommend endoscopy, cytology, and CT urography at 3 and 6 months, every 6 months for the following 2 years, and once a year thereafter for a total of at least 5 years (17).

Table 1. Treatment algorithm for upper urinary tract tumors in the 2015 European Association of Urology Guidelines



CT: Computed tomography

Open, Laparoscopic, and Robotic Radical Nephroureterectomy and Distal Ureterectomy Techniques

The nephrectomy portion of radical surgery for UUTTs has been standardized in terms of surgical principles, regardless of the technique used. In contrast, many different techniques for distal ureterectomy and cuff excision surgery have been developed to date, some of which have been abandoned due to recurrence and difficulties. Some surgical techniques are practiced in combination based on the patient's condition and the surgeon's experience and preference. The following sections provide an outline of the techniques utilized in the surgical treatment of UUTTs.

Open Radical Nephroureterectomy

Single or double incisions may be made based on surgeon experience and the patient's physical build, kidney size, and affected side. For a single incision, a thoracoabdominal incision extending below the umbilicus should be preferred. If a double incision is planned, then a flank incision plus a Gibson or Pfannenstiel incision can be made. It is important to rule out the presence of a second artery and to excise the renal fascia and surrounding adipose tissue before ligating the renal vein. Adrenalectomy is recommended in patients with locally advanced disease and intraoperative signs of adrenal involvement. Cuff resection may be performed transvesically and/or extravesically, and a combined approach with endoscopy provides a comfortable surgery. It is important to remove the ureter as a whole and to close the bladder in 2 layers (18).

Table 2. Classification of high- and low-risk factors in upper urinary tract tumors in the 2015 European Association of Urology Guidelines

Risk factor	Cytology	Number of foci	Tumor size	Pathology	Hydronephrosis	Invasion on CT urography	Previous radical cystectomy
Low	Low	Single	<1 cm	Low	(-)	(-)	(-)
High	High	Multiple	>1 cm	High	(+)	(+)	(+)

CT: Computed tomography

Laparoscopic Radical Nephroureterectomy

First described by Clayman et al. (19) in 1991, the laparoscopic method is preferable for low stage/grade upper ureter or renal pelvis tumors with low risk of invasive disease. Typically, laparoscopic surgery is advantageous in terms of morbidity. Oncologic efficacy and relapse are equivalent to open surgery (19,20). Details to be considered during laparoscopy include avoiding direct contact between instruments and the tumor, avoiding violation of the urinary tract, using organ bags and ensuring en bloc removal of the kidney and ureter cuff, and avoiding laparoscopy in cases of invasive and large tumors (T3/4 and/or N+, M+). The procedure may be retroperitoneal or transperitoneal. Laparoscopy combined with endoscopy facilitates removal of the distal ureter.

Distal ureterectomy and cuff resection are the least standardized part of laparoscopic RNU surgery. The choice is based on surgeon experience, tumor site and potential for spread, and the technical means available (21).

Robotic Radical Nephroureterectomy

Enables fine manipulations that are not possible with the laparoscopic technique, as well as easier suturing and reconstruction. It is particularly advantageous for distal ureter and cuff removal and bladder suturing. As with the other methods, a Foley catheter is recommended for 1 week. Similarly, adrenalectomy is also recommended in this method in cases with adrenal involvement (22).

Approach to bladder cuff resection: Due to the 30-75% recurrence rate in ureteral stumps, RNU with cuff excision is the standard surgical approach. Open and technologically assisted (laparoscopic or robotic) surgeries are possible. Open surgery is associated with greater morbidity, and its nonsuperiority over the laparoscopic or robotic approach in terms of oncologic recurrence has been emphasized (23). Only 1% of UUTs originate in the ureter. The need for RNU is absolute in the high-risk group, but there is still uncertainty regarding the cuff excision technique and whether it is necessary for all patients (1).

Renal pelvis tumors have a better prognosis than ureteral tumors due to the barrier effect of the renal parenchyma (24). In a multicenter renal pelvis tumor series of 4210 patients, Lughezzani et al. (25) evaluated the outcomes of RNU with cuff excision in 2492 patients and RNU alone in 1718 patients. Among patients with locally advanced disease, they determined that the cancer-related mortality rates of pT3-4/N0 and pT(any)/N1-3 patients were 1.25 times and 1.45 times higher, respectively, when cuff excision was not performed. These findings showed that cuff resection is absolutely necessary for these patients, but not performing cuff excision on patients with localized pT1-2/N0 renal pelvis tumors does not affect survival; therefore, they concluded that RNU alone can be performed in T1-2 patients (25).

“Pluck” technique (transurethral resection of ureteral orifice): Prior to nephrectomy, the orifice is dissected and freed to the perivesical area via cystoscopy using a holmium laser or resectoscope. This is followed by nephrectomy and the antegrade removal of the ureter without suturing the bladder. A Foley catheter is left place for 1 week to allow the bladder

incision to heal. The method is contraindicated in patients with distal ureter tumor or CIS (21).

Stripping (intussusception): No longer recommended in EAU guidelines (3). During nephrectomy, a basket or balloon is placed cystoscopically, after which the ureter is ligated. The remaining distal portion is secured in the balloon or basket and traction is applied to the catheter to draw it into the bladder while stripping the ureter from the periureteral tissue, followed by resection of the orifice. Various technical setbacks (such as ureteral rupture) may arise during the procedure (21).

Cleveland technique (transvesical method): Access to the bladder is achieved through 3 mm suprapubic ports, the ureteral orifice is sealed with an endoloop, and the orifice is completely circumscribed to the perivesical area. The distal aspect is removed by proximal traction-assisted dissection during nephrectomy. Seeing the complete orifice sealed with the endoloop is an indicator of safe surgery (26).

Total laparoscopic technique: The orifice and its surroundings are first cauterized using a cystoscope. After nephrectomy, antegrade traction is applied to the ureter and it is mobilized towards the distal aspect. The orifice is everted out of the bladder and secured with an endovascular staple. Seeing the cauterized area is an indicator of surgical integrity (21).

Various researchers have described modified patient positions and different robotic arm paths that are advantageous in robotic RNU. Operative times of 150-190 minutes and blood loss of approximately 130 mL have been reported in different series (27,28). Among more recent publications, Tamhankar et al. (29) reported the average operative time and amount of blood loss in 11 robotic RNU and pelvic lymphadenectomy procedures as 170 minutes (156-270 minutes) and 150 cc (25-500 cc), respectively. The mean length of hospital stay was 3 days (2-8 days). With the exception of 1 patient who developed metastatic systemic recurrence during a 9-month follow-up period, all patients were reported to be disease-free in the final follow-up. As a result, they emphasized the operative morbidity advantage of the robotic approach and its reliability in terms of short-term oncological outcomes (29).

A comparison of different distal ureterectomies (pluck, full laparoscopic, robotic) conducted by Stravodimos et al. (30) showed that none of the techniques was superior. However, they recommended open ureterectomy and cuff excision in patients with excessive tumor load in the distal ureter. They authors stated that due to the high risk of intravesical recurrence, the pluck technique is appropriate for low-stage/grade tumors of the proximal ureter and renal pelvis. It was also emphasized that compared to open ureterectomy, the laparoscopic and robotic methods offer easy bladder suturing after cuff resection and are superior in terms of negative surgical margins and high patient tolerance (30). In another study, Hanna et al. (31) conducted a multicenter comparison of surgical outcomes of 7401 open and 754 laparoscopic operations. Although the low rates of blood transfusion and intraoperative complications in the laparoscopic group were noted, the authors emphasized that the groups showed no difference in terms of postoperative complications and that laparoscopy was a superior alternative to open surgery in terms of morbidity (31).

Li et al. (32) compared cuff resection methods (intravesical, extravesical, transurethral) in 301 patients who underwent RN

and reported no superiority in terms of recurrence or cancer-specific survival. As recommendations, they emphasized orifice coagulation in the transurethral approach and early ureter clamping during nephrectomy to prevent potential spread (32). In 2 large multicenter studies, recurrence and cancer-specific mortality rates following RNU were compared according to pathology (T classification, lymph node metastasis, lymphovascular invasion, sessile tumor and CIS presence) and tumor location. In their study encompassing 2244 patients in 23 centers, Cha et al. (33) reported that tumor pathology was associated with recurrence and cancer-specific mortality over 45 months of follow-up. Raman et al. (34) reached the same conclusion in their study including 1249 patients, and they also reported that tumor location in the ureter or pelvis did not affect recurrence or survival. Zou et al. (35) compared open (n=101) and laparoscopic (n=21) nephroureterectomies and reported that surgical technique did not affect intravesical recurrence or mortality, while history of preoperative tumor in the bladder and presence of hydronephrosis were associated with intravesical recurrence, and tumor pathology (stage, grade, and lymphovascular invasion) was a significant predictor of cancer-specific mortality. Two studies with follow-up periods of 5 years (36) and 13.6 years (37) are noteworthy in terms of the long-term follow-up and survival comparisons between laparoscopic and open NU. Neither study was able to demonstrate a significant difference in survival between the surgical techniques.

In conclusion, when techniques pertaining to distal ureter and cuff resection during NU are compared, open ureterectomy and cuff resection are considered the gold standard. Using a laparoscopic stapler may result in positive surgical margin in the bladder; the transvesical laparoscopic approach, while oncologically reliable, has technical difficulties; and the transurethral approach and intussusception carry the risk of tumor seeding. The long-term follow-up results for robot-assisted distal ureterectomy are still insufficient.

In terms of lymph node dissection, the rate of positivity in Ta and T1 disease is reported as 2.2% and dissection is not recommended. In contrast, lymph node positivity is reported as about 16% in T2 and T3 disease, and dissection is recommended in these cases (3,38).

Lee et al. (39) evaluated the relationship between recurrence in the bladder and preoperative ureteroscopic biopsy in patients who underwent RNU and cuff resection secondary to UUTT. Of 502 patients operated between 1990 and 2013, they reported no significant difference in bladder tumor recurrence between those who underwent preoperative ureteroscopic biopsy (206 patients) and those who did not (296 patients). It was emphasized that a history of bladder tumor, the surgical technique used, and primary tumor pathology are influential in postoperative bladder recurrences (39). In the EAU guidelines, a single dose of mitomycin-C instilled before bladder catheter removal was reported to be effective in preventing early bladder recurrence (3).

Conservative or Local Treatment

Conservative or local treatments are preferred in low-risk patients, those with a functional contralateral kidney, and when other approaches are not an option (solitary kidney or renal

failure) (3). When following a conservative treatment approach, the ipsilateral UUT should be monitored closely.

Segmental resections: For proximal and mid-ureter tumors, open segmental ureterectomy is recommended in the following cases:

- Grade 1-2 T2 disease in which preserving renal function is necessary,
- Tumors that are too large for endoscopic ablation,
- Grade 1-2 TaT1 disease.

The procedure can be performed using open, laparoscopic, or robotic techniques. It enables closure of defects approximately 4 cm in size. A 1 cm safety margin is resected on the proximal and distal aspects of the tumor. A double J stent is left in place for an average of 30-45 days following anastomosis (21,40). Distal segmental ureterectomy is recommended for patients with low stage/grade disease, those who are not eligible for endoscopic surgery, and when preserving renal function is necessary. To avoid tension on the anastomosis, the bladder can be suspended from the psoas muscle (psoas hitch) or a Boari flap can be made. In cases where anastomosis is not possible, the anastomosis can be achieved by forming a tube from a segment of ileum (Monti technique) (21).

Colin et al. (41) compared the 5-year outcomes of RNU (416 patients) and segmental ureterectomy (52 patients) in a multicenter, retrospective study. They reported that surgery type did not affect cancer-specific, recurrence-free, or metastasis-free survival. In selected patients, short-term oncologic outcomes indicate that segmental ureterectomy is also a valid method (41).

Retrograde ureteroscopic technique: First described by Goodman (42) in 1984. In terms of technique, using a rigid ureteroscope without a guide is recommended to avoid suspected tissue damage. Removing the tumor with forceps or basket and then applying laser [holmium:yttrium-aluminum-garnet (YAG)] or electrocautery to the base is recommended. Similarly, a flexible ureteroscope is used for upper ureteral and intrarenal evaluation and treatment (43), but anatomical obstructions (strictures and adhesions) may preclude performing the procedure exactly as described (44).

In their meta-analysis of 736 patients in 22 studies, Cutress et al. (44) reported 53% recurrence, 15% progression, 9% disease-specific mortality, and 19% subsequent NU with a follow-up period of 14-73 months. Complications were observed in 14% of patients (78% were strictures, others included perforation, sepsis, and hemorrhage) (44). Of the recent research examining the treatment efficacy of retrograde surgery, a study by Scotland et al. (45) is noteworthy. In their study, 80 patients with biopsy-proven low-grade UUTs with a mean size of 3.04 cm were followed for a mean of 43.6 months after ureteroscopic laser ablation. All of the patients underwent cystoscopy and ureteroscopy every 3 months until tumor-free. Follow-up of tumor-free patients was done every 6 months for the first 5 years and yearly thereafter. During follow-up, ipsilateral recurrence was observed in 90.5% of the patients, with 31.7% progressing in grade at a mean of 26.3 months. Sixteen patients (20%) underwent RNU after a mean of 23.2 months. Rates of overall and cancer-specific survival at 5 years were 75% and 84%, respectively. It was concluded that ureteroscopic treatment of UUTs >2 cm in size is a treatment option that preserves organ

function and offers an alternative to RNU, provided that the patient is closely monitored due to the risk of recurrence (45).

Antegrade percutaneous technique: Technical advances have led to the abandonment of this method except for patients with diversion, solitary kidney, or anatomic obstacles (strictures, adhesions). Treatment using the antegrade approach is usually conducted in 3 sessions. Technically, renal access is achieved by the same steps used in percutaneous stone extraction surgery (ureteral catheter placement, prone position, access from the calyx at the angle most convenient for the procedure, and renal placement). The tumor is removed by excision or tearing, and the base is coagulated with YAG laser or electrocautery. Multiple access points may be required. NU is performed when peroperative frozen examination reveals invasive high-grade tumor (46). If the same pathology is encountered at any stage of conservative follow-up, the treatment is also NU (47). When peroperative pathology indicates a low-grade tumor, the procedure is concluded by placing a nephrostomy catheter. If there is suspicion of residual tumor, or a biopsy sample will be taken from the base, a second session is performed within the same week (46). If pathology is invasive at this stage, NU should be performed. If examination indicates tumor absence or low-grade pathology and nephrostogram shows no extravasation/obstruction, intrarenal mitomycin-C or BCG can be instilled (48). After 2-4 weeks of intrarenal chemo-immunotherapy, a third endoscopy is done and a biopsy sample is obtained. Follow-up begins after nephrostomy (46,48).

Complications of percutaneous tumor extraction are similar to those of stone extraction surgery: fever, hemorrhage, and additional organ injuries. Furthermore, irrigation pressure must be kept below 40 cm H₂O to avoid tumor seeding due to backflow of the irrigation fluid. Using distilled water is recommended due to its cytolytic property (49). However, there remains a risk of tumor development along the access path and tumor extension due to urinary tract perforation despite all of these precautions (50).

Jarrett et al. (51) reported a recurrence rate of 33% based on the 9-year follow-up of 30 patients. Tumor grade has been reported to be a determinant of recurrence and survival (recurrence was 18% with G1 and 50% with G3). As a result, presence of a multifocal tumor ≥ 1.5 cm in size and the presence of dysplasia were defined as determinants of recurrence (52).

The recurrence rate in patients treated by percutaneous approach is 13-65%. The rates of bladder recurrence, overall survival, and cancer-specific survival have been reported as 15-42%, approximately 92%, and 75-100%, respectively (53). Previous studies retrospectively evaluating endoscopic and open surgical methods reported that 20% of patients treated endoscopically subsequently underwent RNU. It was also reported that in well-selected low-grade patients, cancer-specific survival was similar with endoscopic treatment and RNU, whereas RNU provided a survival advantage in patients with high-grade tumors (44). To determine correct tumor grade, the endoscopic biopsies and pathology specimens of patients who later underwent RNU were evaluated. There was 80% agreement between endoscopic and RNU pathology results. The study showed that with endoscopy, 25% of patients may have overlooked lesions, 50% of which contain undetectable CIS (54).

In another study, comparison of local UUTT patients who underwent endoscopic treatment and those who had RNU showed similar overall and cancer-specific survival rates. However, it is emphasized that further prospective, randomized, multicenter studies were needed to reliably compare oncologic outcomes (55).

Adjuvant therapies: BCG, mitomycin-C, epirubicin, thiotepa, and BCG/interferon have been used in the treatment of urothelial tumors of the UUT, both for primary CIS (56) and after resection and ablation (57,58,59). However, due to insufficient patient numbers, it has not been possible to definitively demonstrate the efficacy of these methods (including mitomycin-C, BCG, and other agents) with scientific evidence (60,61). Nevertheless, BCG is most commonly used after antegrade resection and mitomycin-C is most commonly used after ureteroscopic resection (62). After ureteroscopic treatment, 60 mg mitomycin-C is instilled for 1 hour once a week for 6 weeks using a ureteral catheter (pressure ≤ 20 cm H₂O) or directly into the bladder in cases with proven reflux (63,56).

Following percutaneous resection, BCG therapy is usually recommended 1 week after the second follow-up nephroscopy (after ruling out extravasation and obstruction) and administered once a week for 6 weeks (360 mg BCG/150 mL saline, ≤ 20 cm H₂O pressure and 1 mL/min instillation rate, total of 2.5 hours per session) with intravenous antibiotic prophylaxis (64). In terms of the side effects of adjuvant therapy, the risk of systemic BCG sepsis is particularly noteworthy. Complete healing of the mucosa prior to administration (though not absolutely necessary for mitomycin-C) and low-pressure instillation are very important. Especially after percutaneous resection, routine use of isoniazid, close monitoring for sepsis, and waiting for 2 weeks have been suggested (62,65). A 2018 meta-analysis by Gregg et al. (66) including a total of 13 comparative studies is the most recent research on adjuvant therapies for UUTT. Ultimately, the authors emphasized the need for new therapeutic agents and more randomized clinical trials (66).

Conclusion

The gold standard in the treatment of UUTs is RNU and cuff excision. Unlike the bladder, endoscopic interventions during follow-up require a higher level of technology and experience. Similar to bladder tumors, the local stage and histological grade of the tumor are the main prognostic factors (67,68). For this reason, organ-sparing treatments are recommended for small, superficial, and low-grade tumors in both elective and nonelective procedures (69). The most common conservative technique is retrograde ureteroscopy. However, this procedure cannot be performed due to technical reasons in 25% of patients. An antegrade percutaneous route can be used in these cases and in patients with large intrarenal tumors.

Studies with larger patient numbers and longer follow-up periods are needed to better characterize the effects of adjuvant therapies on survival, recurrence, and prognosis. In the conservative approach, patient compliance with close monitoring is as important a factor as tumor pathology, size, and location. According to the schedule recommended in follow-up protocols, for the first 3 years patients should be

evaluated with ureteroscopy every 6 months in addition to radiological and laboratory exams. If this is not considered feasible, NU and cuff excision should always be the first choice for treatment.

Ethics

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Üst Üriner Sistem Tümörleri Cerrahi ve Konservatif Tedavilerinde Güncel Durum

Current Status in the Surgery and Conservative Management of Upper Urinary System Tumors

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Öz

Üst üriner sistem ürotelyal tümörleri, tüm ürotelyal kanserlerin %5'ini teşkil etmektedir ve standart tedavi nefroureterektomi ile birlikte mesane kaf eksizyonudur. Bu tedavi açık cerrahi ve teknolojik (laparoskopik ve robotik) cerrahiler şeklinde uygulanmaktadır. Endoskopik tedaviler, segmental rezeksiyon, üst üriner sistem immünoterapi tedavisi; konservatif tedaviler olarak değerlendirilmektedir. Üst üriner sistem karsinom *in situ* hastalarında immünoterapi etkin olarak kabul edilmektedir. Ayrıca ümit verici olarak hedefe yönelik moleküller ve gen tedavilerinin gelişimi de beklenmektedir. Seçilmiş hasta gruplarında, gereksiz organ kaybını önlemek ve nefron korumak adına; endoskopik (antegrad perkütan ve retrograd üreteroskopik) tedaviler bir alternatif olarak uygulanmaktadır. Endoskopik yaklaşımla onkolojik sağkalım ve tümör kontrolü; düşük evre ve dereceli tümör olgularında, radikal cerrahi sonuçlarına benzerdir. Endoskopik yaklaşımın avantajı; minimal morbidite ve böbrek fonksiyonlarında korunum sağlanması, dezavantajı; yaşam boyu izlem ve çok sayıda endoskopi gerekliliğidir. Büyük tümöral yükün olduğu olgularda perkütan tedavi uygulanmasına karşın genelde retrograd üreteroskopik yaklaşım tercih edilen seçenektir.

Anahtar Kelimeler: Üst üriner sistem ürotelyal tümörleri, konservatif tedaviler, cerrahi yaklaşım alternatifleri, onkolojik sağkalım, tümör kontrolü

Abstract

Upper urinary tract urothelial cancers constitute 5% of all urothelial cancers and standard therapy is bladder cuff excision with nephroureterectomy. This treatment is performed as open or technologically assisted (laparoscopic and robotic) surgery. Conservative treatment approaches include endoscopic treatments, segmental resection, and upper urinary tract immunotherapy. Upper urinary tract immunotherapy is considered effective in patients with carcinoma *in situ*. In addition, the development of targeted molecules and gene therapies is also anticipated. In selected patient groups, endoscopic (antegrade percutaneous and retrograde ureteroscopic) procedures are being implemented as an alternative to nephroureterectomy in order to prevent unnecessary organ loss and to preserve the nephrons. Oncological survival and tumor control with the endoscopic approach are similar to the outcomes of radical surgery in cases with low-stage and grade tumors. Advantages of the endoscopic approach include minimal morbidity and preservation of kidney function, while disadvantages include life-long follow-up and the need for a large number of endoscopies. In cases with a large tumor burden, the retrograde ureteroscopic approach is generally preferred instead of percutaneous treatment.

Keywords: Upper urinary system urothelial cancers, conservative treatment, alternative surgical approaches, oncologic survival, tumor control

Giriş

Ürotelyal karsinomlar, tümörler arasında sıklık bakımından; meme (veya prostat), akciğer ve kolorektal kanserlerden sonra 4. sıradadır (1). %90-95'i mesane, %5-10'u üst üriner sistem (ÜÜS) kaynaklıdır (2). ÜÜS tümörü (ÜÜST) varlığında, %17 olguda mesane tümörü birlikteliği söz konusudur (3). European Association of Urology (EAU) kılavuzlarında ÜSST tanısında standart yöntemler olarak;

- İdrar sitolojisi,
- Sistoskopi,
- Bilgisayarlı tomografi (BT),

- Ürografi,
- Üreteroskopi ve biyopsiler kullanılmaktadır (3).

Son yayınlarda BT ürografisi; ürotelyal malignansiler için, ÜÜS'nin değerlendirilmesinde en iyi noninvaziv yöntem olarak vurgulanmıştır. Görüntüleme kontrast verilme zamanlaması ve teknikleriyle birlikte malignite açısından şüpheli görünümünün de tanımlamaları tartışılmıştır (4).

Bu standart tanı yöntemleri dışında, karsinoma *in situ* (CIS) ve küçük yassı lezyonlarda; tanı koyma potansiyelini artırmak adına, etkinliği kesin kanıtlanmamış olsa da ek tanı yöntemleri mevcuttur. Dar bant görüntüleme (NBI) ve fotodinamik tanı (PDD) yöntemleri kullanılmaktadır. NBI; farklı 2 dalga boyu

(mavi ve yeşil) ışık ile mukoza ve tümör dokuları arasında kontrastın artırılması prensibine dayanmaktadır (5). Yapılan bir çalışmada yaklaşık %23'lük ek tanı koydurabilme imkanı tanımlanmıştır (6). Benzer şekilde PDD'de prensip, florokrom bir maddenin (5 amino-la-evulnic-acid) dokuda birikmesi ve sonrasında özel dalga boylu bir ışık kaynağı ile bakıldığında; mavi zeminde pembe patolojik dokuların gözlenmesidir. Bu konuda yapılmış 2 çalışmada daha fazla sayıda tümör saptandığı rapor edilmiştir (7,8). Bunların etkinliği net kanıtlanmamış olsa da; geleceğe dair umut vermektedir.

İlk tanıda invaziv tümör varlığı mesane için %15-25, ÜÜS için %60'tır (9). ÜÜST'lerin rekürrensinde; %22-47 mesane, %26 karşı sistemde tümör tespit edilmektedir (10). ÜÜST'lerin, erkeklerde 3 kat sık ve pik yaptığı yaş grubu 70-90 yaşdır (11). Aynı şekilde üreterorenoskopik biyopsiyle; tümör derecesi, boyuttan bağımsız olarak %90 kesinlikle tespit edilebilmektedir (12). ÜÜST'lerde pelvis tümürlü hastaların operasyon [radikal nefroüretrektomi (RNÜ)] materyali incelendiğinde; %60-95 olguda farklı lokalizasyonda, CIS ve displazi görülebilmektedir ve sonuç olarak rekürrenslere, çok odaklı yerleşim eğiliminin eserdir (13). Bu yerleşim özelliği nedeniyle üst üriner kaynaklı tümörlerde standart tedavi RNÜ'dür. Tedavi algoritması Tablo 1'de verilmiştir.

ÜÜST tedavi sonucunu etkileyen en önemli parametre, tümör evre ve derecesidir. Yayılım, mesanede olduğu gibi hematogen, lenfatik ve direkt invazyonlardır. Kas invazyonu 5 yıllık sağkalımı direkt etkiler. T2-T3 tümörde sağkalım; <=%50 iken, T4 tümörde sağkalım <%10'dur (14).

ÜÜST'lerde konservatif ve radikal cerrahi kararı verilirken, hastaların düşük ve yüksek risk grubu olarak sınıflandırılması doğru karar adına hayati önem taşır (15). Düşük ve yüksek risk faktörlerinin tespiti Tablo 2'de belirtilmiştir. Yüksek risk grubundan sadece 1 faktörün varlığı, hastayı yüksek riskli gruba dahil eder. Yüksek risk grubunda altın standart, RNÜ ile beraber kaf eksizyonudur. ÜÜS tümörlerinde konservatif tedavi, düşük riskli hastalar ve zorunlu haller (soliter böbrek, böbrek yetmezliği gibi) için bir seçenektir (3,15). The National Comprehensive Cancer Network 2018 4. versiyon kılavuzlarına göre; düşük risk grubunda, tek başına nefron koruyucu endoskopik (üreteroskopik, perkütan yaklaşımlar) veya ek olarak postoperatif intrapelvik adjuvan tedaviler veya bacillus Calmette-Guérin (BCG) önerilebilmektedir. Renal pelvis ve üst üreterde endoskopik müdahaleler seçilirken, üst-orta-alt üreterde rezeksiyon ve anastomoz veya üreteroskopik yöntemler kullanılabilir (16). Ancak perkütan yaklaşımlarda giriş hattında tümöral yayılım riski unutulmamalıdır. Cerrahi sonrası takipte EAU kılavuzları, 3. ve 6. aylarda ve takip eden 2 yıllık zamanda 6 ayda 1 ve sonrası yılda 1, toplam en az 5 yıl; endoskopi, sitoloji ve BT ürografi önermektedir (17).

Açık, Laparoskopik, Robotik Radikal Nefroüretrektomi ve Distal Üreterektomi Teknikleri ve Kıyaslamaları

ÜÜST tedavisinde radikal cerrahinin nefrektomi kısmı, hangi teknikle olursa olsun cerrahi prensipler açısından standardize olmuştur. Aksine distal üreterektomi ve kaf eksizyonu cerrahisinde günümüze kadar çok farklı teknikler gündeme gelmiş, nüksler ve

zorlukları nedeniyle terk edilen uygulamalar olmuştur. Cerrahi tekniklerin bazıları da hastanın durumu ve cerrahin tecrübe ve inisiyatifini doğrultusunda kombine uygulanmaktadır. ÜÜST cerrahi tedavisinde uygulanan teknikleri aşağıda ana hatlarıyla gözden geçirelim:

Açık Radikal Nefroüretrektomi

Hastanın fiziki yapısı, böbrek boyutu, böbrek lateralizasyonu ve deneyim ile değişimle birlikte, tek insizyon yapılacaksa göbek altına uzatılan torakoabdominal insizyon tercih edilmelidir. Çift insizyon planı varsa flank ile beraber Gibson veya Phannenstiel yapılabilir. Renal ven bağlanmadan önce 2. arter varlığının ekarte edilmesi ve gerota ile beraber çevre yağ dokusunun eksizyonu önemlidir. Lokal ileri evre hastada ve cerrahi sırasında adrenal bölgede patolojik görünüm varsa, adrenaletomi yapılması önerilmektedir. Kaf çıkartılması konusu; transvezikal veya ekstravezikal olabileceği gibi, endoskopi ile kombinasyonlu yaklaşım, cerrahide rahatlık sağlar. Üreterin kesinlikle bütün çıkartılması ve mesane açıklığının 2 kat kapatılması önemlidir (18).

Laparoskopik Radikal Nefroüretrektomi

1991'de ilk kez Clayman ve ark. (19) tarafından tanımlanmıştır. Laparoskopik yöntem, düşük evre ve dereceli renal pelvis veya üst üreter tümörlerinde; invaziv hastalık riski azsa tercih edilmektedir. Klasik olarak laparoskopik cerrahinin morbidite avantajları vardır. Onkolojik etkinlik ve nüks açık cerrahi ile aynıdır (19,20). Laparoskopide dikkat edilmesi gereken incelikler; enstrümanların tümör ile direkt temas ettirilmemesi, üriner sistemin açılmaması, organ torbası kullanımı, böbrek ve üreter kafının bütün olarak çıkartılması; ayrıca invaziv ve büyük tümörlerde (T3/4 ve veya N+, M+), laparoskopinin tercih edilmemesi şeklinde sayılabilir. İşlem retroperitoneal ve transperitoneal olabilir. Distal üreterin çıkartılmasında endoskopi ile kombine laparoskopik kolaylık sağlamaktadır.

Laparoskopik RNÜ'de; distal üreterektomi ve kaf çıkartılması cerrahinin en standardize olmamış kısmıdır. Seçim cerrahin deneyimine, tümörün lokalizasyonuna, yayılabilme potansiyeline ve teknik imkanlara göredir (21).

Robotik Radikal Nefroüretrektomi

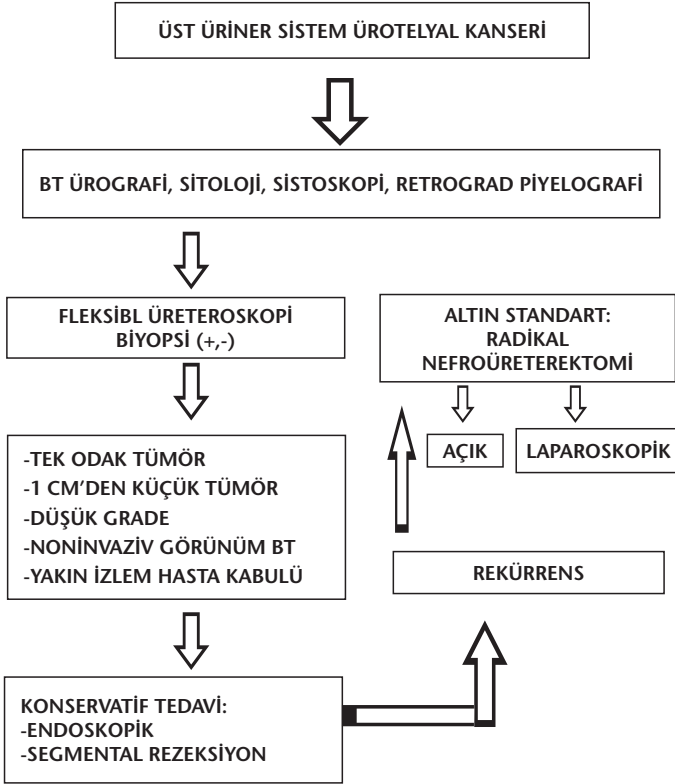
Laparoskopik tekniğin imkan vermediği ince manipülasyonlara ve daha rahat sütürasyon ve rekonstrüksiyona imkan sağlar. Özellikle distal üreter ve kaf çıkartılmasında ve mesane sütürasyonunda avantaj sağlar. Foley kateterin 1 hafta kadar kalması diğer yöntemlerde olduğu gibi önerilir. Klinik olarak adrenaletomi diğer cerrahilerde olduğu gibi bu yöntemde de tutulum varlığında önerilir (22).

Mesaneden kaf çıkartılmasına yaklaşım: Üreteral güdüklerde %30-75 oranlarında rekürrenslere olması nedeniyle; standart cerrahi yaklaşım, RNÜ ve birlikte kaf eksizyonudur. Açık ve teknolojik (laparoskopik veya robotik) cerrahi yapılabilir. Açık cerrahi daha morbid kabul edilmekte ve onkolojik rekürrens açısından laparoskopik veya robotik yaklaşıma üstünlüğünün olmadığı vurgulanmaktadır (23). ÜÜST'lerin sadece %1'i üreter kaynaklıdır. Yüksek riskli grupta RNÜ kesin, ancak

kaf eksizyonunun tekniği ve her hastaya yapıma gerekliliği tartışmalıdır (1).

Renal pelvis tümörlerinde prognoz, böbrek parankimi bariyer etkisi ile üreter tümörlerinden daha iyidir (24). Lughezzani ve ark. (25) 4210 hastalık çok merkezli renal pelvis tümörü serilerinde; 2492 hastada RNÜ ve kaf eksizyonu, 1718 hastada yalnızca RNÜ sonuçlarını değerlendirmişlerdir. Lokal ileri hastada; pT3-4N0 ve pT (herhangi) N1-3 olan hastalarda, kaf eksizyonu yapılmadığında kansere bağlı mortalite oranını 1,25 kat ve 1,45 kat daha yüksek bulmuşlardır. Bu sonuçlara dayanarak, bu hastalarda mutlaka kaf çıkartılmasının gerekliliği, ancak böbrek pelvis tümürlü pT1-2N0 olan lokalize hastalarda kaf eksizyonu yapılmamasının sağkalımı etkilemediği gösterilmiştir ve T1-2 hastalarda sadece RNÜ yapılabileceği yönünde öneride bulunmuşlardır (25).

Tablo 1. Üst üriner sistem tümörü; European Association of Urology Guidelines 2015 tedavi algoritması



BT: Bilgisayarlı tomografi

Pluck tekniği (transüretral rezeksiyon orifis): Nefrektomi öncesi sistoskopi ile orifisin, perivezikal alana kadar holmium lazer veya rezektoskopla kesilip serbestlenmesidir. Devamında nefrektomi ve üreterin antegrad olarak mesaneye sütür konulmaksızın alınmasıdır. Mesane açıklığının iyileşmesi adına, 1 haftalık foley sondalı takip yapılır. Yöntem distal üreterde tümör veya CIS durumunda, kontrendikedir (21).

Stripping (intususepsiyon): EUA kılavuzlarında artık önerilmemektedir (3). Sistoskopik olarak yerleştirilen basket veya balon sonrası nefrektomide: üreterin belli bir yerden kesilip, kalan distal kısmının ise balon veya baskete sıkıştırılıp, distalden çekilerek periüreteral dokudan sıyrılıp mesane içinden doğrultulması ve ofisin rezeksiyonudur. Teknik olarak uygulama sırasında çeşitli aksamalar (üreterin kopması gibi) çıkabilmektedir (21).

Cleveland tekniği (transvezikal yöntem): Suprapubik 3 mm portlarla mesaneye girilip; üreter orifisi endoloop ile mühürlenir, sonrası orifis çepeçevre perivezikale kadar kesilir. Distal kısım nefrektomi sırasında; proksimalden traksiyon yardımıyla diseksiyonlarla çıkartılır. İşlemden endoloop ile mühürlenmiş orifisin bütün olarak gözlenmesi emniyetli cerrahinin göstergesidir (26).

Total laparoskopik teknik: Önce sistoskopi ile orifis ve çevresi koterize edilir. Nefrektomi sonrasında antegrad olarak üreter traksiyona alınır, distale kadar serbestlenip orifis mesane dışına evert edilir ve endovasküler stapler konur, koterize edilen kısmı görmek işlemin bütünlüğü adına belirleyicidir (21).

Farklı araştırmacılar robotik RN'de avantaj sağlayan modifiye hasta yatış açıları ve farklı hatlardan yerleştirilen robot kolları tarif etmişlerdir. Cerrahi süreler farklı serilerde 150-190 dakika arası ve kan kayıpları yaklaşık 130 mL olarak raporlanmıştır (27,28). Son yayınlar gözden geçirildiğinde; Tamhankar ark.'nın (29) 11 hastalık robotik RN ve pelvik lenfadenektomi uygulamalarında; ortalama cerrahi süresi 170 dakika (156-270 dakika) ve kan kaybı 150 cc (25-500 cc) idi. Ortalama hastanede kalış süresi 3 gündü (2-8 gün). Dokuz ay takip süresinde sadece 1 hastada metastatik sistemik rekürrens gelişimi dışında diğer tüm hastalar son takipte hastaliksız olarak raporlanmış; sonuçta robotik yaklaşımın cerrahi morbidite avantajları ile kısa dönem onkolojik takip açısından da güvenilirliği vurgulanmıştır (29).

Stravodimos ve ark.'nın (30) çalışmalarında; farklı distal üreterektomiler (pluck, tam laparoskopik, robotik) kıyaslanmış birbirlerine üstünlüğünün olmadığı gösterilmiştir. Öneri olarak; distal üreterde fazla tümör yükü varlığında, açık üreterektomi ve kaf çıkartılması vurgulanmıştır. Pluck tekniğinin, yüksek

Tablo 2. Üst üriner sistem tümörü European Association of Urology Guidelines 2015; düşük ve yüksek risk faktörleri sınıflaması

Risk faktörü	Sitoloji	Odak sayısı	Tümör boyutu	Patoloji	Hidronefroz	BT ürografide invaziv özellik	Öncesi radikal sistektomi
Düşük	Düşük	Tek	<1 cm	Düşük	(-)	(-)	(-)
Yüksek	Yüksek	Multi	>1 cm	Yüksek	(+)	(+)	(+)

BT: Bilgisayarlı tomografi

intravezikal rekürrens riskinden dolayı düşük evre ve dereceli proksimal üreter ve renal pelvis tümörlerinde uygun olduğu vurgulanmıştır. Açık üreterektomiye kıyasla, laparoskopik veya robotik yöntemde; kaf çıkartılması sonrası mesaneye sütür konulabilmesi avantajı ve yüksek hasta toleransı ile beraber negatif cerrahi sınır adına üstünlük vurgulanmıştır (30). Hanna ve ark. (31) açık (7401 hasta) ve laparoskopik (754 hasta) çok merkezli cerrahi sonuçları kıyaslamışlardır. Laparoskopik grupta kan transfüzyonu ve intraoperatif komplikasyon düşüklüğü vurgulanırken, postop komplikasyonların gruplar arası farksızlığı ve sonuçta açık cerrahiye kıyasla laparoskopinin morbidite üstünlüğü açısından alternatif olduğu vurgulanmıştır (31).

Li ve ark. (32) RN'li 301 hastada kaf çıkartılmasını (intravezikal, ektravezikal, transüretal) kıyaslamışlar; rekürrens ve kansere özgü sağkalım açısından, yöntemlerin birbirine üstünlüğünün olmadığını tespit etmişlerdir. Öneri olarak transüretal yaklaşımda; potansiyel yayılımı önlemek için orifis koagülasyonunu ve nefrektomi sırasında erken üreter klemlenmesini vurgulamışlardır (32).

Çok merkezli 2 büyük çalışmada; RNÜ sonrası rekürrens ve kansere özgü mortalite; patolojik (T sınıflaması, lenf nodu metastazi, lenfovasküler invazyon, sesil tümör ve CIS varlığı) açıdan ve tümör lokalizasyonu açısından kıyaslanmıştır.

Cha ve ark. (33) (2244 hasta ve 23 merkez) çalışmalarında, 45 aylık izlemde tümör patolojisinin; rekürrens ve kansere özgü mortalite ile ilişkili olduğunu bildirmiştir. Raman ve ark. (34) (1249 hasta) çalışmalarında aynı sonuca ulaşmış ve ek olarak tümörün üreter veya pelvis lokalizasyonlu oluşunun nüks ve sağkalıma etkisinin olmadığını bildirmiştir. Zou ve ark. (35) açık (101 hasta) ve laparoskopik (21 hasta) NÜ'yi karşılaştırmışlardır. İntravezikal rekürrens ve mortalitede, cerrahi tekniğin etkisiz olduğunu ve intravezikal rekürrenste; preop mesanede tümör hikayesi ile hidronefroz varlığının etkili olduğunu, kansere özgü mortalite öngörmede; tümör patolojisinin (evre, derecelendirme ve lenfovasküler invazyon) etkili olduğunu bildirmişlerdir (35). Literatürde; laparoskopik ve açık NÜ için uzun süreli takip ve sağkalım kıyası adına, 5 yıl (36) ve 13,6 yıl (37) takipli 2 çalışma dikkati çekmektedir. Her ikisinde de; cerrahi teknikle sağkalımlar arasında fark saptanmamıştır.

Sonuç olarak, nefroüreterektomi sırasında distal üreter ve kaf çıkartılması teknikleri kıyaslandığında; altın standart, açık üreterektomi ve kaf çıkartılması olarak kabul edilmektedir. Laparoskopik stapler kullanımında; mesanede cerrahi sınır pozitifliği olabileceği, transvezikal laparoskopik yaklaşımın; onkolojik güvenilir ancak teknik olarak zorluklar içerdiği, transüretal yaklaşım ve intususepsiyonun; tümör ekimi adına riskli olduğu belirtilmiştir. Robot yardımlı distal üreter çıkartılması adına uzun dönem takip sonuçlarının henüz yetersizliği belirtilmektedir.

Lenf nodu diseksiyonu hususunda, TaT1 hastalıkta pozitiflik oranı %2,2 olarak bildirilmiştir ve diseksiyon önerilmemektedir. T2 T3 hastalıkta pozitiflik %16 civarı bildirilmiş ve diseksiyon önerilmektedir (3,38).

Lee ve ark. (39), ÜÜST'ye sekonder RN ve mesaneden kaf çıkartılması uygulanmış hastalarda; mesane rekürrensi ile cerrahi öncesi üreteroskopik biyopsi ilişkisini değerlendirmişlerdir. Çalışmalarında, 1990-2013 yılları arasında opere edilmiş 502 hastada mesanede tümör rekürrensinde; cerrahi öncesi üreteroskopik biyopsi yapılan (206 hasta) ve yapılmayanlar (296 hasta) arasında anlamlı fark olmadığını bildirmişlerdir. Postoperatif mesane rekürrenslerinde; mesanede tümör özgeçmiş, cerrahi teknik ve primer tümör patolojisinin etkili olduğu vurgulanmıştır (39). EAU kılavuzlarında; erken dönem mesane rekürrensi önlemede, mesane kateteri çıkmadan önce tek doz mitomisin-C'nin etkisi bildirilmektedir (3).

Konservatif veya Lokalize Tedaviler

Konservatif veya lokalize tedaviler; düşük riskli hastalarda karşı böbrek fonksiyonel olduğu hallerde ve zorunlu olgularda (soliter böbrek veya renal yetmezlik) tercih edilmektedir (3). Konservatif tedavi uygulandığında ipsilateral ÜÜS yakın takip edilmelidir.

Segmental rezeksiyonlar: Proksimal ve orta üreter tümörlerinde, açık segmental üreterektomi önerisi;

- Renal fonksiyonların korunmasının gerekli olduğu grade 1-2 T2 olgularda,

- Endoskopik ablasyon uygulanmayacak büyüklükteki olgularda,

- TaT1 grade 1-2 olgularda yapılmaktadır.

İşlem teknik olarak; açık, laparoskopik veya robotik olabilir. Yaklaşık 4 cm'lik defektin kapatılmasına imkan sağlar. Tümörün proksimal ve distalinden, 1'er cm'lik emniyet marjı bırakılır. Double J stent anastomoz sonrası ortalama 30-45 gün kalır (21,40). Distal segmental üreterektomi önerisi; düşük evre ve dereceli, endoskopik olarak yapılamayan ve böbrek fonksiyonunun korunma zorunluluğu olan olgularda yapılmaktadır. Anastomozun gergin olmaması adına; mesane psoasa asılabilir (psoas hitch) veya Boari flep yapılabilir. Anastomozun imkansız olduğu olgularda, ileum segmentinden tüp yapılarak anastomoz tamamlanabilir (Monti tekniği) (21).

Colin ve ark. (41) RNÜ (416 hasta) ve segmental üreterektomi (52 hasta) hastalarını çok merkezli retrospektif olarak 5 yıllık değerlendirmişlerdir. Cerrahi tipinin kansere özgü rekürrenssiz ve metastazsız sağkalımları etkilemediğini bildirmişlerdir. Seçilmiş olgularda kısa dönem onkolojik sonuçlar, segmental üreterektominin de geçerli bir metot olduğunu göstermektedir (41).

Retrograd üreteroskopik teknik: İlk kez 1984'te Goodman (42) tariflemiştir. Teknik olarak rijit üreteroskop ile, şüpheli doku hasarı olmasın diye, guide kullanmadan önerilmektedir. Tümörün forseps veya basketle çıkartılması ve sonrasında tabana lazer [holmium:ytrium-aluminum-garnet (YAG)] veya elektrokoterizasyon yapılması önerilir. Benzer şekilde üst üreter ve böbrek içi değerlendirme ve tedavide fleksibl üreteroskop kullanılır (43); ancak anatomik engellerden dolayı (darlık ve yapışıklıklar vs.) işlemin tam olarak tariflenen şekilde yapılamaması olasıdır (44).

Cutress ve ark. (44) (736 hasta, 22 çalışma) metaanalizinde, 14-73 ay takip süreli hastalarda %53 rekürrens, %15 progresyon, %9 mortalite, %19 nefroüreterektomiye gidış bildirmiştir.

Komplikasyon %14 (%78 darlık, geriye kalanlar; perforasyon sepsis ve kanama) olarak gözlenmiştir (44). Retrograd cerrahinin tedavide etkinliğinin değerlendirilmesi amaçlı yapılmış son çalışmalar incelendiğinde; Scotland ve ark.'nın (45) çalışması dikkat çekmektedir. Çalışmada; biyopsi ile kanıtlanmış düşük dereceli ve ortalama tümör boyutu 3,04 cm (en az 1 lezyonu olan) ÜÜST'li 80 hasta, üreteroskopik lazer tümör ablasyonu sonrası ortalama 43,6 ay takip edilmiştir. Hastaların tamamına; tümörsüz hale gelene kadar her 3 ayda 1 sistoskopi ve üreteroskopi yapılmıştır. Tümörsüz hale gelen hastalarda takip ilk 5 yıl 6 ayda 1 ve sonrasında yılda 1 kez olarak planlanmıştır. Takiplerde hastaların %90,5'inde ipsilateral nüks (%31,7'si ortalama 26,3 ayda) gözlenmiştir. On altı hastada (%20) ortalama 23,2 ay takip sonrası RNÜ yapılmıştır. Beş yıllık izlemde genel sağkalım %75, kansere özgü sağkalım %84 olarak bildirilmiş ve rekürrens riski nedeniyle sıkı gözetim altında olmak şartıyla; >2 cm ÜÜST'lerin üreteroskopik tedavisi, RNÜ'ye alternatif organ fonksiyonlarını koruyan bir tedavi seçeneğidir; sonucuna ulaşılmıştır (45).

Antegrad perkütan teknik: Yöntem, teknik gelişmelerden dolayı; diversiyonlu hastalar, soliter böbrek veya anatomik engeller (darlık, yapışıklık) dışında terk edilmeye başlanmıştır. Antegrad yaklaşım tedavisi genelde 3 seanstir. Teknik olarak böbreğe giriş aşamaları perkütan taş cerrahisi ile aynıdır (üreter kateteri konulması, prone pozisyonu, işlem için en uygun açılı kaliksten giriş ve renaks konulması). Tümör kesilerek veya kopararak alınır. Taban, YAG lazer veya elektrokoterle koagüle edilir. Çoklu giriş gerekebilir. Peroperatif frozen incelemede invaziv yüksek grade tümör varlığında, nefroureterektomi yapılır (46). Aynı patolojiyle konservatif izlem sürecinin herhangi bir aşamasında karşılaşırsa, tedavi yine NÜ'dür (47). Peroperatif patolojide; düşük grade tümör varlığında işlem, nefrostomi kateter konularak sonlandırılır. Eğer rezidü tümör şüphesi var veya taban biyopsisi alınacak ise, aynı hafta içinde 2. seans yapılır (46). Bu aşamanın patolojisi invaziv ise yine NÜ yapılmalıdır. Eğer sonuçta tümörü yok veya düşük grade gelirse ve çekilen nefrostogramda ekstrasvazyon-obstrüksiyon yok ise intrarenal mitomisin-C veya BCG uygulanabilir (48). Intrarenal kemo-immünoterapiden 2-4 hafta sonra, 3. kez endoskopi yapıp biyopsi alınır. Nefrostomi çekilmesini takiben izlem başlar (46,48).

Perkütan tümör cerrahisi komplikasyonları tıpkı taş cerrahisi komplikasyonları gibi: ateş, kanama ve ek organ yaralanmalarıdır. Ek olarak girişim sırasında, ters akım ile sisteme irrigasyon sıvısı içinde tümör hücreleri yollamamak adına; irrigasyon basıncını 40 cm su değerinin altında tutmak gerekir. Ayrıca sitolitik özelliği nedeniyle distile su kullanımı önerilmektedir (49). Tüm bu tedbirlere rağmen üreter sistem perforasyonu ile dışarıya tümör yayılımı ve giriş hattında tümör gelişme riski de unutulmamalıdır (50).

Jarrett ve ark. (51) 30 hastanın 9 yıllık takibinde rekürrensi %33 olarak bildirmiştir. Tümörün derecesi nüks ve sağkalımda belirleyici olarak rapor edilmiştir (rekürrens G1'de %18, G3'de %50). Sonuçta rekürrens için çok odaklı, >=1,5 cm tümör ve displazi varlığı belirleyicidir tanımı yapılmıştır (52).

Perkütan yaklaşımla tedavi olan hastalarda rekürrens %13-65'tir. Mesane rekürrensi %15-42 ve genel sağkalım %92'lerde, kansere özgü sağkalım ise %75-100 arasında bildirilmektedir (53).

Endoskopik ve açık cerrahi yöntemlerin retrospektif değerlendirildiği çalışmalarda endoskopik tedavi hastalarının yaklaşık %20'sinin RNÜ'ye gittiği; iyi seçilmiş düşük derece hastalarda kansere özgü sağkalımın, endoskopik tedavilerde RNÜ ile benzer; ancak yüksek derece tümörlü hastalarda sağkalımın, RNÜ lehine olduğu bildirilmiştir (44). Doğru tümör derecesini belirlemede; endoskopik biyopsiler ve sonradan RNÜ'ye gitmiş hastaların, patoloji materyalleri değerlendirilmiştir. Endoskopik patoloji sonuçları %80 oranında RNÜ patoloji sonuçları ile örtüşmüştür. Endoskopide %25 hastada gözden kaçan lezyonların olabileceği ve bunların %50'sinde tespit edilemeyen CIS olduğu gösterilmiştir (54).

Lokalle ÜÜS tümörlerinde endoskopik tedavi ve RNÜ hastaları kıyaslandığında, genel ve kansere özgü sağkalım farksız olarak bulunmuştur. Ancak onkolojik sonuçların güvenilir bir şekilde kıyaslanabilmesi için, daha çok prospektif, randomize ve çok merkezli çalışmaya gerek olduğu vurgulanmıştır (55).

Adjuvan tedaviler: ÜÜS ürotelyal tümörlerinde; BCG, mitomisin-C, epirubisin, tiotepa veya BCG/interferon; gerek primer CIS tedavisinde (56), gerekse rezeksiyon ve ablasyon sonrasında kullanılmıştır (57,58,59).

Ancak hasta sayılarının yetersizliği nedeniyle yöntemin etkinliğini (mitomisin-C, BCG ve diğer ajanlar için dahil), kesin bir bilimsel temele dayandırmak mümkün olmamıştır (60,61). Buna rağmen; antegrad rezeksiyon sonrası en çok BCG, üreteroskopik rezeksiyon sonrası en çok mitomisin-C kullanılmaktadır (62). Üreteroskopik tedavi sonrası üreter kateteri ile (basınç <=20 cm suyu geçmeyecek şekilde) veya reflü varlığının ispatı halinde direkt mesane içine; 60 mg mitomisin-C, haftada 1, 6 hafta birer saatlik uygulamalar yapılmıştır (63,56).

Perkütan rezeksiyon sonrası genellikle 2. kontrol nefroskopiye takiben 1. hafta sonunda (ekstrasvazyon ve obstrüksiyon ekarte edildikten sonra) intravenöz antibiyotik profilaksisi eşliğinde 6 hafta; haftada 1 kez (360 mg BCG/150 mL serum fizyolojik, <=20 cm su basıncı ile 1 mL/dakika uygulama hızında; seans başı toplam 2,5 saat süreyle) önerilmektedir (64). Adjuvan uygulama yan etkisi hususunda özellikle BCG'nin sistemik sepsis riski dikkate değerdir. Uygulama öncesi mukozanın tam iyileşmiş olması (mitomisin-C için aynı kesinlik yoktur) ve düşük basınçlı uygulama çok önemlidir. Özellikle perkütan rezeksiyon sonrası; 2 hafta beklenmesi, septik tablo açısından yakın takip, rutin izoniiazid kullanımı gibi incelikler bildirilmiştir (62,65). ÜÜST'lerde adjuvan tedavilerle ilgili en son 2018 yılında Gregg ve ark. (66) tarafından toplam 13 karşılaştırmalı araştırmanın metanalizi yapılmıştır. Sonuçta kesin yararın tespiti noktasında, gelecekte bulunacak yeni tedavi ajanlarına ihtiyaç olduğuna ve daha fazla randomize klinik çalışmanın gerekliliğine vurgu yapılmıştır (66).

Sonuç

ÜÜS tümörlerinde tedavide altın standart; RNÜ ve kaf eksizyonudur. Mesaneden farklı olarak takiplerde endoskopik girişimler daha yüksek teknoloji ve tecrübe gerektirmektedir. Tümörün; lokal evresi, histolojik derecesi, mesanede olduğu gibi en önemli prognostik faktördür (67,68). Bu nedenle zorunlu olgular ve elektif durumlarda; küçük boyutlu, yüzeysel ve düşük dereceli tümörlerde, organ koruyucu tedaviler önerilmektedir (69). Konservatif olarak en çok kullanılan teknik, retrograd üreteroskopi'dir. Ancak olguların %25'inde teknik nedenlerden ötürü işlem yapılamamaktadır; bu durumlarda veya büyük çaplı intrarenal tümörlerde, antegrad perkütan yol kullanılabilir. Adjuvan tedavilerin, sağkalım rekürrens ve prognoz üzerine etkilerinin daha çok hasta ve daha uzun takip süresi ile yapılan çalışmalarla desteklenmesi gerekmektedir. Konservatif yaklaşımda; tümörün patolojisi, boyut ve lokalizasyon özellikleri kadar önemli diğer bir faktör de hastaların yakın takip uyumlarıdır. İzlem protokollerinde önerilen şemaya göre; hastalar ilk 3 yıl içinde, radyolojik ve laboratuvar incelemeleri dışında 6 ayda 1 kez üreteroskopi ile değerlendirilmeli; eğer mümkün olamayacağı düşünülüyorsa, NÜ ve kaf eksizyonu her zaman ilk seçenek olmalıdır.

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A Rare Case Mimicking Collecting System Tumor: Antopol-Goldman Lesion

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Abstract

Antopol-Goldman (AG) lesion is a benign condition characterized by flank pain, hematuria, and radiologically detected filling defect in the renal pelvis. It is clinically important because it is confused with renal parenchymal and collecting system tumors. In this case report, we present a 75-year-old male patient who was evaluated with the suspicion of renal pelvis tumor but was diagnosed with AG lesion and treated conservatively after excluding malignancy with radiology, endoscopy, and pathology. Our aim is to emphasize the importance of diagnostic flexible ureterorenoscopy before planning radical treatment in patients with hematuria, flank pain, and radiological signs of filling defect in the renal pelvis.

Keywords: Subepithelial pelvic hematoma, Antopol-Goldman lesion, collecting system tumor, hematuria

Introduction

Antopol-Goldman (AG) lesion, also called subepithelial pelvic hematoma, was first described by Antopol and Goldman in 1948. They published a report of 7 patients who underwent radical nephrectomy for a diagnosis of collecting system and/or renal tumor (1).

AG lesions are benign and diagnosed based on hematuria, flank pain, and radiologically detected filling defect in the renal pelvis. It regresses clinically and radiologically with a conservative therapeutic approach. The objective of this case report is to present a 75-year-old male patient who was evaluated with the suspicion of a right pelvis tumor but was diagnosed with AG lesion and managed with conservative treatment after excluding malignancy with radiology, endoscopy, and pathology.

Case Report

A 75-year-old male patient presented to the emergency department with complaints of painless gross hematuria with blood clots. His medical history was unremarkable except for a myeloproliferative disorder. He had no history of trauma, tobacco consumption, or use of anticoagulant or antiaggregant agents. His hemoglobin level was 8.09 g/dL, platelet count was 56,400, and renal function tests were high (creatinine: 3.22 mg/dL, urea: 79 mg/dL). In previous tests, his creatinine level was 2.62 mg/dL and it was considered chronic kidney disease. On ultrasound (US) examination, the right renal pelvis and calyces had a distinct appearance and a lesion

40x40 mm in size invading the lower calyx in particular was observed. Unenhanced computed tomography (CT) of the abdomen performed due to elevated creatinine level revealed a 40x45 mm space-occupying heterogeneous lesion in the right renal pelvis (Figure 1). The average Hounsfield unit value was 61.68. A collecting system tumor or hematoma related to the hemorrhage was not clearly distinguished. Although a right nephroureterectomy was initially planned, we decided to confirm the diagnosis with endoscopy because of the disrupted kidney function. Diagnostic cystoscopy and right diagnostic ureterorenoscopy were carried out. There was no tumoral structure in the bladder, but hematuric jet flow was observed from the right ureteral orifice. No space-occupying mass in the ureteral segments or renal pelvis was seen in ureterorenoscopy. There were hyperemic areas in the renal pelvis (Figure 2). A punch biopsy was taken from these areas. Histopathological results showed no malignancy, thus transitional cell carcinoma of the collecting system was excluded (Figure 3).

With a clinical diagnosis of AG lesion, we opted for a conservative treatment approach with analgesic agents and bed rest. During the follow-up period, his hematuria improved and abdominal CT at 3 months showed that the space-occupying lesion in the right renal pelvis had disappeared (Figure 4). Written informed consent was obtained from the patient.

Discussion

AG lesion is a rare benign disorder that is difficult to diagnose because it is easily mistaken for renal parenchymal and

collecting system tumors. Although it occurs in every age group regardless of gender, it is more common in the elderly. However, 1 neonatal case and a few cases in patients younger than 40 years old have also been reported (2,3).

Although several factors are believed to be involved in the etiology, it has not been fully elucidated. Factors such as the usage of analgesics and anticoagulants have been implicated (4). Besides these factors, trauma, underlying congenital malformations, diabetes, hypertension, drug addiction, and amyloidosis have been also reported as associated factors (5). Although none of these factors were present in our case, we suspect that the lesion may have been caused by thrombocytopenia associated with the patient's known myeloproliferative disorder.

Medical history and especially radiological examination are supportive of the diagnosis in patients with AG lesions, who present with hematuria. The most common symptoms of AG lesion are hematuria and flank pain (2,5). Unfortunately, diagnosing AG lesions with radiological methods alone is difficult. Therefore, patients are usually diagnosed based on histopathological examination of specimens obtained during

partial or radical nephrectomy. Although a heterogeneous space-occupying lesion may be detected in US, CT should be carried out in order to define the hemorrhagic component with its heterogeneous hyperdense appearance (4). In our case, a space-occupying lesion extending from the renal pelvis to the lower calyx was diagnosed with US and verified with unenhanced abdominal CT, which was preferred due to the presence of the renal failure.

Following the description of AG lesion in 1948, the increase in reported cases led urologists to implement medical treatments and follow-up instead of urgent surgery. Cardin et al. (4) first reported the successive treatment of patients with AG lesion using a conservative approach. They recommended a conservative follow-up approach in patients who had a history of coagulopathy and anticoagulant agent use, a negative ureterorenoscopic examination, and improvement in hematuria symptoms. In recent years, the diagnosis of renal pelvic lesions has been facilitated by increasing use of flexible ureterorenoscopy, and thus conservative approaches have gained momentum. Altay et al. (2) did not detect any tumoral structure in the urinary system with flexible ureterorenoscopy

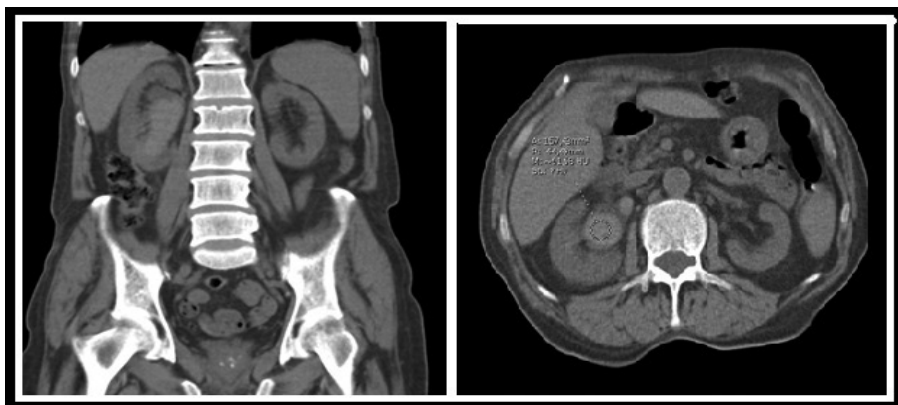


Figure 1. Hyperdense space-occupying lesion extending from the right renal pelvis to the lower calyx in the coronal and axial sections of the computed tomography

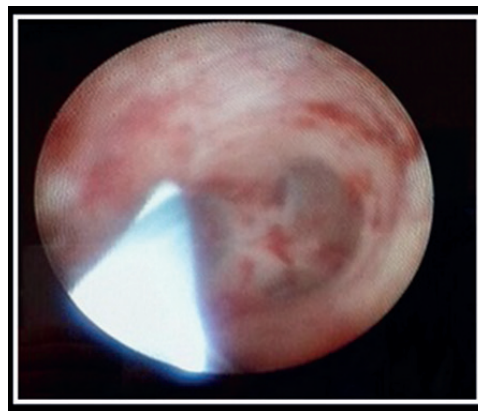


Figure 2. Hyperemia and hemorrhagic loci in the renal pelvis in right diagnostic ureterorenoscopy

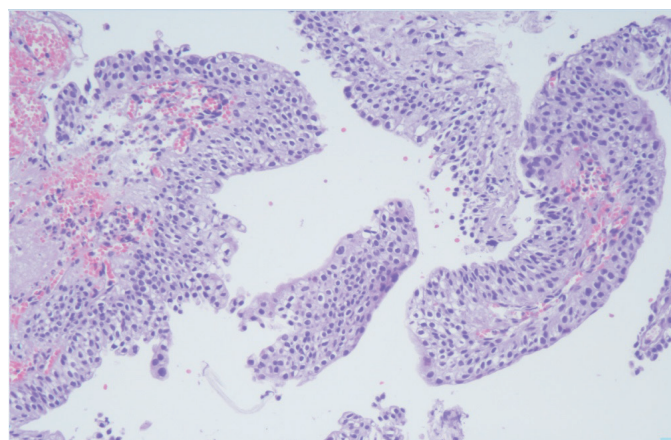


Figure 3. Papillary urothelial hyperplasia that looks like normal epithelium with hematoxylin and eosin stain in 200x magnification



Figure 4. Regression of the mass in follow-up computed tomography

in an 80-year-old patient who presented with gross hematuria. They diagnosed the patient with AG lesion and treated the patient with tranexamic acid and fibrinolytics for 4 weeks after insertion of a double J catheter. They reported that the lesion had disappeared in the follow-up imaging done at 3 months. Gayer et al. (6) diagnosed AG lesions in 7 patients with coagulopathy, and reported that the lesions improved with conservative follow-up. They emphasized the importance of informing the radiologist during the request for radiological imaging. In our case, after the radiologist's initial report in favor of hematoma, the flexible ureterorenoscopy was carried out and no space-occupying lesion was detected in the renal pelvis. The lesion regressed during follow-up.

In conclusion, AG lesion should be kept in mind in patients with radiological findings of filling defect in the renal pelvis, and if possible, diagnostic flexible ureterorenoscopy should be performed to avoid radical surgery and its complications.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.G.Ş., E.Ş., O.Ö., İ.Y., İ.E., E.G., V.T., Concept: K.G.Ş., E.Ş., O.Ö., İ.Y., Design: İ.Y., İ.E., E.G., V.T.,

Data Collection or Processing: E.Ş., O.Ö., İ.Y., İ.E., Analysis or Interpretation: K.G.Ş., E.Ş., O.Ö., V.T., Literature Search: K.G.Ş., İ.E., E.G., V.T., Writing: K.G.Ş., E.Ş., O.Ö., İ.Y., İ.E., E.G., V.T.

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Urethral Leiomyoma: A Case Report

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Abstract

Leiomyomas are benign smooth muscle uterine masses most frequently seen in females during the period when they can give birth. Extruterine leiomyomas are seen rare and where they are observed the most is the genitourinary tract. In general, patients come up with urinary and soft tissue mass near the urethral meatus related problems. Here we report a case of distal urethral leiomyoma in a 40-year old woman who was admitted with urethral obstructive symptoms and was operated for periurethral mass. Leiomyomas originating from the smooth muscle of the urethra, a rare location, are generally diagnosed following surgery. These leiomyomas should be treated with great care during surgery due to their unusual location. Patients who undergo surgery due to the presence of urethral stricture can also be seen after myomectomy.

Keywords: Leiomyoma, urethra, distal urethral leiomyoma, muscle uterine mass

Introduction

Bladder and urethral leiomyomas are rare entities (1). Buttner (2) was the first person to report the first incidence of urethral leiomyoma. They may show various clinical symptoms depending on their site and size, which, at the urethral level forming especially in the adjacency of vaginal wall, include recurrent urinary tract infections, voiding dysfunction, foreign body sensation, pain and dyspareunia (3). Here we report a case of urethral leiomyoma in a patient with recurrent urological complaints. The leiomyoma was successfully removed by surgical resection without damaging the urinary tract and no recurrence has been detected to date.

Case Report

A 40-year-old woman with a history of urological complaints presented in 2017 with a perineal mass that had increased in size for 2 years, dyspareunia, and persistent dysuria. Urinalysis was negative for leukocytes and no growth was detected in urine culture. On physical examination, we detected a tender polypoid round perineal mass approximately 4 cm in diameter below the labia minora on the right side. Distant from the vaginal opening, the 4x4 cm perineal mass extended in the anteroinferior direction from the urethral meatus. As the mass extended towards both the urethra and front of the vagina, it appeared to be excisable. Ultrasonography (USG) revealed that the uterus, bilateral ovaries, and bladder were normal.

The patient was informed about her condition and the benefits and potential risks of surgery. After obtaining written informed consent for the procedure, the patient underwent myomectomy under general anesthesia in sterile conditions.

Following the elevation of perineal mucosal flaps, local excision of the mass was performed with vaginal approach under spinal anesthesia. The mass was easily separated from the structures surrounding the anterior urethral wall using electrocautery. Vicryl 3/0 sutures were used to close up the mucosal tissues. Foley catheter was removed after 30 days and postoperative recovery was uneventful. The symptoms reported by the patient had fully resolved as of final follow-up at postoperative 1 year, no recurrence was observed, and the patient was asymptomatic. The mass had a macroscopic diameter of 2.5 cm, smooth surface, and was pink and hard (Figure 1). In the examination of the mass, it was non-encapsulated, firm, gray-white, and showed no hemorrhage, necrosis, or cystic degeneration. Hematoxylin-eosin staining under microscopy revealed cells that appeared to be smooth muscle fascicles, which may be indicative of leiomyomas (Figure 2). The myoma tumor cells were regular and no atypia or mitosis were observed. Immunohistochemistry showed positive staining for vimentin, actin, and desmin in the tumor cells (Figure 3). Section image of the sample of well-encapsulated, solid, homogeneous mass appearing with no bleeding, necrosis, or cystic changes showed a leiomyoma tumor with muscle fiber areas.

Discussion

The female urethra is 4-5 cm in length with a diameter of 5-6 mm. After extending down the anterior wall of the vagina, its external orifice is located about 2.5 cm behind the clitoris. The urethra is present in both sexes and its main function is urine excretion (4). Disorders of female urethral meatus are quite varied; in addition, the vulva and vagina are also affected by their own diseases. Histologically, the parts closer to the bladder comprise transitional multilayered non-keratinized and occasionally glandular epithelium. Malignant masses of the urethra are very rare and include transitional cell carcinoma, squamous cell carcinoma, adenocarcinoma. And among the benign urethral masses are polyps, papillomas, hemangiomas, fibroma, leiomyomas, fibromyomas and adenomas (5). While it is a fact that leiomyomas are seen rarely, polyps and papillomas are the most frequently seen benign tumors.

Leiomyomas which origin from smooth muscles are benign mesenchymal tumors (6,7,8). In women of birth age, they are the most frequently seen uterine masses. But, there have also been cases in which they have occurred in uncommon sites and displayed unusual growth patterns (9). The sites where extrauterine leiomyomas most frequently develop are vulva, ovaries, urethra, and bladder in the genitourinary tract or where less frequently develop is in the gastrointestinal system, but can occur in almost any tissue that contains smooth muscle. They mainly affect women between the ages of 30-50 years (7). There are debates about their degree of estrogen dependence, and diagnosis is made by histopathological examination of the relevant tissue (6). Urethral leiomyomas grow in a hormone-dependent manner like uterine leiomyomas, and may also express estrogen and progesterone receptors (10). In women of reproductive age, they are inclined to enlarge during pregnancy and regress in the postpartum period (11). Whereas the anterior wall of the vagina is the site where paraurethral leiomyomas develop, the anterior wall of the proximal urethra is where urethral leiomyomas most frequently do (12).

Patients with urethral leiomyomas are usually asymptomatic, but sometimes an enlarged mass on the anterior vaginal wall obstructs the urethral meatus and causes obstructive symptoms. Common symptoms include dysuria, weak urine flow, mass, dyspareunia, post-voiding drip, frequent bowel movements,

and irritative lower urinary system symptoms. Occasionally, patients present with recurrent urinary tract infections (13,14). It should be kept in mind that acute urinary retention may develop in complete stenosis. Malignant degeneration and metastasis have not yet been reported (15). In case urethral strictures develop, urethral and paraurethral lesions need to be removed with caution in order to avoid postoperative incontinence much as vulvar lesions have not been linked with important postoperative complications so far. Leiomyoma should be included in diagnostic evaluations in patients with urethral stricture. It should be considered in the differential diagnosis of intraurethral neoplasms. As the surgical approach may differ accordingly it is also important to distinguish whether they are urethral or periurethral masses.

In majority of the cases in the literature, urethral leiomyomas have been defined as intraluminal masses which stem from the proximal urethra and extending outward from the meatus to the posterior (16). In our case, the leiomyoma was overwhelmingly a perineal mass which extended downward from the distal urethra, and resulted from the anterior urethral wall. A mass originating from the anterior wall of the vagina may cause dysuria by occluding the urethral meatus. In our case, the leiomyoma did not invade the urethra, but caused intense dysuria. These complaints disappeared after surgical treatment. The kidneys and bladder are the urinary system organs most commonly affected by leiomyomas, while the urethra is a rare location for such tumors (14,15). The etiopathogenesis of leiomyoma is unknown; however it is thought to be hormone-dependent to a certain degree. This theory is supported by evidence of tumor growth during pregnancy described by some authors and the presence of smooth muscle hyperplasia, which is stimulated by high estrogen levels. On the other hand, other authors reject the hormonal origin of urethral leiomyomas, citing the fact that some cases occur in post-menopausal women or that existing tumors are non-invasive (8). The patient in our case was a fertile woman, which may support the hormonal origin of smooth muscle hyperplasia in the development of leiomyomas.

In terms of macroscopic appearance, the tumor is usually a hard, round, smooth, pink lesion. Although its diameter ranges from 1 cm to 3-4 cm, a case with a diameter of 40 cm has been reported (6). The clinical symptoms that occur during this

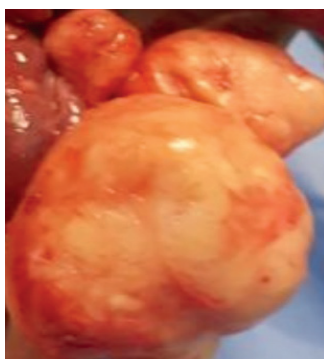


Figure 1. Macroscopic appearance following surgical removal

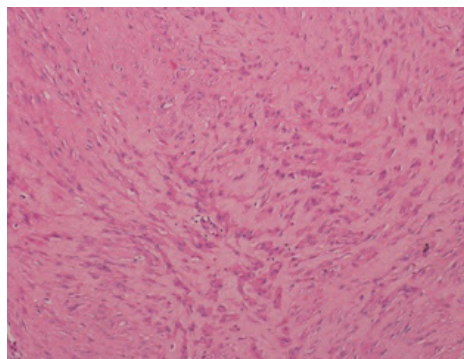


Figure 2. Microscopic appearance with hematoxylin and eosin staining

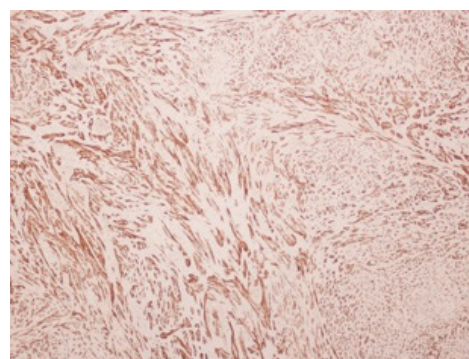


Figure 3. Microscopic appearance with desmin staining

process depend on the site and size of the tumor. In the clinical diagnosis of this disease, a complete physical examination of the vulva and thorough history taking are quite important. While a preliminary diagnosis can be made visually by external USG and magnetic resonance imaging, conclusive diagnosis is reached after the histopathological confirmation (6). Leiomyomas have a characteristic myomic appearance in USG (16).

The treatment of urethral leiomyoma is always surgical, and the modality used depends on the level of urethral tumor. The prognosis for this type of tumor is excellent without malignant transformation (3,8). The surgical approach depends on tumor size and location. Lower urinary tract symptoms regress following the complete removal of the urethral leiomyoma. The presence of a tumor on the anterior wall of the vagina damages the urethral mucosa, which results in dysuria and urethral hemorrhage. Following its surgical removal, the prognosis is excellent, generally with no malignant transformation. Our patient also had no complaints during the first postoperative year.

Physical examination of patients who present with dysuria, dyspareunia, and perineal mass should not be ignored, and benign masses such as leiomyoma should be kept in mind in the differential diagnosis. During surgical excision, care should be taken not to damage the urethra, and an indwelling urinary catheter should be left in place for an extended time to prevent complications such as stenosis or fistula.

Ethics

Informed Consent: It was obtained.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A., M.G., M.S., Concept: M.A., S.Ü., Design: S.Ü., M.A., Data Collection or Processing: M.A., M.G., M.S., Analysis or Interpretation: M.A., M.G., M.S., Literature Search: M.A., M.G., M.S., S.Ü., Writing: M.A., M.G., M.S., S.Ü.

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