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

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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.

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2) Abstract and keywords (Turkish and English),

3) Main text,

4) Acknowledgements (optional),

5) References,

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- Title

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- Results
- Discussion
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- Conclusion
- Acknowledgements
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Preparation of research articles, systematic reviews, and meta-analyses must comply with study design guidelines: CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consortstatement.org/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

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Introduction

Main Text

Conclusions

Tables/Figures

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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.

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Any grants or financial support received for the paper

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

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

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

Example:

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

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

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Contents

Original Article

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Reflection of Adjuvant Treatment Approaches for Early Stage Testis Tumors in Our Clinic

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Abstract

Objective: Treatment modalities applied after orchiectomy in early-stage germ cell tumors (GCTs) include significant changes in each new study. In this study we reevaluated the treatment approaches used in our hospital between 2010-2014 according to current guidelines.

Materials and Methods: We retrospectively evaluated the oncologic treatments and follow-up data of 32 patients who underwent radical orchiectomy between January 2010 and December 2014 due to testicular tumor and were diagnosed with early stage GCT in the Urology Clinic of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital of University of Health Sciences.

Results: Of 19 patients diagnosed with stage 1 seminomas, 3 patients in the low risk group were followed. Of 4 patients who received single-dose carboplatin therapy, 2 were at low risk and 2 were at high risk. Therefore, 2 patients at low-risk had overtreatment. Twelve patients were treated with radiotherapy (RT) that was no longer recommended in guidelines after 2014. Two patients in the low risk group of stage 1 non-seminoma were followed. One of them had recurrence at 12 months, and received 3 cycles of bleomycin + etoposide + cisplatin (BEP) according to current guidelines. Four patients with stage 1 non-seminoma underwent 2 cycles of BEP because they were considered at high risk. These patients are now recommended to receive 1 cycle BEP according to the current guidelines. While 4 patients with stage 1 mixed GCT were followed because of low risk, one patient was administered 2 cycle of BEP based on the old guidelines, at that time because of high risk. In the seminoma group that was administered RT, acute myeloblastic leukemia and oligospermia toxicity were detected, but these were not observed in the carboplatin group. One of high-risk non-seminoma patients who received 2 doses of BEP developed Myelodysplastic syndrome.

Conclusion: Early-stage GCTs have high cancer-specific and overall survival rates with appropriate treatment approaches. Although there are still controversial issues regarding their management, treatment approaches are changing with each study. Therefore, it is crucial to remain informed about current international guidelines and new scientific studies.

Keywords: Adjuvant treatments, early stage, current guidelines, radical orchiectomy, testicular tumor

Introduction

Testicular cancer accounts for 1-1.5% of all cancers in men and 5% of male urological malignancies. It is usually seen between the ages of 15 and 35. In the USA, it is the most common malignancy among men aged 20-40 years and the second most common malignancy after leukemia among adolescents aged 15-19 years. The prevalence of bilateral germ cell tumor (GCT) is 2.5%, with 0.6% of these being synchronous tumors and 1.9% being metachronous contralateral tumors (1).

The vast majority (90-95%) of testicular tumors are GCTs. The most common histological type of GCT is seminoma (55%), which peaks between the ages of 30-40 years. Non-seminomas account for 40% and peak between the ages of 20-30 years (2). Stage 1 seminomas comprise the majority (80-85%) of GCTs diagnosed in daily practice (3,4). The 10-year overall

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survival (OS) rates for stage 1, which is considered early stage, are over 95%.

The primary treatment is inguinal orchiectomy, and postoperative treatment methods vary depending on the tumor's stage and histopathological type. Postoperative treatment options include long-term active surveillance, radiotherapy (RT), and chemotherapy (CT) for stage 1 seminomas and CT, retroperitoneal lymph node dissection (RPLND), and active surveillance for stage 1 non-seminomas; however, the strength of these recommendations has changed continuously (1).

In this study, we aimed to present the treatment approaches used in our clinic after radical orchiectomy for seminomas and non-seminomas in patients with early testicular cancer and to discuss these in light of the updated 2017 guidelines of the European Association of Urology (EAU).

Materials and Methods

We retrospectively reviewed the pathology and radiological imaging results of 77 patients who underwent radical orchiectomy due to testicular tumor in the Urology Clinic of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital of University of Health Sciences between January 2010 and December 2014. Because the study was a retrospective data analysis, ethics committee approval was not sought. The patients were given information about the study and informed postoperatively that their oncological data such as the recurrence, and overall survival would be evaluated without using their names. Of the 77 patients screened, we included the oncological treatment and follow-up data of 32 patients who had early testicular tumors (stage 1) according to clinical staging. The stage 1 patients were evaluated in terms of age at diagnosis, tumor histopathology, postoperative follow-up, RT and CT received, occurrence of relapse during follow-up, treatment received for relapse, mean follow-up period, disease-free survival (DFS), and OS. We aimed to evaluate changes in adjuvant therapy approaches by comparing the treatments administered to each patient during the study period to the adjuvant therapy currently recommended according to the risk-based treatment options in the current EAU guidelines.

Results

GCTs were detected in 69 of the 77 patients who underwent inguinal orchiectomy for a diagnosis of testicular tumor. Of these patients, 32 were stage 1, 4 were stage IS, 9 were stage 2, and 24 were stage 3. The 32 patients who had stage 1 testicular cancer were included in the study.

The mean age of these patients was 32.6±10.61 (8-60) years. Nineteen patients (54.9%) had pure seminoma (17 classical, 1 anaplastic, 1 spermatocytic), 7 patients (21.8%) had non-seminoma tumors, and 6 patients (18.8%) had mixed GCTs. Two patients (6.25%) had bilateral synchronous stage 1 seminomas. Tumors were located on the left side in 10 patients (31.2%), on the right side in 20 patients (62.5%), and bilaterally in 2 patients (6.25%). The distribution of the patients based on their histopathological features is presented in Table 1. Mean tumor size was 4.48±2.04 (1.2-9) cm. Intratubular germ cell neoplasia was detected in 17 patients (40.47%).

Nine patients (28.12%), including 3 with seminoma, 2 with non-seminoma, and 4 with mixed GCTs were scheduled for follow-up. Of these 9 patients, 1 patient with a seminoma and 1 patient with a mixed GCT did not attend follow-up regularly. Recurrence was detected at 12 months in 1 patient with non-seminoma. This patient underwent CT with 3 cycles of bleomycin + etoposide + cisplatin (BEP) protocol and exhibited

Table 1. Distribution of stage 1 germ cell tumor patients according to histopathology, adjuvant treatment, disease-free survival, and overall survival

	Seminoma	Non-seminoma	Mixed	Total
Patient number, n	19	7	6	32
Follow-up, n Recurrence (+) Recurrence (-) No follow-up	3 - 2 1	2 1 1 -	4 - 3 1	9 1 6 2
RT, n Recurrence (+) Recurrence (-) No follow-up	12 - 11 1	- - - -	- - - -	12 - 11 1
Single-dose carboplatin, n Recurrence (+) Recurrence (-) No follow-up	4 1 3 -	- - - -	- - - -	4 1 3 -
BEP, n Recurrence (+) Recurrence (-) No follow-up	- - - -	4 - 4 -	1 - - 1	5 - 4 1
Refused treatment, n	-	1	1	2
DFS, (months)-mean	64.94±6.45	26.27±6.14	36±6.14	48.29±9.74
OS, (months)-mean	68.11±8.01	31.36±5.24	38±7.12	48.73±10.07

DFS: Disease-free survival, OS: Overall survival, BEP: Bleomycin + etoposide + cisplatin, RT: Radiotherapy

no recurrence in the following 12-month follow-up period. The mean follow-up period of the other 6 patients who were followed was 40±10.7 (32-64) months and no recurrence was observed.

Twelve patients with seminoma (37.5%) were treated with RT. Although 1 of these patients was lost to follow-up after RT, the other 11 exhibited no recurrence during the mean follow-up period of 64±11.8 (28-76) months. Five of the 12 patients underwent RT of 20 Gy in 10 fractions to the lymph nodes in the paraaortic region and ipsilateral pelvis (hockey stick field), while the other 7 patients were treated with RT of 20 Gy applied unilaterally to the paraaortic region. Of the 11 patients followed after RT, 1 patient developed acute myeloblastic leukemia (AML) thought to be secondary to RT at 57 months. Oligospermia developed postoperatively in 2 patients and showed no improvement even at 70 months after RT.

As adjuvant CT, 4 patients (12.5%) received a single dose of carboplatin because they had stage 1 seminomas, whereas 5 patients (15.6%) with non-seminomas and mixed GCTs received BEP. One of the patients who received a single dose of carboplatin had bilateral seminomas, developed recurrence at 23 months, and subsequently underwent 4 cycles of BEP. One of the 5 BEP-treated patients was not followed after CT, but no recurrence was observed in the other 4 patients during a mean follow-up period of 52±23.12 (18-76) months. Only 1 patient (25%) developed Myelodysplastic syndrome (MDS) at 72 months.

With the exception of the patient who developed AML and 2 patients with persistent oligospermia, no acute or late severe (grade >2) toxicity was observed in any of the patients in the other groups. Mean DFS of the patients was 48.29±9.74 (21-60) months and OS was 48.73±10.07 (24-64) months (Table 1).

Table 2 shows the comparison of the adjuvant therapies provided to these patients at our clinic between January 2010 and December 2014, as determined in our retrospective analysis, and the adjuvant therapies recommended in the EAU 2017 updated guidelines.

Discussion

Seminomas have an occult metastasis rate of 10-15% and systemic recurrence rate of 1-4% after retroperitoneal therapy (5). Poor prognostic factors for relapse in seminoma are a primary tumor size larger than 4 cm and the presence of rete testis invasion.

Twenty years ago, RT administered as a dog-leg field to the retroperitoneal and ipsilateral pelvic lymph nodes as adjuvant therapy for stage 1 seminomas had a success rate of 95% (6), with post-RT relapse rate <5-10%. Disease-specific survival reached 100% with BEP administered at relapse (7). In later years, evidence showing that single-dose carboplatin provided similar oncological outcomes with fewer side effects led to RT losing favor as a first-line treatment (8).

Since 2014, the EAU guidelines have no longer recommended adjuvant RT for stage 1 seminomas due to the long-term risks of RT in terms of cardiovascular toxicity (9.6% of patients within 5-8 years), gonadal toxicity (8% permanent oligospermia), and secondary malignant neoplasm (18% risk in 25 years, most commonly leukemia) (9).

In the present study, treatment planned before 2014 for the 12 seminoma patients included RT of 20 Gy delivered in 10 fractions in a hockey-stick field to the paraaortic and ipsilateral pelvic lymph nodes in 5 patients, and 20 Gy RT applied unilaterally to the paraaortic area in 7 patients. If treatment were planned for these 12 patients today, none would undergo RT (Table 2).

Single-dose carboplatin began to appear in guidelines as an A-level recommendation in 2010 because it provided the same oncological efficacy as RT with fewer side effects (10). As of 2014, the EAU guidelines prioritized active surveillance for stage 1 seminoma and recommended single-dose carboplatin in the presence of risk factors (9). According to Ondrusova et al. (11), recurrence is detected in the retroperitoneum after adjuvant single-dose carboplatin in 9.1% of patients, but that a cure can be achieved in these cases with 3 doses of BEP. Chau et al.

Table 2. Comparison of the adjuvant therapies provided to the study patients and the adjuvant therapies recommended in the European Association of Urology 2017 updated guidelines

Stage 1 GCT groups	Adjuvant treatment given	Adjuvant treatment recommended in EAU 2017 guideline
Low-risk seminoma	Unilateral RT to the paraaortic area (n=6) Single-dose carboplatin (n=2) Follow-up (n=3)	Follow-up (n=6) Follow-up (n=2) Follow-up (n=3)
High-risk seminoma	Unilateral RT to the paraaortic area (n=1) RT in hockey-stick field (unilateral paraaortic area + ipsilateral pelvic bone) (n=5) Single-dose carboplatin (n=2)	Single-dose carboplatin (n=1) Single-dose carboplatin (n=5) Single-dose carboplatin (n=2)
Low-risk non-seminoma	Follow-up (n=2)	Follow-up (n=2)
Recurrence of low-risk non-seminoma during follow-up	3 cycles of BEP (n=1)	3 cycles of BEP (n=1)
High-risk non-seminoma	2 cycles of BEP (n=4)	1 cycle of BEP (n=4)
Low-risk mixed GCT	Follow-up (n=4)	Follow-up (n=4)
High-risk mixed GCT	2 cycles of BEP (n=1)	1 cycle of BEP (n=1)

GCT: Germ cell tumor, RT: Radiotherapy, BEP: Bleomycin + etoposide + cisplatin, EAU: European Association of Urology

(12) claimed that the timing of CT does not affect oncological outcomes, but in practice they recommend initiating CT within the first 60 days after orchiectomy.

In our study, single-dose carboplatin was administered to 4 patients with stage 1 seminomas. Two of these patients were low-risk, and active surveillance would have been more appropriate as an initial management strategy according to current guidelines (Table 2).

The growing trend toward active surveillance stems from the fact that patients under active surveillance have a relapse rate of 15-20% and these cases can be treated effectively with RT or CT. The average time to relapse during active surveillance is 12-18 months, though 29% of relapses occur after longer intervals (13). In light of these data, active surveillance was included as a level B recommendation in guidelines starting in 2010 (10). Since 2014, the EAU guidelines endorse active surveillance as a level A recommendation for stage 1 seminoma (9). The effect of these risk factors (rete testis invasion and tumor size) on oncological outcomes is still debated (14,15,16,17).

In our study, only 3 of the 19 stage 1 seminoma cases was followed with active surveillance. However, based on current knowledge, this approach could have been applied with 8 other low-risk patients. It can be concluded that single-dose carboplatin in 2 and RT in 6 of those 8 patients was unnecessary (Table 2).

In the literature, secondary malignancies (predominantly leukemia, as well as renal, lung, and pancreatic cancers and neurofibrosarcoma) are reported at a rate of 5-8% in patients with stage 1 seminomas who have undergone RT (18). Similarly, in our study, AML was observed in 1 patient (9%) after RT, while no secondary malignancy was observed in the carboplatin or active surveillance groups. While it is reported that fertility rates improve 5 years after adjuvant RT and that 8% of patients have permanent oligospermia, we found that 2 patients (18%) in our study experienced persistent oligospermia even after 70 months as late toxicity. This toxicity was not observed in the carboplatin and active surveillance groups.

While one-third of non-seminomas are diagnosed at stage 1, more than 30% of these have occult metastasis at time of diagnosis and 30% will recur without additional treatment. The most important prognostic indicator for occult metastasis in this group is the presence of lymphovascular invasion (LVI). Approximately 33% of all patients with stage 1 non-seminomas have LVI (19). Other important prognostic risk factors are a proliferation rate >70% and percentage of embryonal carcinoma >50%. In the presence of LVI, relapse occurred in 14-22% and metastasis developed in 48% of patients who did not receive postoperative adjuvant therapy (20).

The 20-year long-term relapse rate of patients under active surveillance is 27-30% (21). Eighty percent of these relapses occur within the first 12 months, 12% occur in the second year, 6% occur in the third year, and the rate falls to 1% in the 4th and 5th years (21). In this group, 5 years of close follow-up is imperative as routine practice (22). Computed tomography done at 3 and 12 months is very valuable. It has been determined that computed tomography using a low-dose protocol, which reduces the risk of secondary malignancy due to radiation exposure through frequent computed tomography scans, reduces the risk of radiation by 55% (23).

In our study, 2 low-risk patients from the 7 patients with stage 1 non-seminomas were managed with active surveillance. Only 1 patient had relapse at 12 months and received 3 cycles of BEP. Although this treatment approach was implemented before 2014, it still complies with current guidelines (Table 2).

Two-dose BEP CT has been recommended for many years to reduce the risk of relapse in the presence of LVI. In a Swedish and Norwegian Testicular Cancer Group (SWENOTECA) study carried out in 2009, it was shown that single-dose BEP therapy in the presence of LVI reduced relapse to 2.3% over 8.1 years of follow-up and caused fewer side effects (14), and BEP was subsequently included as a level A recommendation in EAU guidelines as of 2014. Three or 4 doses of BEP is recommended for relapses occurring after single-dose BEP (24).

These patients may experience pulmonary toxicity (pneumonitis, pulmonary fibrosis, etc.) due to bleomycin, which can be fatal in 1-3% of patients (25). There may be a 3.1-fold higher risk of cardiovascular disease (myocardial infarction, coronary artery disease, etc.) compared to the normal population after BEP administration (26). Although Chamie et al. (27) reported higher risk of secondary solid malignancy due to CT some studies report a 0.5-1% risk of hematological malignancy as a result of high-dose etoposide (28). The adverse effect of cisplatin-based CT on fertility and sexual function is not yet known (29).

In our study, 4 patients with stage 1 non-seminomas were treated with 2 doses of BEP because they were considered high risk. These patients were treated before the latest changes in the guidelines. Had they been diagnosed today, they would be candidates for a single-dose BEP protocol (Table 2). In only 1 of these 4 patients (25%), MDS appeared as a secondary hematologic malignancy at 72 months. This rate seems to be high due to the low number of patients and short follow-up times, and since there was no group in our study that received single-dose BEP, we were unable to compare the relative effect of receiving 1 and 2 doses of BEP.

In a 2008 study by the German Testicular Cancer Study Group, the 2-year DFS rate was 99.41% in the group that received single-dose BEP and 92.37% in the RPLND group (30). Therefore, although RPLND is the most common treatment for stage 1 non-seminoma in the USA, is recommended as first-line treatment for high-risk patients in current EAU guidelines, and it is less effective than CT with single-dose BEP. Similar to the EAU guidelines, none of the 7 patients with stage 1 seminomas underwent RPLND in our study (Table 2).

Due to their non-seminoma component, mixed GCTs are also treated like non-seminomas. Four of the 6 patients with stage 1 mixed GCTs in our study were followed because they were considered low-risk, while 1 high-risk patient received 2 cycles of BEP based on previous guidelines (Table 2).

The other patient refused treatment and was not followed (Table 1). For non-seminomas and GCTs with vascular invasion (VI), single-dose BEP is the first-line treatment, and follow-up or RPLND are alternative options. In the absence of VI, follow-up is preferred, and single-dose BEP or RPLND are recommended as alternative options.

In the field of urooncology, new research can lead to drastic and frequent changes, especially in post-orchiectomy treatment approaches for stage 1 testicular tumors. This is clearly demonstrated by the fact that most treatment approaches implemented correctly with the patients in our study according to the guidelines of seven years ago are now obsolete. Our results support the prevailing view that carboplatin for stage 1 seminomas is safer than RT in terms of late cardiovascular toxicity, gonadal toxicity, and secondary malignant neoplasm; however, the results of long-term follow-up are needed to confirm this.

Study Limitations

The limitations of study include short follow-up periods, a small patient population, and the retrospective design of the study. The new treatment schemes presented in the EAU guidelines after 2014 indicate similar cancer survival rates with fewer side effects. However, prospective studies involving larger numbers of patients followed for longer periods will provide a more realistic view of the effects of the existing guidelines on toxicity and patient survival.

Conclusion

With current treatment approaches, testicular tumors detected in the early stage have a high likelihood of being cured and show low relapse rates. Although postoperative follow-up and adjuvant therapy options vary depending on the tumors' histopathology and risk factors, OS rates are quite high. Due to these excellent survival rates and the possible side effects of adjuvant therapy, less toxic treatment options are also preferred in the current EAU guidelines, and treatment protocols can change nearly every year. Therefore, it is essential in clinical practice that every center that deals with testicular tumors stays informed about emerging studies and guidelines.

Ethics

Ethics Committee Approval: Ethics committee approval was not sought for this retrospective study.

Informed Consent: The patients were given information about the study and informed postoperatively that their oncological data such as the recurrence, and overall survival would be evaluated without using their names.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Orijinal Makale / *Original Article*

Bulletin of Urooncology 2018;17:39-44'te yayımlanan İngilizce makalenin birebir Türkçe versiyonudur.

Erken Evre Testis Tümöründe Adjuvan Tedavi Yaklaşımlarının Kliniğimizdeki Yansıması

Reflection of Adjuvant Treatment Approaches for Early Stage Testis Tumors in Our Clinic

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Öz

Amaç: Erken evre germ hücreli tümörlerde (GHT) orşiektomi sonrası uygulanabilecek tedavi yaklaşımları her yeni çalışmada önemli değişiklikler içermektedir. Biz de hastanemizde 2010-2014 yılları arasında uygulanmış olan tedavi yaklaşımlarını güncel kılavuzlar eşliğinde yeniden değerlendirip sunmayı planladık.

Gereç ve Yöntem: Ocak 2010-Aralık 2014 yılları arasında Sağlık Bilimleri Üniversitesi Dr. Abdurrahman Yurtaslan Ankara Onkoloji Eğitim ve Araştırma Hastanesi Üroloji Kliniği'nde testis tümörü nedeniyle radikal orşiektomi yapılan hastalardan erken evre (evre 1) GHT saptanan 32 hastanın onkolojik tedavi ve takip verilerini retrospektif olarak değerlendirdik.

Bulgular: Evre 1 seminom saptanan 19 hastadan düşük risk grubundaki 3 hasta A düzeyinde önerilen izlem protokolüne alındı. Tek doz karboplatin tedavisi uygulanan 4 hastanın ikisi düşük risk, ikisi yüksek risk grubundaydı. Bu nedenle düşük riskli iki hastaya fazla tedavi uygulanmış oldu. 2014'ten bu yana artık kılavuzlarda yeri olmayan radyoterapi (RT) ise 12 hastaya uygulandı. Evre 1 nonseminom saptanan düşük risk grubundaki 2 hasta izlem protokolüne alındı, hastaların birinde 12. ayda nüks gelişti ve güncel kılavuzlara uygun olarak 3 kür bleomisin + etoposid + sisplatin (BEP) protokolü uygulandı. Evre 1 nonseminom 4 hastaya ise yüksek risk grubunda olduğu için iki kür BEP uygulandı. Bu 4 hasta güncel kılavuza göre tek kür BEP protokolüne adaydır. Evre 1 miks GHT tanısı olan 4 hasta düşük risk grubunda olduğu için izleme alınırken, birine yüksek risk grubunda olduğu için o dönemki eski kılavuz bilgilerine dayanılarak 2 kür BEP uygulandı. RT alan seminom hastalarının birinde 57. ayda akut miyeloblastik lösemi, ikisinde 70. ayda düzelmeyen oligospermi toksisite olarak saptanırken; karboplatin grubunda bu durum izlenmedi. İki doz BEP alan yüksek riskli nonseminom hastalarının birinde 72. ayda Miyelodisplastik sendrom gelişirken; yeni kılavuzlarda bu grup için önerilen tek doz BEP uygulanmış hastamız olmadığından, BEP dozlarının geç dönem toksisiteye etkisi açısından bir karşılaştırma yapılamadı.

Sonuç: Erken evre GHT'ler uygun tedavi yaklaşımları ile yüksek kansere özgü sağkalım ve %100'ü bulan genel sağkalım oranlarına sahiptir. Tedavide halen tartışmalı konular yer alsa da, her yeni çalışma ile tedavi yaklaşımı farklı bir boyutta şekillenmektedir. Uluslararası güncel kılavuzların ve yeni bilimsel çalışmaların takibi bu anlamda oldukça önemlidir.

Anahtar Kelimeler: Adjuvan tedaviler, erken evre, güncel kılavuzlar, radikal orşiektomi, testis tümörü

Abstract

Objective: Treatment modalities applied after orchiectomy in early-stage germ cell tumors (GCTs) include significant changes in each new study. In this study we reevaluated the treatment approaches used in our hospital between 2010-2014 according to current guidelines.

Materials and Methods: We retrospectively evaluated the oncologic treatments and follow-up data of 32 patients who underwent radical orchiectomy between January 2010 and December 2014 due to testicular tumor and were diagnosed with early stage GCT in the Urology Clinic of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital of University of Health Sciences.

Results: Of 19 patients diagnosed with stage 1 seminomas, 3 patients in the low risk group were followed. Of 4 patients who received single-dose carboplatin therapy, 2 were at low risk and 2 were at high risk. Therefore, 2 patients at low-risk had overtreatment. Twelve patients were treated with radiotherapy (RT) that was no longer recommended in guidelines after 2014. Two patients in the low risk group of stage 1 non-seminoma were followed. One of them had recurrence at 12 months, and received 3 cycles of bleomycin + etoposide + cisplatin (BEP) according to current guidelines. Four patients with stage 1 non-seminoma underwent 2 cycles of BEP because they were considered at high risk. These patients are now recommended to receive 1 cycle BEP according to the current guidelines. While 4 patients with stage 1 mixed GCT were followed because of low risk, one patient was administered 2 cycle of BEP based on the old guidelines, at that time because of high risk. In the seminoma group that was administered RT, acute myeloblastic leukemia and oligospermia toxicity were detected, but these were not observed in carboplatin group. One of high-risk non-seminoma patients who received 2 doses of BEP developed Myelodysplastic syndrome.

Conclusion: Early-stage GCTs have high cancer-specific and overall survival rates with appropriate treatment approaches. Although there are still controversial issues regarding their management, treatment approaches are changing with each study. Therefore, it is crucial to remain informed about current international guidelines and new scientific studies.

Keywords: Adjuvant treatments, early stage, current guidelines, radical orchiectomy, testicular tumor

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Giriş

Testis kanseri, erkeklerde görülen tüm kanserlerin %1-1,5'ini, erkek ürolojik malignitelerinin ise %5'ini oluşturmaktadır. Sıklıkla 15-35 yaş arasında görülmektedir. ABD'de 20-40 yaş arası erkeklerde en yaygın rastlanan malignite, 15-19 yaş arası adolesanlarda ise lösemiden sonra görülen ikinci en yaygın malignitedir. Bilateral germ hücreli tümörlerde (GHT) görülme oranı %2,5 olup; bunun %0,6'sı senkron, %1,9'u ise metakron kontrlateral tümör şeklindedir (1).

Testis tümörlerinin %90-95'ini GHT oluşturmaktadır. GHT'lerin en sık görülen histolojik tipi seminom (%55) olup, 30-40 yaş arasında pik yaparlar. Nonseminomların ise görülme oranı %40 olup, 20-30 yaş arasında pik yaparlar (2). GHT'lerin günlük pratikte, tanı anında en sık görülen grubu (%80-85) evre 1 seminomdur (3,4). Erken evre olarak kabul edilen evre 1'de 10 yıllık genel sağkalım (GSK) oranları %95 üzerindedir.

Primer tedavi inguinal orşiektomi olup tümörün evresine ve histopatolojik özelliğine göre postoperatif dönemde seçilecek tedavi yöntemleri değişmektedir. Evre 1 seminomda postop dönemde uzun yıllar boyunca aktif izlem, radyoterapi (RT) ve kemoterapi (KT); evre 1 nonseminomda ise KT, retroperitoneal lenf nodu diseksiyonu (RPLND) ve aktif izlem uygulanan tedavi seçenekleri olarak yer almakla beraber, öneri dereceleri sürekli değişim göstermiştir (1).

Bu çalışmamızda kliniğimizdeki erken evre testis kanserleri olgularında, seminom ve nonseminom tiplerinde radikal orşiektomi sonrasında izlenmiş olan tedavi yaklaşımlarını sunmayı ve Avrupa Üroloji Derneği (EAU) 2017 güncel kılavuzları eşliğinde yorumlamayı planladık.

Gereç ve Yöntem

Ocak 2010-Aralık 2014 yılları arasında Sağlık Bilimleri Üniversitesi Dr. Abdurrahman Yurtaslan Ankara Onkoloji Eğitim ve Araştırma Hastanesi Üroloji Kliniği'nde testis tümörü nedeniyle radikal orşiektomi yapılan 77 hastanın patoloji ve radyolojik görüntüleme sonuçlarını retrospektif olarak araştırdık. Çalışmaya dahil edilen tüm hastalardan operasyon için bilgilendirilmiş onam sağlanmıştır. Çalışma retrospektif olduğundan, etik kurul onayı alınmamakla beraber, Helsinki Bildirgesi'ne uygun olarak tasarlanmıştır. Mevcut hastalar içerisinde klinik evrelemeye göre erken evre testis tümörü (evre 1) olan 32 hastanın onkolojik tedavi ve takip verilerini çalışmamıza dahil ettik. Evre 1 hastalarda tanı yaşı, tümör çapı, tümör histopatolojisi, postoperatif dönemde izlem, RT ve KT seçeneklerinden hangilerinin uygulandığını; takip süresinde nüks gelişip gelişmediğini, nüks geliştiğinde tedavi planı olarak ne yapıldığını; ortalama takip süresi, hastalıksız sağkalım (HSK) ve GSK sürelerini vererek inceledik. Güncel EAU kılavuzlarına göre riske dayalı tedavi seçenekleri içerisinde şu anda verilmesi önerilen adjuvan tedavi seçeneklerini, her hasta için tedavi verildiği dönemle kıyaslayarak; adjuvan tedavi yönetiminde ne gibi değişiklikler olduğunu karşılaştırmayı amaçladık.

Bulgular

Testis tümörü tanısıyla yapılan 77 inguinal orşiektomi olgusunun 69'unda GHT bulundu. Bu olgulardan 32'si evre 1, 4'ü evre 1S, 9'u evre 2, 24'ü evre 3 olarak evrelendirildi. Erken evre testis kanseri olarak değerlendirilen 32 hasta çalışmaya dahil edildi.

Erken evredeki hastaların yaş ortalaması 32,26±10,61 (8-60) idi. On dokuz hasta (%54,9) pür seminom (17 klasik, 1 anaplastik, 1 spermatositik seminom), 7 hasta (%21,8) nonseminom, 6 hasta (%18,8) ise miks GHT olarak değerlendirildi. İki hastada (%6,25) bilateral senkron evre 1 seminom saptandı. Tümör yerleşimi 10 hastada (%31,2) sol, 20 (%62,5) hastada sağda iken, 2 hastada (%6,25) ise bilateraldir. Hastaların histopatolojik incelemelerine göre dağılımı Tablo 1' de verilmiştir. Tümör boyutu ortalama 4,48±2,04 cm (1,2-9) idi. On yedi olguda (%40,47) intratübüler germ hücreli neoplazi saptandı.

Üç seminom, iki nonseminom ve dört miks GHT içeren 9 olgu (%28,12) izleme alındı. Bu 9 olgu içerisinde bir seminom olgusu, bir miks GHT olgusu takiplere düzenli devam etmezken; bir non seminom olgusunda 12. ayda nüks gelişti. KT olarak 3 kür BEP protokolü uygulanan bu hastada, sonraki 12 aylık takipte nüks gözlenmedi. İzleme alınan diğer 6 hastada ortalama izlem süresi 40±10,7 ay (32-64 ay) olup nüks görülmedi.

On iki seminom olgusu (%37,5) RT ile tedavi edildi; bu olgulardan biri RT sonrası takipsiz kalırken, diğer 11 olguda 4±11,8 aylık (28-76 ay) ortalama takip süresi boyunca nüks saptanmadı. On iki olgunun 5'inde hokey sopası şeklinde paraaortik alan ve ipsilateral pelvisteki lenf nodlarına 20 Gy RT (10 fraksiyonda) uygulanırken, 7 hastada ise sadece unilateral paraaortik alana 20 Gy RT uygulandı. RT sonrası takip edilen 11 hastanın 1'inde 57. ayda RT'ye sekonder olduğu düşünülen akut miyeloblastik lösemi (AML) gelişti. İki hastada ise RT sonrası 70 aylık bir süre geçmiş olmasına rağmen, postoperatif dönemde gelişen oligosperminin düzelmemiş olduğunu gözlemledik.

Adjuvan KT olarak 4 hastaya (%12,5) evre 1 seminom olduğu için tek doz karboplatin, nonseminom ve miks GHT olan 5 hastaya (%15,6) ise BEP protokolü uygulandı. Tek doz karboplatin uygulanan hastalardan birinde bilateral seminom mevcut olup bu hastada 23. ayda nüks gelişmesi üzerine 4 kür BEP uygulandı. BEP uygulanan 5 hastanın biri KT sonrası takipsiz kalırken, ortalama takip süresi 52±23,12 ay (18-76 ay) olan diğer 4 hastada nüks izlenmedi. Sadece bir hastada (%25) 72. ayda Miyelodisplastik sendrom (MDS) gelişti.

AML gelişen bir hasta ve düzelmeyen oligospermi gelişen iki hasta dışında diğer gruplardaki hiçbir hastada akut ve geç dönem ciddi (grade >2) toksisite gözlenmedi. Hastaların ortalama HSK süreleri 48,29±9,74 ay (21-60 ay), GSK süreleri 48,73±10,07 ay (24-64 ay) olarak hesaplandı (Tablo 1).

Retrospektif olarak incelediğimiz bu hastalara, kliniğimizde Ocak 2010-Aralık 2014 yılları arasında verilmiş olan adjuvan tedaviler ile EAU 2017 güncel kılavuzuna göre verilmesi önerilen adjuvan tedavilerin karşılaştırılması Tablo 2'de gösterilmiştir.

Tartışma

Seminomlarda gizli metastaz oranı %10-15, retroperitoneal tedavi sonrası sistemik nüks gelişme oranı ise %1-4'tür (5). Seminomda relaps açısından kötü prognostik faktörler primer

tümör boyutunun 4 cm'den büyük olması ve rete testis invazyonu varlığıdır.

Yirmi yıl önce, evre 1 seminomların adjuvan tedavisinde retroperitoneal ve ipsilateral pelvisteki lenf nodlarına köpek bacağı (dog-leg) şeklinde uygulanan RT'nin başarı oranı %95 iken (6); RT sonrası gözlenen relaps oranları <%5-10'du. Relaps durumunda verilen BEP ile hastalık spesifik sağkalım %100'ü bulmaktaydı (7). Sonraki yıllarda tek doz karboplatinin daha az yan etki ile benzer onkolojik sonuçlar içermesinin gösterilmesi nedeniyle RT tedavide ilk tercih özelliğini yitirmiştir (8).

RT'nin geç dönemde oluşturduğu kardiyovasküler toksisite (5-8 yıl içinde hastaların %9,6'sında), gonadal toksisite (%8 kalıcı oligospermi) ve sekonder malign neoplazm (25 yıl içinde %18 risk, en sık lösemi görülmekte) riskleri göz önüne alınarak; 2014'ten itibaren EAU kılavuzlarında, evre 1 seminomda adjuvan RT artık önerilmemektedir (9).

Bizim çalışmamızda ise tedavileri 2014'ten önce planlanmış olan 12 seminom olgunun 5'inde hokey sopası şeklinde paraaortik alan ve ipsilateral pelvisteki lenf nodlarına 20 Gy RT (10 fraksiyonda) uygulanırken, 7 hastada sadece unilateral paraaortik alana 20 Gy RT uygulandı. Eğer bu 12 olguya bugün tedavi planlansaydı, hiçbirine RT uygulanmayacaktı (Tablo 2).

Tek doz karboplatinin RT'ye göre daha az yan etkiyle aynı onkolojik etkinlikte olması sonucu 2010'da A düzeyinde öneri

Tablo 1. Evre 1 germ hücreli tümörlü hastaların histopatoloji, adjuvan tedavi, hastalıksız sağkalım ve genel sağkalım sürelerine göre dağılımı

	Seminom	Non seminom	Miks	Toplam
Hasta sayısı, n	19	7	6	32
İzlem, n Nüks (+) Nüks (-) Takipsiz	3 - 2 1	2 1 1 -	4 - 3 1	9 1 6 2
RT, n Nüks (+) Nüks (-) Takipsiz	12 - 11 1	- - - -	- - - -	12 - 11 1
Tek doz karboplatin, n Nüks (+) Nüks (-) Takipsiz	4 1 3 -	- - - -	- - - -	4 1 3 -
BEP, n Nüks (+) Nüks (-) Takipsiz	- - - -	4 - 4 -	1 - - 1	5 - 4 1
Tedaviyi istemeyen, n	-	1	1	2
HSK (ay)-ortalama	64,94±6,45	26,27±6,14	36±6,14	48,29±9,74
GSK (ay)-ortalama	68,11±8,01	31,36±5,24	38±7,12	48,73±10,07

HSK: Hastalıksız sağkalım, GSK: Genel sağkalım, BEP: Bleomisin + etoposid + sisplatin, RT: Radyoterapi

Tablo 2. Kliniğimizdeki evre 1 germ hücreli tümörlü hastalara verilmiş olan adjuvan tedaviler ile Avrupa Üroloji Derneği 2017 güncel kılavuzuna göre verilmesi önerilen adjuvan tedavilerin karşılaştırılması

Evre 1 germ hücreli tümör grupları	Verilmiş adjuvan tedavi şekli	EAU 2017 kılavuzuna göre verilmesi önerilen adjuvan tedavi şekli
Düşük riskli seminom	Unilateral paraaortik alana RT (n=6) Tek doz karboplatin (n=2) İzlem (n=3)	İzlem (n=6) İzlem (n=2) İzlem (n=3)
Yüksek riskli seminom	Unilateral paraaortik alana RT (n=1) Hokey sopası şeklinde (unilateral paraaortik alan + ipsilateral pelvik bilgeye) RT (n=5) Tek doz karboplatin (n=2)	Tek doz karboplatin (n=1) Tek doz karboplatin (n=5) Tek doz karboplatin (n=2)
Düşük riskli nonseminom	İzlem (n=2)	İzlem (n=2)
Düşük riskli nonseminomda izlem sonrası nüks	3 kür BEP (n=1)	3 kür BEP (n=1)
Yüksek riskli nonseminom	2 kür BEP (n=4)	1 kür BEP (n=4)
Düşük riskli miks GHT	İzlem (n=4)	İzlem (n=4)
Yüksek riskli miks GHT	2 kür BEP (n=1)	1 kür BEP (n=1)

GHT: Germ hücreli tümör, BEP: Bleomisin + etoposid + sisplatin, RT: Radyoterapi, EAU: Avrupa Üroloji Derneği

olarak kılavuzlarda yer almaya başladı (10). 2014'ten itibaren EAU kılavuzlarında evre 1 seminomda aktif izlem öne çıkarak, tek doz karboplatin risk faktörü varlığında önerilmeye başlandı (9). Ondrusova ve ark.'na (11) göre, adjuvan tek doz karboplatin sonrası retroperitonda %9,1 oranında saptanırken; bu hastalarda 3 doz BEP sonrası kür sağlamak mümkündür. Chau ve ark. (12) KT'ye başlama süresinin onkolojik sonuçları etkilemediğini belirtmekle beraber, pratik uygulamada orşiektomi sonrası ilk 60 gün içerisinde KT'ye başlanmasını önermektedir.

Bizim çalışmamızda, evre 1 seminom olan 4 olguya tek doz karboplatin uygulanmıştır. Bu hastalardan ikisi düşük riskli olup bugünkü kılavuzlara göre ilk seçenek olarak aktif izleme alınmaları daha uygun olurdu (Tablo 2).

Aktif izlem uygulanan hastalarda relapsın %15-20 olarak saptanması, relaps olması halinde RT veya KT ile başarı sağlanabilmesi aktif izlemi öne çıkarmaya başladı. Aktif izlemde relapsa kadar geçen ortalama süre 12-18 ay olup relapsların %29'u daha uzun sürede gerçekleşmektedir (13). Bu gelişmeler ışığında, 2010'da aktif izlem kılavuzlarda B düzeyinde önerilmeye başlandı (10). 2014'ten itibaren ise, EAU kılavuzları evre 1 seminomda aktif izlemi A düzeyinde önermektedir (9). Bu risk faktörlerinin (rete testis invazyonu ve tümör çapı) onkolojik sonuçlar üzerine etkisi ise halen tartışılmaktadır (14,15,16,17).

Bizim çalışmamızda ise, 19 evre 1 seminom olgusundan sadece üçü aktif izleme alınmıştır. Oysaki bugünkü bilgilerimiz ışığında, düşük riskli olan 8 hasta daha aktif izleme alınabilirdi. Bu 8 hastadan ikisine tek doz karboplatinin, altısına ise RT'nin fazladan uygulanmış olduğunu söyleyebiliriz (Tablo 2).

Literatürde adjuvan RT uygulanan evre 1 seminomlu hastalarda %5-8 oranında sekonder malignite (başta lösemi olmak üzere, renal, akciğer, pankreas kanserleri, nörofibrosarkom) bildirilmiştir (18). Bizim çalışmamızda da benzer şekilde RT sonrası 1 hastada (%9) AML gözlenirken, karboplatin ve aktif izlem gruplarında sekonder malignite gözlenmemiştir. Adjuvan RT'den 5 yıl sonra fertilite oranlarında düzelme olduğu, kalıcı oligosperminin %8 hastada saptandığı bildirilirken; çalışmamızda 70 ay geçmesine rağmen iki hastada (%18) düzelmeyen oligospermiyi geç dönem toksisite olarak belirledik. Bu toksisiteye, karboplatin ve aktif izlem gruplarında rastlayamadık.

Nonseminomların tanı anında 1/3'ü evre 1 iken; bunların %30'dan fazlası tanı anında gizli metastaza sahiptir ve ek tedavi yapılmazsa %30'u nüks edecektir. Bu grupta gizli metastazı öngören en önemli prognostik gösterge, lenfovasküler invazyon (LVİ) varlığıdır. Tüm evre 1 nonseminom hastaların yaklaşık %33'ü LVİ'ye sahiptir (19). Diğer önemli prognostik risk faktörleri ise; proliferasyon oranının >%70 olması ve embriyonel karsinom yüzdesinin >%50 olmasıdır. LVİ varlığında postoperatif adjuvan tedavi verilmeyen hastaların %14-22'sinde relaps, %48'inde ise metastaz geliştiği gözlenmiştir (20).

Aktif izleme alınan hastaların 20 yıllık uzun dönem takibinde relaps oranı %27-30'dur (21). Bu relapsların %80'i ilk 12 ayda, %12'si ikinci yılda ve %6'sı üçüncü yılda görülmekte; 4. ve 5. yıllarda %1'e düşmektedir (21). Bu grupta rutin olarak 5 yıllık yakın izlem zorunludur (22). Üçüncü ve on ikinci aylarda çekilecek bilgisayarlı tomografi çok değerlidir. Sık bilgisayarlı tomografi çekimlerinin yol açabileceği radyasyona bağlı sekonder malignite riskini azaltmak için, son yıllarda kullanılan düşük doz protokollü bilgisayarlı tomografinin radyasyon riskini %55 azalttığı saptanmıştır (23).

Çalışmamızda, evre 1 nonseminom olduğu saptanan 7 hastadan düşük risk grubunda yer alan iki hasta izlem protokolüne alındı. Sadece bir hastada 12. ayda nüks gelişti ve 3 kür BEP uygulandı. Bu uygulamanın 2014 öncesinde yapılmasına rağmen bugünkü güncel kılavuzlara uygun olduğunu görmekteyiz (Tablo 2).

İki doz BEP KT'si uzun yıllar boyunca LVİ varlığında relaps riskini azaltmada önerilmiştir. 2009'da yapılan Swedish and Norwegian Testicular Cancer Group (SWENOTECA) çalışmasında, LVİ varlığında tek doz BEP tedavisinin 8,1 yıllık takipte relapsı %2,3'e düşürdüğü ve daha az yan etki sağladığı gösterilmiş (14) ve güncel EAU kılavuzlarında 2014'ten sonra A derecesinde önerilmeye başlanmıştır. Tek doz BEP sonrası relapslarda ise, üç veya dört doz BEP önerilmektedir (24).

Bu hastalarda, bleomisine bağlı pulmoner toksisite (pnömonitis, pulmoner fibrosis vs.) gerçekleşebilmekte ve hastaların %1-3'ünde ölümcül seyredebilmektedir (25). Kardiyovasküler hastalık riski (miyokard enfarktüsü, koroner arter hastalığı vs.) BEP uygulaması sonrası normal popülasyona göre 3,1 kat artış gösterebilmektedir (26). Chamie ve ark. (27) KT'ye bağlı artmış sekonder solid malignite riskini bildirirken; bazı çalışmalarda yüksek doz etoposid sonucu %0,5-1 oranında hematolojik malignite riski bildirilmiştir (28). Sisplatin temelli KT'nin infertilite ve cinsel fonksiyonlar üzerine olumsuz etkisi henüz bilinmemektedir (29).

Çalışmamızda, evre 1 nonseminom olan 4 hastaya yüksek risk grubunda olduğu için iki doz BEP uygulanmıştır. Bu 4 hasta da kılavuzlardaki son değişiklik öncesi tedavi aldığı için iki doz BEP uygulanmış olduğunu görmekteyiz. Bugün tanı alsalardı, tek doz BEP protokolüne aday olacaklardı (Tablo 2). Bu 4 hastanın sadece birinde (%25) 72. ayda MDS sekonder hematolojik malignite olarak karşımıza çıktı. Az hasta sayısı ve kısa takip süreleri nedeniyle bu oran yüksek gibi gözükmektedir ve çalışmamızda tek doz BEP alan bir grup olmadığı için tek doz ve iki doz BEP almanın bu duruma etkisini karşılaştıramadık.

German Testicular Cancer Study Group'un 2008'de yaptığı çalışmada, 2 yıllık HSK oranı tek doz BEP alan grupta %99,41, RPLND grubunda %92,37 bulunmuştur (30). Bu nedenle her ne kadar ABD'de evre 1 nonseminomda en yaygın uygulanan tedavi olsa da, güncel EAU kılavuzlarında RPLND, yüksek riskli hastalarda ilk seçenek tedavi değildir ve etkinliği tek doz BEP KT'sinden daha azdır. Bizim çalışmamızda da, EAU kılavuzlarına benzer olarak, evre 1 nonseminom tanılı 7 hastanın hiçbirine RPLND uygulanmamıştır (Tablo 2).

Miks GHT'ler de nonseminom komponentinden dolayı nonseminomlar gibi tedavi edilmektedir. Buna uygun olarak çalışmamızda saptadığımız evre 1 miks GHT tanısı olan 6 hastadan 4'ü düşük risk grubunda olduğu için izleme alınırken, 1'ine yüksek risk grubunda olduğu için o dönemki eski kılavuz bilgilerine dayanılarak 2 kür BEP uygulanmıştır (Tablo 2).

Bir hasta ise tedaviyi kabul etmeyerek takipsiz kalmıştır (Tablo 1). Nonseminomlarda ve miks GHT'lerde vasküler invazyon (VI) varlığında ilk seçenek tek doz BEP, ikinci seçenek ise izlem veya RPLND'dir. VI yokluğunda ise ilk seçenek olarak izlem, ikinci seçenek olarak ise tek doz BEP veya RPLND önerilmektedir.

Üroonkoloji alanında özellikle de evre 1 testis tümörlerinde orşiektomi sonrası tedavi yaklaşımlarında, her yeni çalışma ile kısa süreli aralıklarla çok fazla değişiklik olduğunu görmekteyiz. Çalışmamızda değerlendirdiğimiz hastalara 7 yıl önceki kılavuzlara göre doğru uygulanan yaklaşımların büyük çoğunun bugün için geçerliliğinin kalmaması bu durumun bir ispatıdır. Evre 1 seminomlarda her ne kadar geç dönem kardiyovasküler toksisite, gonadal toksisite ve sekonder malign neoplazm açısından karboplatin RT'den daha masum denilse de ve çalışmamızda buna paralel bulgular saptamış olsak da bunu doğrulamak için uzun dönem takip sürelerine ihtiyaç bulunmaktadır.

Çalışmanın Kısıtlılıkları

Çalışmadaki kısıtlılıklarımız; kısa takip süreleri, hasta sayısının az olması, çalışmanın retrospektif dizaynıdır. 2014 sonrası EAU kılavuzlarında bahsedilen yeni tedavi şemaları, daha az yan etki ile benzer onkolojik sağkalım oranları belirtmektedir. Ancak daha geniş sayıda hasta içeren, uzun takip süreli prospektif çalışmalar, mevcut kılavuzların toksisite ve hasta sağkalım süreleri üzerine etkilerini daha gerçekçi olarak gözlemlememizi sağlayacaktır.

Sonuç

Erken evrede saptanan testis tümörlerinde mevcut tedavi yaklaşımları ile kür sağlanma olasılığı yüksek olup nüks gözlenme oranı düşüktür. Tümörün histopatolojisine ve risk faktörlerine bağlı olarak postoperatif takip ve adjuvan tedavi seçenekleri değişmekle beraber, GSK oranları oldukça yüksektir. Güncel EAU kılavuzlarında da bu mükemmel sağkalım oranlarına paralel olarak adjuvan tedavinin yan etkileri nedeniyle daha az toksisitesi olan seçenekler tercih edilmekte ve tedavi protokolleri neredeyse her yıl değişebilmektedir. Bu nedenle testis tümörü ile ilgilenen her kliniğin güncel çalışmaları ve kılavuzları takip etmesi klinik pratikte büyük önem taşımaktadır.

Etik

Etik Kurul Onayı: Retrospektif bir çalışma olduğundan etik kurul başvurusu yapılmamıştır.

Hasta Onayı: Hastalara çalışma ile ilgili bilgi verilip; cerrahi sonrası mevcut nüks, sağkalım gibi onkolojik verileriyle ilgili hasta adı kullanılmadan değerlendirme yapılacağı söylenip gereken sözlü onay alınmıştır.

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Original Article

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Evaluation of General Characteristics of Renal Cell Carcinoma Patients: A Single Center Experience

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Abstract

Objective: Renal cancer (RC) accounts for 3.2% of all newly diagnosed cancers and approximately 90% of RC cases are renal cell carcinoma (RCC). Smoking and hypertension are the most important risk factors. The aim of our study was to evaluate the general characteristics of RCC patients in Bolu, Turkey.

Materials and Methods: Patients who visited our medical oncology clinic and were diagnosed with RCC between January 1st, 2012 and May 31st, 2017 were evaluated retrospectively.

Results: Eighty-one patients were diagnosed with RCC during the study period. The median age of the patients was 62 years (range: 38-87 years). Fifty-seven (70.4%) of the patients were male and 24 (29.6%) were female. Thirty patients (37.1%) were diagnosed incidentally. Forty-eight (59.3%) of the patients were smokers. The most common comorbidity was hypertension (58%). Radical nephrectomy was performed in 59 (72.8%) of the patients. The most common histological subtype was clear cell carcinoma (72.8%) and 39 (48.1%) were stage 1 when evaluated according to the stage of RCC. Of the 16 patients with metastatic disease, 11 (13.6%) received interferon therapy, and 5 patients (6.2%) refused treatment. After interferon treatment, 7 patients received targeted therapy with sunitinib/pazopanib as second-line treatment, 5 received everolimus as third-line treatment, and 3 received axitinib treatment as fourth-line treatment. Ten patients with bone metastasis underwent palliative radiotherapy. The median follow-up time of the patients was 21 months (0-123 months). Sixty-five patients (80.2%) survived this period.

Conclusion: Smoking cessation and effective treatment of hypertension, preventable etiological factors of RCC, and incidental diagnosis of early RCC are very important. With early diagnosis, the partial nephrectomy rate might be increased.

Keywords: Renal cell carcinoma, etiology, Bolu

Introduction

Renal cancer (RC) accounts for 3.2% of all newly diagnosed cancers, 4.1% in males and 2.5% in females (1). Approximately 90% of RCs are renal cell carcinoma (RCC). Based on tumor morphology, immunohistochemistry, cytogenetics, and other molecular studies, the subtypes of RCC are clear cell, papillary, chromophobe, and collecting-duct or Bellini duct tumors. The most common subtype of RCC is clear cell carcinoma, with a rate of approximately 80% (2,3,4). Cigarette smoking and hypertension are the most important risk factors in the development of RCC (5,6). Surgery is very important in the treatment of RCC (7). As more patients are diagnosed in the early stages, partial nephrectomy is increasingly used instead of radical nephrectomy for treatment. RCC is a radioresistant tumor; thus, radiotherapy (RT) cannot be used in its treatment. RT can only be performed as palliative treatment in conditions such as brain and bone metastasis (8,9). Systemic treatment is not necessary

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until RCC has reached the metastatic stage. Targeted treatment agents such as sunitinib, pazopanib, sorafenib, bevacizumab, axitinib, everolimus, and temsirolimus are used in the treatment of metastatic disease (10,11). Our study aimed to evaluate the general characteristics of patients with RCC in Bolu, Turkey.

Materials and Methods

The written and digital records of patients with RCC who were diagnosed between January 1st, 2012 and May 31st, 2017 at the Department of Medical Oncology Outpatient Clinic of Abant İzzet Baysal University Faculty of Medicine were reviewed retrospectively. Age, gender, symptoms at presentation, smoking and alcohol habits, comorbid diseases, family history of cancer, surgical modality, tumor histology, tumor diameter, grade, stage, metastasis location, medical treatment, and final follow-up dates of the RCC patients were recorded.

Results

A total of 1870 patients visited our outpatient clinic between January 1st, 2012 and May 31st, 2017, 81 (4.3%) of whom were diagnosed with RCC. The median age of the patients was 62 years (range: 38-87 years). Forty-nine (60.5%) of the patients were less than 65 years of age and 32 (39.5%) were over 65 years of age. Fifty-seven (70.4%) of the patients were male and 24 (29.6%) were female.

For 30 patients (37.1%) the renal mass was detected incidentally. Presenting symptoms in the other patients included abdominal pain in 26 patients (32.1%), hematuria in 7 (8.6%), abdominal pain and hematuria in 6 (7.4%), weight loss and fatigue in 6 (7.4%), and back pain in 6 patients (7.4%).

Forty-eight (59.3%) of the patients smoked cigarettes and 33 (40.7%) did not smoke. Twenty women (83.3%) and 28 men (49.1%) smoked. The smoking duration of the patients was 33 pack-years (range: 6-100 pack-years). Seventy-five (92.6%) of the patients did not use alcohol, while 6 (7.4%) consumed alcohol.

Forty-three (53.1%) of the RCC patients had comorbid diseases and 38 (46.9%) did not. These comorbidities included hypertension in 25 patients (58.1%), second primary cancer in 7 (16.3%), diabetes mellitus in 6 (13.9%), and hypertension plus diabetes mellitus in 5 patients (11.7%). Seventy patients (86.4%) had no family history of cancer, while 11 patients (13.6%) had a family history of cancer. The patients' Eastern Cooperative Oncology Group (ECOG) performance status was evaluated as grade 1 in 70 patients (86.4%), grade 2 in 8 patients (9.9%), and grade 3 in 3 patients (3.7%) (Table 1).

Radical nephrectomy was performed in 59 patients (72.8%), partial nephrectomy was performed in 17 patients (21%), and 5 patients with metastases did not undergo surgery. Histological subtype was clear cell carcinoma in 59 patients (72.8%), papillary carcinoma in 12 (14.8%), chromophobe cell carcinoma in 8 (9.9%), and collecting duct tumor in 2 patients (2.5%). The median tumor diameter was 6 cm (range: 1.7-18 cm). Tumor diameter was less than 7 cm in 49 (60.5%) of the patients and 7 cm or greater in 32 patients (39.5%). Tumor grade was grade 1 in 12 patients (14.8%), grade 2 in 27 (33.3%), grade 3 in 23 (28.4%), and could not be evaluated in 19 patients (23.5%). Tumors were stage 1 in 39 patients (48.1%), stage 2 in 19 patients (23.5%), stage 3 in 7 patients (8.6%), and stage 4 in 16 patients (19.8%). Bone metastasis occurred in 9 patients (56.2%), lung metastasis occurred in 5 (31.2%), surrenal metastasis occurred in 1 (6.3%), and multiple metastases such as lung, liver, and bone metastases occurred in 1 patient (6.3%). Sixty-five patients (80.2%) had postoperative follow-up. Interferon treatment was given to 11 patients (13.6%) who had metastasis, and five patients (6.2%) refused treatment. Seven patients received sunitinib/pazopanib as second-line treatment, 5 received everolimus as third-line treatment, and 3 patients received axinitinib treatment as fourth-line treatment. Palliative RT was applied to 10 patients with bone metastasis. No patient had brain metastases. The median follow-up time of the patients was 21 months (range: 0-123 months). During this time, 65 patients (80.2%) survived (Table 2).

Table 1. General features of patients

		n	%
Gender	Female	24	29.6
	Male	57	70.4
Cigarette smoking	Yes	48	59.3
	No	33	40.7
Alcohol consumption	Yes	6	7.4
	No	75	92.6
Comorbid diseases	Hypertension	25	58.1
	Second primary cancer	7	16.3
	Diabetes mellitus	6	13.9
	Diabetes mellitus + hypertension	5	11.7

Table 2. Diagnosis and treatment of patients

		n	%
Operation	Radical nephrectomy	59	72.8
	Partial nephrectomy	17	21
	No	5	6.2
Histological subtype	Clear cell carcinoma	59	72.8
	Papillary cell carcinoma	12	14.8
	Chromophobe cell carcinoma	8	9.9
	Collecting duct tumor	2	2.5
Tumor diameter	<7 cm	49	60.5
	>7 cm	32	39.5
Stage	1	39	48.1
	2	19	23.5
	3	7	8.6
	4	16	19.8
Treatment	Postoperative follow-up	65	80.2
	IFN	11	13.6
	Treatment refusal	5	6.2

IFN: Interferon

Discussion

RCC is an age-related disease and is more common in men than in women. According to Surveillance, Epidemiology and End Results Program (SEER) data, the average age at diagnosis is 64 years (12). In a study about RCC conducted by Türk et al. (13), 70% of the patients were male, and the median age of the patients was 57 years. In another study conducted in patients with RCC, 58.5% of the patients were male, and the median age was 57 years (14). The proportion of male patients in our study was greater than that of female patients. The median age at diagnosis in our study, 62 years, was higher than the studies cited above and was similar to that in the SEER data.

Cigarette smoking is currently considered the most important risk factor in the development of RCC. According to SEER data, 20-30% of men and 10-20% of women diagnosed with RCC are smokers (12). In the VITAL study, there was a relationship between cigarette smoking and RCC formation, but no relationship was found with alcohol consumption (15). In our study, 59.3% of the patients were cigarette smokers, and only 7.4% of patients consumed alcohol. Twenty women (83.3%) and 28 men (49.1%) were smokers. Unlike the aforementioned studies, the smoking rate in our study was higher in women than in men. This is mainly due to women being more addicted than men to cigarette smoking and the fact that the prevalence of smoking is presently increasing in women but decreasing in men (16).

Hypertension is also important in the etiology of RCC. Some researchers believe that arterial hypertension arises due to vasoactive amines secreted by RCC and causes RCC formation (15,17,18). Chow et al. (19) observed a relationship between elevated blood pressure and risk of RCC development, and they found that the risk might be decreased with time if blood pressure was well controlled. In another study, it was found that the risk of RCC development was over 2.4 times greater in patients with high blood pressure (20). In our study, hypertension was noted in half of the patients. Effective treatment of hypertension, which plays a significant role in RCC etiology, is very important.

Clear cell carcinoma (80-90%), papillary carcinoma (10-15%), and chromophobe carcinoma (4-5%) are the most common histological subtypes of RCC (21). In a study in which Kuş et al. (22) assessed the histopathological features of RCC patients, the most common histological subtype was clear cell carcinoma, accounting for 88.6% of cases. In another study concerning histological subtype, clear cell carcinoma was the most common subtype with a rate of 85% (13). Consistent with these studies, we also found that the most common histological subtype among our patients was clear cell carcinoma.

Approximately 65% of patients with RCC are asymptomatic in terms of clinical and laboratory factors and are usually diagnosed incidentally (23,24). In particular, the symptom-based diagnosis rate of RCC patients has been reduced because of easier access and more frequent use of abdominal ultrasound and computed tomography. The proportion of incidentally diagnosed patients has increased 3 fold within 20 years (25,26). In our study, the incidental diagnosis rate of RCC was greater than diagnosis by other means.

In terms of tumor stage, a study evaluating 198 patients with RCC reported higher proportions of stage 1 and stage 2 tumors than metastatic disease (14). In another study of the clinical and histopathological features of 230 patients with RCC, the number of stage 1 patients was 110 (49%), a high rate (13). In keeping with the increase in the use of radiological diagnostic tests, the proportion of stage 1 patients in our study was 48.1%, similar to that in recent studies.

Surgery for localized RCC disease is usually curative treatment. Local ablation, partial nephrectomy, or total nephrectomy may be performed, depending on tumor size (27). Similar local recurrence rates have been reported with partial nephrectomy and local ablation therapy. None of the patients in our study underwent local ablative treatment (28). In another study performed in the last 15 years, total nephrectomy was still performed, although the partial nephrectomy rate in patients with a tumor diameter less than 2 cm increased from 15.3% to 61.1%. If the tumor diameter was 2-2.9 cm, the rate increased from 11.0% to 44.2%; if the tumor diameter was 3-3.9 cm, the rate was increased from 7.2% to 31.1% (29). In our study, the total nephrectomy rate was higher than the partial nephrectomy rate.

RT is administered as palliative treatment for bone and brain metastases. In fact, RCC is a radioresistant tumor (30,31,32). No brain metastatic patients were found in our study. Ten patients with bone metastasis had palliative RT treatment.

Targeted therapies are used in metastatic RCC patients. In a recent study comparing the molecular targeted agent sunitinib to interferon, sunitinib yielded higher disease-free survival and response rates. Additionally, in another recent study, pazopanib and sunitinib showed similar efficacy in metastatic disease (33,34). Despite these findings, due to the policies of the Turkish Ministry of Health, interferon is still used as first-line therapy for metastatic RCC. In our study, interferon therapy was started in 11 of the metastatic patients, and 7 patients who showed progression with interferon treatment were treated with targeted agents. Five patients refused treatment.

In our study, the median follow-up time was 21 months, and 65 patients survived. In another study, the median follow-up time was 33 months and 57 patients survived (35). In yet another study, 61 patients survived and the median follow-up time was 46 months (36).

Study Limitations

Limitations of this study include its retrospective design and the small number of patients.

Conclusion

Reduction in cigarette smoking and control of risk factors such as hypertension are important in the prevention of RCC. Renal cell cancer should be diagnosed early because partial nephrectomy can be performed instead of total nephrectomy, especially with small-diameter tumors.

Ethics

Ethics Committee Approval: This study was a retrospective medical record review. For this reason, ethical approval was not received.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ü.Ü., T.T.D., B.Y., N.K., U.Ü., Concept: Ü.Ü., Design: Ü.Ü., T.T.D., Data Collection or Processing: T.T.D., B.Y., N.K., Analysis or Interpretation: Ü.Ü., U.Ü., Literature Search: Ü.Ü., T.T.D., U.Ü., Writing: Ü.Ü.

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Original Article

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What is the Prostate-Specific Antigen Cut-Off Value to Detect Clinically Significant Prostate Cancer According to Age in Turkey?

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Abstract

Objective: To detect a prostate-specific antigen (PSA) cut-off for clinically significant prostate cancer (csPCa) according to age in Turkey.

Materials and Methods: A total of 532 men who had transrectal ultrasound-guided biopsy of the prostate due to elevated PSA and abnormal findings on digital rectal examination between January 2011 and January 2018 were retrospectively evaluated. Elevated PSA was defined as ≥4 ng/mL. Patients were divided into groups 1-5 according to age: 40-49, 50-59, 60-69, 70-79, and ≥80 years. A PSA cut-off value was determined for each group.

Results: The mean age was 66.45±8.21 (41-89) years. There were 20, 112, 222, 154, and 24 patients in groups 1-5, respectively. Mean PSA values were 6.04±3.88 (0.24-16.46) ng/mL, 6.8±4.17 (0.97-35.07) ng/mL, 10.51±8.53 (0.72-128.5) ng/mL, 20.41±36.64 (1.32-250) ng/mL, and 73.28±100.19 (9.33-344.1) ng/mL in groups 1-5, respectively. PSA cut-off values for csPCa were 7.08 ng/mL, 4.71 ng/mL, 7.30 ng/mL, 8.12 ng/mL, and 14.12 ng/mL in groups 1-5, respectively.

Conclusion: There is a correlation between PSA and age in Turkey. Using the PSA cut-off values determined in our study would decrease the number of unnecessary biopsy procedures.

Keywords: Prostate specific antigen, Turkey, prostate cancer

Introduction

Prostate cancer (PCa) has the highest annual incidence rate of all cancers in men and is the second leading cause of cancer deaths in men following small cell lung cancer. After prostate-specific antigen (PSA) was first described by Catalona et al. (1) in 1991, the rate of PCa detection increased dramatically. The United States Food and Drug Administration approved the use of PSA for cancer detection in 1994 (2). For PSA levels of 1-4 ng/mL, its sensitivity and specificity values in PCa detection have been reported as 83% and 38% at PSA: 1 ng/mL; 52% and 72% at 3.1 ng/mL PSA, 32% and 86% at 1 ng/mL PSA, and 20% and 94% at 4.1 ng/mL PSA, respectively (2). According to these values, using a low threshold value will result in a higher PCa detection rate. However, the rate of detection of clinically insignificant cancers will also increase. A low threshold value will also result in low specificity values, which will not allow PCa exclusion.

Various PSA threshold values are used worldwide. Among previous studies with large patient numbers, a threshold value of 2.5 or 3.0 ng/mL was used in the European Randomized Study of Screening for Prostate Cancer (ERSPC) (3) and a threshold of 4.0 ng/mL was used in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) conducted in the United States of America (USA) (4). In the Swedish arm of the ERSPC, referred to as the Göteborg Trial, 3.4 ng/mL was used between 1993-1998, after which a value of 2.5 ng/mL was used (5). In

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1993, Oesterling et al. (6) investigated PSA threshold values for PCa based on age in 537 American subjects and reported PSA threshold values of 2.5 ng/mL, 3.5 ng/mL, 4.5 ng/mL, and 6.5 ng/mL respectively for the 40-49, 50-59, 60-69, and 70-79 age groups.

It is apparent that each country uses its own threshold values for the detection of PCa. However, the determined PSA threshold values are not intended for the detection of clinically significant PCa (csPCa), but for the general detection of PCa. Our aim in this study was to determine age-specific PSA threshold values to be used for the detection of csPCa in Turkey.

Materials and Methods

Following approval (no: 18/44) by the University of Health Sciences, Gülhane Training and Research Hospital Ethics Committee, statistical power analysis indicated that 385 patients were necessary to conduct the study. Consent was obtained from the patients. Data pertaining to 532 consecutive patients who had elevated PSA levels or abnormal findings on digital rectal examination (DRE) and underwent transrectal ultrasound-guided biopsy of the prostate (TRUSbP) between January 2011 and January 2018 were evaluated retrospectively. PSA elevation was defined as PSA ≥4 ng/mL. Patients with elevated PSA levels were treated with oral antibiotherapy for two weeks to rule out the possibility of bacterial prostatitis. Then a second blood sample was taken to determine whether the PSA elevation persisted. Free PSA measurement was also done in this session. Patients with persistent PSA elevation were referred for TRUSbP. Patients with life expectancy <10 years were not subjected to TRUSbP.

TRUSbP was performed using a special ultrasound device that acquires both axial and sagittal images (Logiq 5). At least 12 prostate biopsy cores were obtained using an 18-gauge Tru-Cut (UK Medical) prostate needle.

Patients with PSA ≤10 ng/mL, Gleason (G) score ≤3+3, and ≤2 tumor-containing cores were considered to have clinically insignificant PCa (ciPCa). Patients with values higher than these were diagnosed with csPCa.

Patients were classified by age as group 1: 40-49 years, group 2: 50-59 years, group 3: 60-69 years, group 4: 70-79 years, and group 5: ≥80 years. PSA threshold values were determined for the detection of PCa and csPCa within these age groups. Following the determination of PSA threshold values for PCa and csPCa, a free/total PSA ratio threshold was determined for the PSA range between those two PSA values.

Statistical Analysis

"Statistical Package for Social Sciences 20.0 (SPSS 20.0 for Mac OS)" software package was used for statistical analyses. Descriptive statistics were presented using mean (minimum-maximum) values, frequencies, and percentages. Kolmogorov-Smirnov, Shapiro-Wilk, and Skewness and Kurtosis tests were used to evaluate whether the data conformed to a normal distribution. The Pearson correlation test was used to evaluate correlations between continuous variables. Receiver operating characteristic (ROC) curves were generated for each age group based on PSA level. These ROC curves were used to determine PSA threshold values for the detection of PCa and csPCa. P<0.05 was defined as statistically significant.

Results

Data from a total of 532 patients were analyzed. Mean age of the patients was 66.45±8.21 (41-89) years. Their mean and median PSA values were 15.13±5.21 (0.29-344.1) ng/mL and 7.25 ng/mL. Groups 1, 2, 3, 4, and 5 consisted of 20, 112, 222, 154, and 24 patients, respectively. The mean PSA values in these age groups were 6.04±3.88 (0.24-16.46) ng/mL, 6.8±4.17 (0.97-35.07) ng/mL, 10.51±8.53 (0.72-128.5) ng/mL, 20.41±36.64 (1.32-250) ng/mL, and 73.28±100.19 (9.33-344.1) ng/mL, respectively (Figure 1). PSA level at time of PSA elevation detection was positively correlated with age (p=0.001).

In group 1, TRUSbP revealed PCa in 6 patients, ciPCa in 1 patient (17%) and csPCa in 5 patients (83%). A detailed examination of the pathology results revealed G3+3 PCa in 3 patients (50%) and G3+4 PCa in 3 patients (50%) (Table 1). In ROC curve analyses, areas under the curve for PCa and csPCa detection were 0.480 (p=0.903) and 0.889 (p=0.043), respectively, and PSA thresholds were determined as 2.21 ng/mL for PCa detection and 7.08 ng/mL for csPCa detection (values providing >80% sensitivity) (Table 2). A free/total PSA ratio threshold value for detecting csPCa at PSA values between these thresholds could not be calculated due to the small number of patients.

In group 2, TRUSbP revealed PCa in 22 patients, ciPCa in 10 patients (45%) and csPCa in 12 patients (55%). Pathology results indicated histological grade of G3+3 in 12 patients, G3+4 in 2 patients, G3+5 in 1 patient, G4+3 in 1 patient, G4+4 in 1 patient, G4+5 in 1 patient, G5+3 in 2 patients, G5+4 in 1 patient, and G5+5 in 1 patient (Table 1). In ROC curve analyses, areas under the curve for PCa and csPCa detection were 0.526 (p=0.068) and 0.621 (p=0.209), respectively, and PSA threshold values were determined as 4.15 ng/mL for PCa detection

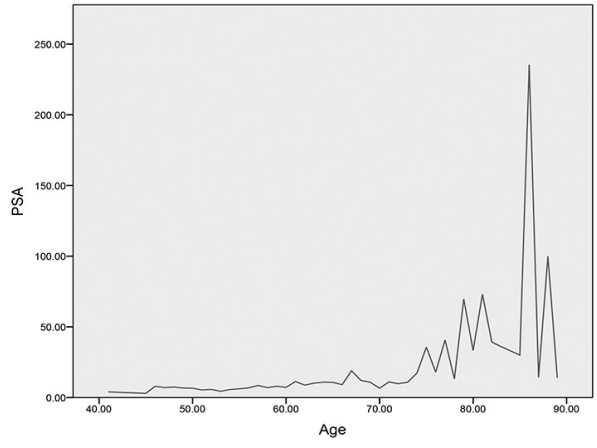

Figure 1. Age-related change in prostate-specific antigen in the presence of prostate cancer in Turkey

PSA: Prostate-specific antigen

Table 1. Age-specific prostate cancer rates in Turkey					
	Age (years)				
	40-49	50-59	60-69	70-79	≥80
Gleason 3+3 + PSA ≤10 ng/mL + ≤2 positive cores	1 (17%)	10 (45%)	12 (21%)	13 (20%)	-
Gleason 3+3 (n, %)	2 (33%)	2 (9%)	10 (17%)	5 (7%)	3 (14%)
Gleason 3+4 (n, %)	3 (50%)	2 (9%)	5 (8%)	10 (15%)	3 (14%)
Gleason 3+5 (n, %)	-	1 (4.5%)	3 (5%)	1 (2%)	-
Gleason 4+3 (n, %)	-	1 (4.5%)	11 (18%)	7 (10%)	1 (5%)
Gleason 4+4 (n, %)	-	1 (4.5%)	3 (5%)	8 (12%)	2 (9%)
Gleason 4+5 (n, %)	-	1 (4.5%)	8 (13%)	7 (10%)	6 (29%)
Gleason 5+3 (n, %)	-	2 (9%)	2 (4%)	2 (3%)	2 (10%)
Gleason 5+4 (n, %)	-	1 (4.5%)	2 (4%)	6 (8%)	4 (19%)
Gleason 5+5 (n, %)	-	1 (4.5%)	2 (4%)	8 (12%)	-
Total (n, %)	6 (100%)	22 (100%)	58 (100%)	67 (100%)	21 (100%)
PSA: Prostate-specific antigen					

and 4.71 ng/mL for csPCa detection (values providing >80% sensitivity) (Table 2). A free/total PSA ratio threshold value for detecting csPCa at PSA values between these thresholds could not be calculated due to the small number of patients.

In group 3, TRUSbP revealed PCa in 58 patients, ciPCa in 12 patients (21%) and csPCa in 46 patients (79%). Detailed evaluation of pathology results revealed histological grade of G3+3 in 22 patients, G3+4 in 5 patients, G3+5 in 3 patients, G4+3 in 11 patients, G4+4 in 3 patients, G4+5 in 8 patients, G5+3 in 2 patients, G5+4 in 2 patients, and G5+5 in 2 patients (Table 1). In ROC curve analyses, areas under the curve for PCa and csPCa detection were 0.681 (p=0.01) and 0.782 (p=0.001), respectively, and PSA threshold values were 6.06 ng/mL for PCa detection and 7.3 ng/mL for csPCa detection (values providing >80% sensitivity) (Table 2). The insufficient number of patients in this group also precluded determination of a free/total PSA ratio threshold value for detecting csPCa at PSA values between these thresholds.

In group 4, TRUSbP revealed PCa in 67 patients, ciPCa in 13 patients (20%) and csPCa in 54 patients (80%). Histological grade according to pathology was G3+3 in 18 patients, G3+4 in 10 patients, G3+5 in 1 patient, G4+3 in 7 patients, G4+4 in 8 patients, G4+5 in 7 patients, G5+3 in 2 patients, G5+4 in 6 patients, and G5+5 in 8 patients (Table 1). In ROC curve analyses, areas under the curve for PCa and csPCa detection were 0.678 (p=0.001) and 0.776 (p=0.001), respectively, and PSA threshold values were determined as 6.12 ng/mL for PCa detection and 8.12 ng/mL for csPCa detection (values providing >80% sensitivity) (Table 2). The free/total PSA ratio threshold value for the detection of csPCa for PSA values between those thresholds was determined to be 0.18 (value providing >80% sensitivity).

In group 5, TRUSbP revealed PCa in 21 patients, all of which were csPCa. Histological grade was G3+3 in 3 patients, G3+4 in 3 patients, G4+3 in 1 patient, G4+4 in 2 patients, G4+5 in 6 patients, G5+3 in 2 patients, and G5+4 in 4 patients (Table 1). ROC curve analysis showed that the area under the curve was 0.775 (p=0.209) and the PSA threshold value was 14.12 ng/mL for the detection of csPCa (values providing >80% sensitivity) (Table 2). Free/total PSA ratio threshold value for csPCa detection could not be determined due to the small number of patients.

Table 2. Age-specific prostate-specific antigen threshold values for prostate cancer detection in Turkey		
	PSA threshold value	
Age (years)	Prostate cancer (ng/mL)	Clinically significant prostate cancer (ng/mL)
40-49	2.21	7.08
50-59	4.15	4.71
60-69	6.06	7.30
70-79	6.12	8.12
≥80*	-	14.12
PSA: Prostate-specific antigen *All patients had clinically significant prostate cancer		

Discussion

The introduction of PSA by Catalona et al. (1) in 1991 resulted in a rapid increase in rates of PCa detection. Following that discovery, large studies related to PSA were planned. The ERSPC commenced in Europe in the same year, and the USA initiated the PLCO Cancer screening trial in 1994. These are the studies currently providing the most extensive information on the utility of PSA monitoring. Another study that also offered valuable data about PSA reported its results around the same time. In a study published by Oesterling et al. (6) in 1993, 2119 healthy males were evaluated between 1989 and 1991 and 471 of the men underwent prostate biopsy. Blood PSA levels were measured and evaluated according to age. They determined that PSA was correlated with age and identified PSA threshold values for PCa detection as 2.5 ng/mL, 3.5 ng/mL, 4.5 ng/mL, and 6.5 ng/mL for the age ranges of 40-49, 50-59, 60-60, and 70-79 years, respectively (6). In 1994, Catalona

et al. (7) accepted >4 ng/mL as the PSA threshold value and investigated its combined use with DRE for the detection of PCa in 6630 volunteers over the age of 50 years. PSA elevation was detected in 15% of the patients, suspicious lesions were detected on DRE in 15%, and both findings were detected in 26% of the patients. PCa detection rates for PSA, DRE, and PSA + DRE were reported to be 4.6%, 3.2%, and 5.8%, respectively (7). In 1998, Catalona et al. (8) investigated free/total PSA ratio and reported a threshold value of 25% for the detection of PCa in patients with PSA levels of 4-10 ng/mL. Trials that began in Europe and the USA in the 1990s began to publish results at the end of the 2000s. In the ERSPC, 162,387 European men were divided into 2 groups, one which underwent PSA screening yearly for 4 years and another which did not undergo screening. Using a PSA threshold value of 2.5 or 3.0 ng/mL, the rate of PCa detection was reported to be 8.2% in the PSA screening group and 4.8% in the non-screened group after 9 years of follow-up (3). After 13 years of follow-up, PCa mortality in the screened group was 21% lower than in the non-screened controls (5). In the PLCO trial, 76,693 men were divided into 2 groups, one which underwent PSA screening yearly for 6 years and a non-screened control group. A PSA threshold value of 4.0 ng/mL was used, and after 7 years of follow-up, the rate of PCa detection was reported to be 116/10,000 in the PSA screening group and 95/10,000 in the control group. PCa mortality rate was 3.7/10,000 in the screened group and 3.4/10,000 in the control group. Differences between the groups were not statistically significant for either evaluation (5). Considering all of these studies together, it is clear that although PSA is integral to current PCa screening, there is no definite PSA threshold value for the detection of PCa. PSA threshold values seem to be determined regionally for each country or continent, and studies are designed according to these values. There are no previous publications that evaluate age-specific PSA threshold values for the detection of PCa, especially csPCa, in Turkey. Therefore, we consider our study to make a valuable contribution to the literature. We also observed a statistically significant positive correlation between PSA level and age in our study. This increase is particularly steep in men over the age of 70. In our study, the age-specific PSA threshold values for the detection of PCa were 2.21 ng/mL, 4.15 ng/mL, 6.06 ng/mL, 6.12 ng/mL, and 14.12 ng/mL for the respective age ranges of 40-49, 50-59, 60-69, 70-79, and ≥80 years.

Research analyzing both PSA and prostatectomy specimens will obviously yield the best evidence regarding the detection of csPCa. In one such study conducted in 2006, Loeb et al. (9) reported that 10% of patients who underwent radical prostatectomy were actually clinically insignificant cases. Recent studies have focused on the detection of csPCa in particular, but analyses of the aforementioned large studies in terms of csPCa have not yet been published. Instead, multiparametric magnetic resonance imaging (MRI) has been used in recent years in an attempt to detect csPCa. Siddiqui et al. (10) reported in a study of 1003 patients that MRI-guided biopsy increased detection rates of high-risk PCa and decreased detection rates of low-risk PCa. However, MRI is an expensive laboratory technique, and determining new PSA threshold values for csPCa should be considered as a more reasonable and inexpensive alternative to using MRI. In our study, the 40-49, 50-59, 60-69, 70-79, and ≥80 year age groups had csPCa ratios of 83%, 55%, 79%, 80%, and 100% and age-specific PSA threshold values for PCa detection of 7.08 ng/mL, 4.71 ng/mL, 7.30 ng/mL 8.12 ng/mL, and 14.52 ng/mL, respectively. In short, the probability of having csPCa increases with age, and PSA threshold values also follow a rising trend. The use of the age-specific PSA threshold values determined in this study will prevent unnecessary biopsies.

For uncertain cases with PSA values between the threshold values that we determined for PCa and csPCa, we thought of using free/total PSA ratio as a marker. However, we were unable to perform calculations for the 40-49, 50-59, 60-69, and ≥80 age groups because the patient numbers were insufficient. We determined a free/total PSA ratio threshold value of 18% for the 70-79 year age group.

Assessing area under the curve in ROC curve analysis is another method of showing how useful a test is. Studies involving ROC curve analysis are generally intended to evaluate the role of PSA in the detection of PCa. ROC areas under the curve for PSA have been reported as 0.63 by Wang et al. (11), 0.83 by Ma et al. (12), and 0.80 by Lee et al. (13). No previous studies have examined the ROC area under the curve based on age. The areas under the curve in our ROC curve analyses using PSA for PCa detection were 0.480, 0.526, 0.681, 0.678, and 0.775 for the age ranges of 40-49, 50-59, 60-69, 70-79, and ≥80 years, respectively. This shows that the use of PSA for the detection of PCa becomes increasingly significant with age, and consistent with the literature, leads to the conclusion that PSA is important for PCa detection. Furthermore, there are no studies in the literature that evaluate the ROC area under the curve with the aim of detecting csPCa. Our study is a first in the international literature in this respect. In our study, the areas under the curve in ROC curves created using PSA for the detection of csPCa were 0.889, 0.621, 0.782, 0.776, and 0.775 for the age ranges of 40-49, 50-59, 60-69, 70-79, and ≥80 years, respectively. Thus, we have shown that the area under the curve is larger when using PSA for the detection of csPCa rather than PCa, and that the use of PSA for csPCa is more meaningful.

Study Limitations

The most important limitations of this study are its retrospective design and the small number of patients, especially in the 40-49 years and ≥80 years age groups. Another limitation is that although the literature emphasizes the importance of detecting csPCa, PSA is still used for PCa screening. For this reason, the use of PSA solely for csPCa is controversial. The fact that our study was conducted in the province of Ankara and does not directly represent the whole of Turkey can be considered another limitation. However, according to population data, the Ankara province receives the most immigration after Istanbul. Therefore, we believe the province of Ankara provides a good reflection of Turkey overall, and the title was written accordingly.

Conclusion

PSA levels increase with age in Turkey, and using the PSA threshold values determined in this study for the detection of csPCa may prevent unnecessary biopsies.

Ethics

Ethics Committee Approval: Approval was obtained from the University of Health Sciences, Gülhane Training and Research Hospital Ethics Committee (no: 18/44).

Informed Consent: It was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

Conflict of Interest: No conflict of interest was declared by the authors.

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Orijinal Makale / *Original Article*

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Türkiye'de Klinik Önemli Prostat Kanseri Saptamada Yaşa Göre Prostat Spesifik Antijen Eşik Değerleri Ne Olmalıdır?

What is the Prostate-Specific Antigen Cut-Off Value to Detect Clinically Significant Prostate Cancer According to Age in Turkey?

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Öz

Amaç: Türkiye'de klinik önemli prostat kanseri (KÖPK) saptanmasında kullanılabilecek yaşa göre prostat spesifik antijen (PSA) eşik değerlerini saptamayı amaçladık.

Gereç ve Yöntem: Ocak 2011 ile Ocak 2018 yılları arasında PSA yüksekliği tespit edilmiş veya parmakla rektal muayenede anormal bulgular saptanmış ve sonrasında transrektal ultrason prostat biyopsisi uygulanmış 532 hastanın verileri retrospektif olarak değerlendirildi. PSA yüksekliği tanımı "PSA ≥4 ng/mL" olarak belirlendi. Hastalar yaş grubuna göre; grup 1: 40-49 yaş arası, grup 2: 50-59 yaş arası, grup 3: 60-69 yaş arası, grup 4: 70-79 yaş arası ve grup 5: ≥80 yaş üstü olarak sınıflandırıldı. Belirlenen gruplardaki KÖPK saptanması için PSA eşik değerleri belirlendi.

Bulgular: Hastaların ortalama yaşı 66,45±8,21 yıl (41-89) olarak tespit edildi. Grup 1, 2, 3, 4 ve 5'te sırası ile 20, 112, 222, 154 ve 24 hasta mevcut idi. Grup 1, 2, 3, 4 ve 5'te ortalama PSA değerleri sırası ile 6,04±3,88 (0,24-16,46) ng/mL, 6,8±4,17 (0,97-35,07) ng/mL, 10,51±8,53 (0,72-128,5) ng/mL, 20,41±36,64 (1,32-250) ng/mL ve 73,28±100,19 (9,33-344,1) ng/mL olarak tespit edildi. Grup 1, 2, 3, 4 ve 5'te KÖPK saptanmasındaki PSA eşik değerleri 7,08 ng/mL, 4,71 ng/mL, 7,30 ng/mL, 8,12 ng/ml ve 14,12 ng/mL olarak saptandı.

Sonuç: Türkiye'de PSA değeri yaş ile artış göstermektedir ve KÖPK saptanması için belirttiğimiz PSA eşik değerlerinin kullanılması gereksiz biyopsileri önleyebilecektir.

Anahtar Kelimeler: Prostat spesifik antijen, Türkiye, prostat kanseri

Abstract

Objective: To detect a prostate-specific antigen (PSA) cut-off for clinically significant prostate cancer (csPCa) according to age in Turkey.

Materials and Methods: A total of 532 men who had transrectal ultrasound-guided biopsy of the prostate due to elevated PSA and abnormal findings on digital rectal examination between January 2011 and January 2018 were retrospectively evaluated. Elevated PSA was defined as ≥4 ng/mL. Patients were divided into groups 1-5 according to age: 40-49, 50-59, 60-69, 70-79, and ≥80 years. A PSA cut-off value was determined for each group.

Results: The mean age was 66.45±8.21 (41-89) years. There were 20, 112, 222, 154, and 24 patients in groups 1-5, respectively. Mean PSA values were 6.04±3.88 (0.24-16.46) ng/mL, 6.8±4.17 (0.97-35.07) ng/mL, 10.51±8.53 (0.72-128.5) ng/mL, 20.41±36.64 (1.32-250) ng/mL, and 73.28±100.19 (9.33-344.1) ng/mL in groups 1-5, respectively. PSA cut-off values for csPCa were 7.08 ng/mL, 4.71 ng/mL, 7.30 ng/mL, 8.12 ng/mL, and 14.12 ng/mL in groups 1-5, respectively.

Conclusion: There is a correlation between PSA and age in Turkey. Using the PSA cut-off values determined in our study would decrease the number of unnecessary biopsy procedures.

Keywords: Prostate-specific antigen, Turkey, prostate cancer

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Giriş

Prostat kanseri (PK) erkeklerde bir yıllık süre içerisinde en sık saptanan ve akciğerin küçük hücreli karsinomundan sonra ikinci sık olarak erkek birey ölümüne neden olan kanser türü olarak rapor edilmektedir. 1991 yılında Catalona ve ark. (1) tarafından prostat spesifik antijenin (PSA) ilk defa dünyaya tanıtılmasından sonra PK saptanma oranı hızla artmıştır. 1994 yılında PSA'nın Amerika Gıda ve İlaç İdaresi tarafından kanser saptanması amacı ile kullanımı onaylanmıştır (2). PSA'nın 1 ile 4 ng/mL arası değerlerde olduğunda PK saptamasındaki duyarlılık ve özgüllük değerleri; PSA 1 ng/mL iken %83 ve %3, 2,1 ng/mL iken %52 ve %72, 3,1 ng/mL iken %32 ve %86, 4,1 ng/mL iken %20 ve %94 olarak rapor edilmiştir (2). Bu değerlere göre düşük eşik değeri kullanılması artmış PK saptanma oranına neden olacaktır. Bunun yanında klinik önemsiz kanserlerin saptanma oranı da artacaktır. Düşük eşik değeri aynı zamanda düşük özgüllük değerlerine neden olacak ve bu değerle de PK dışlaması yapılamayacaktır.

Dünyada çeşitli PSA eşik değerleri kullanılmaktadır. Geniş hasta sayılı serilerde Avrupa "The European Randomized Study of Screening for Prostate Cancer (ERSPC)" çalışmasında 2,5 veya 3,0 ng/mL değerlerini eşik değer olarak kullanmış (3), Amerika Birleşik Devletleri (ABD) "Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)" çalışmasında 4,0 ng/mL değerini kullanmıştır (4). ERSPC'nin "Gotheborg Çalışması" olarak adlandırdığı İsveç kolunda 1993-1998 yılları arasında 3,4 ng/mL değeri, sonrasında 2,5 ng/mL değeri kullanılmıştır (5). 1993 yılında Oesterling ve ark. (6) ABD'de 537 hastalık serilerinde PK saptanmasında PSA'nın yaşa göre eşik değerlerini araştırmış ve 40-49, 50-59, 60-69, 70-79 yaş aralıkları için PSA eşik değerlerini 2,5 ng/mL, 3,5 ng/mL, 4,5 ng/mL, 6,5 ng/mL olarak rapor etmişlerdir.

Görüldüğü gibi her ülke PK saptamasında kendi eşik değerini kullanmaktadır. Bunun yanında saptanmış PSA eşik değerleri klinik önemli PK (KÖPK) saptamasını değil, genel PK saptamasını amaçlar niteliktedir. Biz bu çalışmamızda Türkiye'de KÖPK saptanmasında kullanılabilecek yaşa göre PSA eşik değerlerini saptamayı amaçladık.

Gereç ve Yöntem

Sağlık Bilimleri Üniversitesi, Gülhane Eğitim ve Araştırma Hastanesi Etik Kurulu'ndan (no: 18/44) etik kurul onayının alınmasını takiben istatistiksel olarak güç analizi uygulandı ve 385 hasta ile çalışmanın yapılabileceği görüldü. Hastaların onamı alındı. Ardından Ocak 2011 ile Ocak 2018 yılları arasında PSA yüksekliği tespit edilmiş veya parmakla rektal muayenede (PRM) anormal bulgular saptanmış ve sonrasında transrektal ultrason prostat biyopsisi (TRUSbP) uygulanmış 532 hastanın verileri retrospektif olarak değerlendirildi. PSA yüksekliği tanımı "PSA ≥4 ng/mL" olarak belirlendi. PSA yüksekliği tespit edilmiş hastalar 2 hafta boyunca oral antibiyoterapi ile tedavi edilerek bakteriyel prostatit ihtimali dışlandı. Ardında hastalardan ikinci kez kan numunesi alınarak PSA yüksekliğinin devam edip etmediği teyit edildi. Bu seansta hastalarda serbest PSA ölçümü de yapıldı. PSA yüksekliği halen devam eden hastalar TRUSbP'ye yönlendirildi. TRUSbP dışlama kriteri olarak "hastanın yaşam beklentisinin <10 yıl olması" kuralı uygulandı.

TRUSbP hem aksiyal hem sagittal görüntü veren özel bir ultrason cihazı kullanılarak uygulandı (Logiq 5). Standart olarak en az 12 ayrı noktadan 18-gauge Tru-Cut (UK Medical) prostat iğnesi kullanılarak prostat biyopsi örneği alındı.

Klinik önemsiz PK (KÖsizPK) PSA ≤10 ng/mL + Gleason (G) skoru ≤3+3+ tümörlü kor sayısı ≤2 olan hastalar tanımlandı. Yukarıdaki kriterlerden daha yüksek değerlere sahip hastalar KÖPK'ye sahip hastalar olarak tanımlandı.

Hastalar yaş grubuna göre; grup 1: 40-49 yaş arası, grup 2: 50-59 yaş arası, grup 3: 60-69 yaş arası, grup 4: 70-79 yaş arası ve grup 5 ≥80 yaş üstü olarak sınıflandırıldı. Belirlenen gruplardaki PK ve KÖPK saptanması için PSA eşik değerleri belirlendi. PK ve KÖPK için PSA eşik değerleri belirlenmesini müteakip, bu iki değer arasındaki değerler için serbest PSA/PSA oranı eşik değeri belirlendi.

İstatistiksel Analiz

İstatistiksel analiz "Statistical Package for Social Sciences 20.0 software (SPSS 20.0 for Mac)" isimli program kullanılarak yapıldı. Tanımlayıcı istatistikler ortalama (minimum-maksimum), frekans ve yüzdeler kullanılarak sunuldu. Verilerin normal dağılıma uyup uymadığını değerlendirmek amacı ile Kolmogorov-Smirnov, Shapiro-Wilk, Kurtosis ve Skewness testleri kullanıldı. İki sürekli değişken arasında korelasyon olup olmadığını değerlendirmek amacı ile Pearson korelasyon testi kullanıldı. Her yaş grubuna göre PSA kullanılarak alıcı işlem karakteristikleri (ROC) eğrisi oluşturuldu. Bu ROC eğriler kullanılarak PK ve KÖPK saptanması için PSA eşik değerleri belirlendi. P<0,05 istatistiksel anlamlı olarak tanımlandı.

Bulgular

Toplam 532 hastanın verileri incelendi. Hastaların ortalama yaşı 66,45±8,21 yıl (41-89) olarak tespit edildi. Hastaların ortalama ve ortanca PSA değerleri 15,13±5,21 (0,29-344,1) ng/mL ve 7,25 ng/mL olarak tespit edildi. Grup 1, 2, 3, 4 ve 5'te sırası ile 20, 112, 222, 154 ve 24 hasta mevcut idi. Ortalama PSA değerleri sırası ile 6,04±3,88 (0,24-16,46) ng/mL, 6,8±4,17 (0,97-35,07) ng/mL, 10,51±8,53 (0,72-128,5) ng/mL, 20,41±36,64 (1,32-250) ng/mL ve 73,28±100,19 (9,33-344,1) ng/mL olarak tespit edildi (Şekil 1). PSA yüksekliği

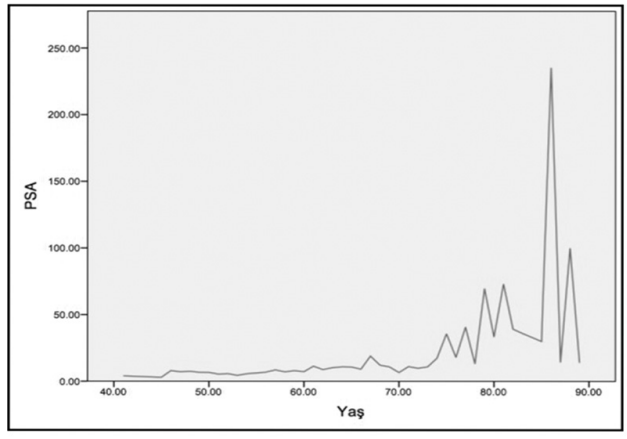
saptanma anındaki PSA değerlerinin yaş ile kolere olarak arttığı tespit edildi (p=0,001).

TRUSbP sonrası grup 1'de 6 hastada PK, 1 hastada (%17) KÖsizPK, 5 hastada (%83) KÖPK saptandı. Patoloji sonuçları detaylı incelendiğinde 3 hastada (%50) G3+3, 3 hastada (%50) G3+4 PK saptandığı tespit edildi (Tablo 1). ROC eğrisi analizleri değerlendirildiğinde eğri altında kalan alanın PK ve KÖPK saptamada sırası ile 0,480 (p=0,903) ve 0,889 (p=0,043) olduğu ve PSA eşik değerlerinin PK tespiti için 2,21 ng/mL, KÖPK tespiti için 7,08 ng/mL (>%80 sensitivite sağlayan değerler) olduğu saptandı (Tablo 2). Bu değerler arasında kalan PSA değerleri için KÖPK saptamada serbest PSA/PSA oranı eşik değeri hasta sayısının az olmasından dolayı hesaplanamadı.

TRUSbP sonrası grup 2'de 22 hastada PK, 10 hastada (%45) KÖsizPK, 12 hastada (%55) KÖPK saptandı. Patoloji sonuçları detaylı incelendiğinde 12 hastada G3+3, 2 hastada G3+4, 1 hastada G3+5, 1 hastada G4+3, 1 hastada G4+4, 1 hastada G4+5, 2 hastada G5+3, 1 hastada G5+4 ve 1 hastada G5+5 PK saptandığı tespit edildi (Tablo 1). ROC eğrisi analizleri değerlendirildiğinde eğri altında kalan alanın PK ve KÖPK saptamada sırası ile 0,526 (p=0,068) ve 0,621 (p=0,209) olduğu ve PSA eşik değerlerinin PK tespiti için 4,15 ng/mL, KÖPK tespiti için 4,71 ng/mL (>%80 sensitivite sağlayan değerler) olduğu saptandı (Tablo 2). Bu değerler arasında kalan PSA değerleri için KÖPK saptamada serbest PSA/PSA oranı eşik değeri hasta sayısının az olmasından dolayı hesaplanamadı.

TRUSbP sonrası grup 3'te 58 hastada PK, 12 hastada (%21) KÖsizPK, 46 hastada (%79) KÖPK saptandı. Patoloji sonuçları detaylı incelendiğinde 22 hastada G3+3, 5 hastada G3+4, 3 hastada G3+5, 11 hastada G4+3, 3 hastada G4+4, 8 hastada G4+5, 2 hastada G5+3, 2 hastada G5+4 ve 2 hastada G5+5 PK saptandığı tespit edildi (Tablo 1). ROC eğrisi analizleri değerlendirildiğinde eğri altında kalan alanın PK ve KÖPK saptamada sırası ile 0,681 (p=0,01) ve 0,782 (p=0,001) olduğu ve PSA eşik değerlerinin PK tespiti için 6,06 ng/mL, KÖPK tespiti için 7,3 ng/mL (>%80 sensitivite sağlayan değerler) olduğu saptandı (Tablo 2). Bu değerler arasında kalan PSA değerleri için KÖPK saptamada serbest PSA/PSA oranı eşik değeri hasta sayısının az olmasından dolayı hesaplanamadı.

TRUSbP sonrası grup 4'te 67 hastada PK, 13 hastada (%20) KÖsizPK, 54 hastada (%80) KÖPK saptandı. Patoloji sonuçları detaylı incelendiğinde 18 hastada G3+3, 10 hastada G3+4, 1 hastada G3+5, 7 hastada G4+3, 8 hastada G4+4, 7 hastada G4+5, 2 hastada G5+3, 6 hastada G5+4 ve 8 hastada G5+5 PK saptandığı tespit edildi (Tablo 1). ROC eğrisi analizleri değerlendirildiğinde eğri altında kalan alanın PK ve KÖPK saptamada sırası ile 0,678 (p=0,001) ve 0,776 (p=0,001) olduğu ve PSA eşik değerlerinin PK tespiti için 6,12 ng/mL, KÖPK tespiti



Şekil 1. Türkiye'de prostat kanseri varlığında yaşa göre prostat spesifik antijen değişimi

PSA: Prostat spesifik antijen

Tablo 1. Türkiye'de yaşa göre prostat kanseri oranları

	Yaş				
	40-49	**50-59**	**60-69**	**70-79**	**≥80**
Gleason 3+3 + PSA ≤10 ng/mL + tümörlü kor sayısı ≤2	1 (%17)	10 (%45)	12 (%21)	13 (%20)	-
Gleason 3+3 (n, %)	2 (%33)	2 (%9)	10 (%17)	5 (%7)	3 (%14)
Gleason 3+4 (n, %)	3 (%50)	2 (%9)	5 (%8)	10 (%15)	3 (%14)
Gleason 3+5 (n, %)	-	1 (%4,5)	3 (%5)	1 (%2)	-
Gleason 4+3 (n, %)	-	1 (%4,5)	11 (%18)	7 (%10)	1 (%5)
Gleason 4+4 (n, %)	-	1 (%4,5)	3 (%5)	8 (%12)	2 (%9)
Gleason 4+5 (n, %)	-	1 (%4,5)	8 (%13)	7 (%10)	6 (%29)
Gleason 5+3 (n, %)	-	2 (%9)	2 (%4)	2 (%3)	2 (%10)
Gleason 5+4 (n, %)	-	1 (%4,5)	2 (%4)	6 (%8)	4 (%19)
Gleason 5+5 (n, %)	-	1 (%4,5)	2 (%4)	8 (%12)	-
Toplam (n, %)	6 (%100)	22 (%100)	58 (%100)	67 (%100)	21 (%100)

PSA: Prostat spesifik antijen

Tablo 2. Türkiye'de yaşa göre prostat kanseri saptamada prostat spesifik antijen eşik değerleri

	PSA eşik değeri	
Yaş (yıl)	**Prostat kanseri için (ng/mL)**	**Klinik önemli prostat kanseri için (ng/mL)**
40-49	2,21	7,08
50-59	4,15	4,71
60-69	6,06	7,30
70-79	6,12	8,12
≥80*	-	14,12

PSA: Prostat spesifik antijen
*Tüm hastalar klinik önemli prostat kanserine sahiptir

için 8,12 ng/mL (>%80 sensitivite sağlayan değerler) olduğu saptandı (Tablo 2). Bu değerler arasında kalan PSA değerleri için KÖPK saptamada serbest PSA/PSA oranı eşik değerinin 0,18 olduğu tespit edildi (>%80 sensitivite sağlayan değerler).

TRUSbP sonrası grup 5'te 21 hastada PK saptandı. Bu hastaların hepsinin KÖPK'ye sahip olduğu gözlendi. Patoloji sonuçları detaylı incelendiğinde 3 hastada G3+3, 3 hastada G3+4, 1 hastada G4+3, 2 hastada G4+4, 6 hastada G4+5, 2 hastada G5+3 ve 4 hastada G5+4 PK saptandığı tespit edildi (Tablo 1). ROC eğrisi analizleri değerlendirildiğinde eğri altında kalan alanın KÖPK saptamada 0,775 (p=0,209) olduğu ve PSA eşik değerlerinin KÖPK tespiti için 14,12 ng/mL (>%80 sensitivite sağlayan değerler) olduğu saptandı (Tablo 2). Bu değerler arasında kalan PSA değerleri için KÖPK saptamada serbest PSA/PSA oranı eşik değeri hasta sayısının az olmasından dolayı hesaplanamadı.

Tartışma

1991 yılında Catalona ve ark.'nın (1) PSA'yı dünyaya ilk kez tanıtmaları sonrasında PK saptanma oranı hızla artmaya başlamıştır. Bu tarihten sonra PSA ile ilgili geniş çalışmalar planlanmıştır. Aynı yıl Avrupa ülkeleri ERSPC çalışmasına başlamış, ABD ise 1994 yılında PLCO çalışmasına başlamıştır. Bu çalışmalar günümüzde PSA takibinin yapılmasının uygun olup olmadığı konusunda insanlığa en geniş bilgileri sunan çalışmalardır. Aynı zamanlarda PSA ile ilgili değerli veriler sunan başka bir çalışma da sonuçlarını rapor etmiştir. Oesterling ve ark. (6) tarafından 1993 yılında literatüre sunulan bu çalışmada 1989 ile 1991 yılları arasında 2119 sağlıklı erkek ele alınmış ve bunların 471 tanesine prostat biyopsisi uygulanmıştır. Bu hastaların alınmış olan kanlarında PSA değerleri ölçülmüş ve yaşa göre değerlendirilme yapılmıştır. PSA'nın yaş ile kolere olduğu ve yaşa göre PK saptanmasındaki PSA eşik değerlerinin 40-49, 50-59, 60-60, 70-79 yaş aralıkları için 2,5 ng/mL, 3,5 ng/mL, 4,5 ng/mL, 6,5 ng/mL olduğu rapor edilmiştir (6). Catalona ve ark. (7) 1994 yılında PSA eşik değerini >4 ng/mL olarak kabul etmiş ve PRM ile kombine kullanımının PK saptamadaki yerini araştırmıştır. Bu yayında 50 yaş üzeri 6630 gönüllü ele alınmış; %15 hastada PSA yüksekliği, %15 hastada PRM'de şüpheli lezyon, %26 hastada her ikisi birden saptanmıştır. PSA yüksekliği, PRM ve ikisinin kombine kullanımının PK saptama oranı %4,6, %3,2, %5,8 olarak rapor edilmiştir (7). Catalona ve ark. (8) 1998 yılında serbest/total PSA oranını incelemiş ve PSA 4-10 ng/mL arasında olduğu durumlarda PK saptanması için serbest PSA/PSA oranı eşik değerinin %25 olduğunu rapor etmişlerdir. Avrupa'da ve ABD'de 1990'lı yıllarda başlayan çalışmaların sonuçları 2000'li yılların sonunda yayınlanmaya başlanmıştır. ERSPC çalışmasında Avrupa ülkelerinde 162,387 erkek 4 yıl yılda bir kez PSA taraması yapılan ve bu taramanın yapılmadığı 2 gruba ayrılmıştır. PSA eşik değeri olarak 2,5 veya 3,0 ng/mL kullanılmış ve 9 yıllık takip sonrasında PSA taramasının yapıldığı grupta PK saptanma oranı %8,2, PSA taramasının yapılmadığı grupta %4,8 olarak rapor edilmiştir (3). On üç yıllık takip sonrasında tarama yapılan grupta %21 oranında PK mortalitesinde azalma saptanmıştır (5). PLCO çalışmasında 76,693 erkek 6 yıl boyunca yılda bir kez PSA taraması yapılan ve bu taramanın yapılmadığı 2 gruba ayrılmıştır. PSA eşik değeri olarak 4,0 ng/mL kullanılmış ve 7 yıllık takip sonrası PSA taramasının yapıldığı grupta PK saptanma oranı 116/10,000, taramanın yapılmadığı grupta PK saptanma oranı 95/10.000 olarak rapor edilmiştir. PK mortalite oranları değerlendirildiğinde ise tarama yapılan ve yapılmayan grupta 3,7/10000 ve 3,4/10000 olarak rapor edilmiştir. Her iki incelemede de farkın istatistiksel anlamlı olmadığı rapor edilmiştir (5). Tüm bu çalışmalar düşünüldüğünde PSA'nın günümüzde PK taraması için gerekli olduğu, ancak PK saptanması için net bir PSA eşik değerinin olmadığı anlaşılmaktadır. Aynı zamanda her ülke ya da kıtanın kendi PSA eşik değerini belirleyip çalışmalarını o değere göre dizayn ettiği görülmektedir. Türkiye'de PK ve özellikle KÖPK saptanmasında PSA eşik değerini yaşa göre değerlendiren bir yayın bulunmamaktadır. Bu nedenle mevcut çalışmamızı değerli bir çalışma olarak nitelendirmekteyiz. Bizim çalışmamızda da PSA değeri yaş ile orantılı olarak istatistiksel anlamlı artış göstermektedir. Bu artış özellikle 70 yaş üzerinde daha yüksek bir ivme göstermektedir. Bizim çalışmamızda yaşa göre PK saptanmasındaki PSA eşik değerlerinin 40-49, 50-59, 60-69, 70-79 ve ≥80 yaş aralıkları için 2,21 ng/mL, 4,15 ng/mL, 6,06 ng/mL, 6,12 ng/mL ve 14,12 ng/mL olduğu gösterilmiştir.

Düşünüldüğünde KÖPK saptanmasında ideal yayının PSA ile prostatektomi materyallerinin incelenmesinde doğacağı kolayca fark edilir. Bu şekilde tasarlanarak 2006 yılında Loeb ve ark. (9) yaptığı bir çalışmada radikal prostatektomi uygulanmış hastaların %10'unun aslında klinik önemsiz olduğu rapor edilmiştir. Son yıllarda yapılan çalışmalarda özellikle KÖPK saptanması hedeflenmektedir, ancak yukarıda bahsettiğimiz geniş hasta sayılı çalışmaların KÖPK yönünden değerlendirilmesi

henüz literatüre sunulmamıştır. Bunun yerine son yıllarda KÖPK saptanmasında multiparametrik manyetik rezonans görüntüleme (MRI) kullanılmaya çalışılmaktadır. Siddiqui ve ark. (10) 1003 hastalı çalışmasında MRI kullanılarak yapılan biyopsinin yüksek riskli PK saptanmasını artırdığını, düşük riskli PK saptanma oranını ise azalttığını rapor etmiştir. Ancak, MRI pahalı bir laboratuvar yöntemidir ve MRI yerine KÖPK için yeni PSA eşik değerleri belirlemek daha akılcı ve ucuz bir yöntem olarak düşünülmelidir. Bizim çalışmamızda yaşa göre KÖPK oranları 40-49, 50-59, 60-69, 70-79, ve ≥80 yaş aralıkları için %83, %55, %79, %80, %100 ve yaşa göre PK saptanmasındaki PSA eşik değerleri 7,08 ng/mL, 4,71 ng/mL, 7,30 ng/mL, 8,12 ng/mL ve 14,52 ng/mL olarak saptanmıştır. Özet olarak yaş arttıkça KÖPK yakalama ihtimali artmakta, bununla birlikte PSA eşik değerleri de kabaca artmaktadır. Saptamış olduğumuz yaşa göre PSA eşik değerlerinin kullanılması gereksiz biyopsileri önleyecektir.

Öte yandan PK ve KÖPK için saptadığımız PSA eşik değerleri arasında kalan değerler için serbest PSA/PSA oranı kullanmayı düşündük. Ancak 40-49, 50-59, 60-69 ve ≥80 yaş aralıkları için hasta sayımız yetersiz olduğu için hesaplama yapamadık. Yetmiş ile yetmiş dokuz yaş aralığı için ise serbest PSA/PSA oranı eşik değerini %18 olarak saptadık.

ROC eğrisi altında kalan alanın değerlendirilmesi ise bir tetkikin ne kadar yararlı bir tetkik olduğunu gösteren diğer bir yöntemdir. ROC eğrisi içeren çalışmalar genellikle PSA'nın PK saptamasındaki yerini incelemeye yöneliktir. Wang ve ark. (11) PSA kullanarak geliştirdikleri ROC eğrisinde eğri altında kalan alanın 0,63 olduğunu, Ma ve ark. (12) 0,83 olduğunu, Lee ve ark. (13) 0,80 olduğunu rapor etmişlerdir. Yaşa göre ROC eğrisi altında kalan alanı inceleyen bir yayın bulunmamaktadır. Biz çalışmamızda PK saptamasında PSA kullanılarak oluşturulan ROC eğrilerinin altında kalan alanları değerlendirdiğimizde 40-49, 50-59, 60-69, 70-79 ve ≥80 yaş aralıkları için sırası ile 0,480, 0,526, 0,681, 0,678 ve 0,775 olduğunu saptadık. Yani yaş ilerledikçe PSA'nın PK saptanmasında kullanımının anlamlılığı da artmaktadır ve literatür ile benzer olarak PSA'nın PK saptanmasında önemli olduğu sonucuna varılmaktadır. Öte yandan literatürde ROC eğrisi altında kalan alanı KÖPK saptamak amacı ile değerlendiren bir çalışma da bulunmamaktadır. Bizim çalışmamız bu açıdan dünyada bir ilktir. Çalışmamızda KÖPK saptanmasında PSA kullanılarak oluşturulan ROC eğrilerinde eğri altında kalan alanların 40-49, 50-59, 60-69, 70-79, ve ≥80 yaş aralıkları için sırası ile 0,889, 0,621, 0,782, 0,776, ve 0,775 olduğunu saptadık. Böylece, PSA'nın PK değil de KÖPK saptanması amacıyla kullanımı ile eğri altında kalan alanların arttığını ve PSA'nın KÖPK için kullanımının daha anlamlı bir yöntem olduğunu ortaya koyduk.

Çalışmanın Kısıtlılıkları

Olgu sayımızın özellikle 40-49 ve ≥80 yaş aralıklarında az olması ve çalışmamızın retrospektif olması en önemli dezavantajımızdır. Bir diğer kısıtlılık da literatürlerin KÖPK saptanmasının önemini vurgulamasına rağmen PSA'nın halen PK taraması için kullanılmasıdır. Bu nedenle PSA'nın sadece KÖPK için kullanımı tartışmaya açık bir konudur. Diğer bir kısıtlılık olarak da çalışmamızın Ankara ilinde yapılması ve tüm Türkiye'yi yansıtmaması düşünülebilir. Ancak nüfus verilerine göre Ankara ili İstanbul'dan sonra en çok göç alan ilimizdir. Bu durum göz önüne alınarak Ankara ilinin tüm Türkiye'yi yansıtabileceği düşünülmüş ve konunun başlığı o şekilde tasarlanmıştır.

Sonuç

Türkiye'de PSA değeri yaş ile artış göstermektedir ve KÖPK saptanması için belirttiğimiz PSA eşik değerlerinin kullanılması gereksiz biyopsileri önleyebilecektir.

Etik

Etik Kurul Onayı: Sağlık Bilimleri Üniversitesi, Gülhane Eğitim ve Araştırma Hastanesi'nden etik kurul onayı alınmıştır (no: 18/44).

Hasta Onayı: Hastaların onamı alındı.

Hakem Değerlendirmesi: Editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

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Long-Term Outcomes of Patients Who Underwent Ureterocutaneostomy

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Abstract

Objective: Ureterocutaneostomy (UCS) is a urinary diversion (UD) method which is used rarely in a carefully selected patient group. In this study, we aimed to present the data and long-term outcomes of patients who underwent UCS treatment in our clinic.

Materials and Methods: A total of 36 patients who underwent UCS between January 2000 and December 2017 were included in the study. All patients had unilateral or bilateral ureteral-skin anastomosis. The demographic data, diagnoses, comorbidities, side of UCS (unilateral-bilateral), anesthesia method, operation time, and complications of the patients were recorded from the hospital registry system. The complications and survival status of the patients until the study date were evaluated. The study data were presented as mean (minimum-maximum) and number (percent).

Results: Mean follow-up time was 128.5 (8-192) months. The mean American Society of Anesthesiologists score was 3.25. The patients had significant comorbidities, mainly hypertension, chronic obstructive pulmonary disease, and coronary artery disease. UCS was performed most frequently after radical cystectomy due to muscle-invasive bladder tumour (75%) and was usually bilateral (75%). The most common indications for UCS were significant comorbidities (55%). Only 3 (8.33%) patients developed ureteral-skin anastomosis, 6 (16.66%) patients developed pyelonephritis, and 9 patients died during the follow-up period.

Conclusion: Although UCS is not a first-line UD method, it should still be kept in mind in the 21st century for patients unable to tolerate segment excision from the gastrointestinal tract and postoperative complications due to comorbidities.

Keywords: Ureterocutaneostomy, urinary diversion, bladder tumour, survival, complication

Introduction

Ureterocutaneostomy (UCS) was first described by Johnston (1) 40 years ago as a bilateral end-to-end cutaneous ureterostomy for urinary diversion (UD). Johnston initially described it as a diversion method for children with congenital urinary obstruction, and it was later used in adults with pelvic malignancy.

Bladder tumors are the fourth most common tumor in men and the second most prevalent of all genitourinary system tumors. At time of diagnosis, 20-25% of tumors are muscle-invasive. The gold standard treatment of muscle-invasive tumors includes radical cystectomy, extended lymph node dissection, and UD (2). Surgery for invasive bladder cancer may be conducted for curative or palliative purposes. If a palliative intervention is planned, the simplest and quickest method of diversion is best.

UD was first described by Simon (3) in 1852, and after the ileal conduit (IC) technique was popularized by Bricker (4) in 1950, this technique became a standard treatment method. UD is not practiced only after cystectomy, but is also used in cases of neurogenic bladder and congenital anomalies of the bladder. UD procedures performed for these reasons do not require cystectomy. The abdominal wall, urethra, and rectosigmoid colon are the main sites involved in UD (5). The patient's general health status, disease-specific health condition, expectations

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of postoperative quality of life, and renal function are factors evaluated when choosing UD type. Orthotopic ileal neobladder substitution seems to be the method that best complies with the physiological anatomy and provides the patient with the best outcomes in terms of quality of life and cosmesis. However, this method has some drawbacks. The main disadvantages of orthotopic substitution include the presence of a locally advanced bladder tumor and involvement of the urethra or bladder neck, long-term complication rates, the possible need for clean intermittent catheterization, and being a long and technically difficult surgical procedure. In such cases, incontinent UD types such as IC and UCS serve as alternative methods. As UCS does not involve taking a segment from the gastrointestinal system (GIS), patients are spared the potential adverse effects of this additional intervention. In particular, UCS is preferable as palliative treatment in cases with significant comorbidities, limited life expectancy, history of or plan for future intestinal radiotherapy (RT), or comorbid intestinal pathologies (ulcerative colitis, Crohn's disease) (6). In this study, we aimed to evaluate the long-term results of patients who underwent UCS in our clinic between 2000 and 2016.

Materials and Methods

Patient Selection and Data Collection

A total of 36 patients who underwent UCS between January 2000 and December 2017 were included in the study. Patients' demographic data, diagnoses, additional diseases, side of UCS (unilateral or bilateral), anesthesia method, operation time, and complications were recorded from the hospital records system. Signed informed consent forms were obtained from all patients for the UCS procedure. Postoperative complications and survival data until the date of the study were recorded. The study was designed in accordance with the Declaration of Helsinki and because the study was retrospective, ethics committee approval was not obtained.

Ureterocutaneostomy Procedure

Patients were operated in the supine position under general anesthesia or with a combination of epidural and spinal anesthesia. A median incision was made. The ureters were bilaterally (or unilaterally) dissected down to the ureterovesical junction and cut and spatulated after this point. A 4 Fr ureteral catheter was inserted into the ureter lumen and fixed with 2/0 Vicryl Rapide sutures from the middle of the ureter. The ureters were extruded from the skin lateral to the rectus muscle and fixed on the rectus abdominis fascia with 4/0 Vicryl sutures at 12, 3, 6, and 9 o'clock approximately 3.5 cm proximally from the endpoint. The distal end of the ureter was also fixed to the skin with 4/0 Vicryl sutures from four quadrants. Immediately after the procedure, the UCS orifices were taken into the stoma in the operation room. The ureteral catheters were removed on postoperative day 10.

The study data were expressed as means (minimum-maximum) and numbers (percentage).

Results

The mean age of the patients was 74.4 years and 66.7% were male. The mean follow-up period was 128.5 months (range 8-192 months). Patients were at moderate to high risk regarding anesthesia, with a mean American Society of Anesthesiologists (ASA) score of 3.25 (range 2-5). Surgery was conducted under a combination of epidural and spinal anesthesia in 24 patients (66.6%) and under general anesthesia in 12 patients (33.4%). The mean surgery time was 89.4 minutes. UCS usually followed radical cystectomy performed due to muscle-invasive bladder tumor (75%). UCS indication was based on the presence of significant comorbidities in 20 patients (55.5%), history of pelvic RT in 12 patients (33.3%), and presence of inflammatory bowel disease in 4 patients (11.1%). In our patients, the UCS procedure was usually bilateral (75%). Six of the 9 patients who underwent unilateral UCS had solitary kidneys and these patients were over the age of 70 years and had multiple comorbidities. The demographic data of the patients and the characteristics of the UCS procedure are summarized in Table 1.

During follow-up, only 3 (8.33%) patients developed ureterocutaneous anastomotic stricture at postoperative 98 months, which was treated by ureteral dilation and implantation of a 3-month 6 Fr double-J stent. Pyelonephritis developed in 6 patients and 9 patients died during follow-up. The causes of mortality were systemic metastases due to bladder tumor recurrence in 5 patients and myocardial infarction in 4 patients. The patients' long-term follow-up data and complications are shown in Table 2.

Table 1. Demographic characteristics of ureterocutaneostomy patients

Variable	Value*
Patient number	36
Age (years)	74.4 (54-81)
BMI (kg/m^2)	23.8 (21.2-27.5)
Sex	
Female	12 (33.3)
Male	24 (66.7)
Comorbid diseases	
Diabetes mellitus	15
Hypertension	27
Chronic obstructive pulmonary disease	24
Coronary artery disease	24
Chronic kidney disease	14
Crohn's disease	12
UCS indications	
Major comorbidities	20 (55.5)
Pelvic RT history	12 (33.3)
Inflammatory bowel disease	4 (11.1)
ASA score	3.25 (2-5)
Anesthesia method	
General anesthesia	12 (33.4%)
Spinal + epidural anesthesia	24 (66.6%)
Pathology with UCS (%)	
Muscle-invasive bladder tumor	27 (75)
Neurogenic bladder	9 (25)
UCS procedure	
Unilateral	9 (25)
Bilateral	27 (75)
Surgery duration (min)	89.4 (30-150)

BMI: Body mass index, RT: Radiotherapy, ASA: American Society of Anesthesiologists, UCS: Ureterocutanostomy
*Values expressed as mean (minimum-maximum) or number (percent)

Table 2. The ureterocutaneostomy patients' long-term follow-up data		
Complications	**Value***	**Duration****
Ureterocutaneous anastomosis stricture	3 (8.33)	98 (76-112)
Pyelonephritis	6 (16.66)	63.5 (58-69)
Ureteral retraction	1 (2.77)	110.4
Stoma necrosis	1 (2.77)	122.8
Death	9 (25)	76.33 (68-82)
*Values expressed as number (percent) **Times are given as mean (minimum-maximum) in months		

Discussion

Many factors are considered when selecting a method of UD, including the patient's age, manual dexterity, physical build, mental and physical condition, renal functions, any comorbid intestinal pathologies, and prognosis of the primary disease, as well as the patient's expectations, preferences, and fears, and the training, experience, and skill of the physician. In addition, the cost of the procedure must also be taken into account (7). As there is no single option suitable for every patient, it is important to know and consider the different diversion methods. The implantation of ureters to the skin (ureterocutaneostomy) is the easiest method of UD and is the only diversion method that does not require removing a segment from the GIS. The main indications for UCS are the planning of palliative treatment, the presence of significant comorbidities, low life expectancy, a history of intestinal RT or planned intestinal RT, and the presence of pathologies that preclude the use of an intestinal segment (ulcerative colitis, Crohn's disease) (6). There are high complication rates, especially involving stoma necrosis, stenosis, and stricture, and patients often require ureteral catheterization. Therefore, the IC is the most preferred method of UD (33-63%) (8,9,10). Formed by the anastomosis of the ureter to the skin, UCS is indicated for palliative purposes in patients with a poor general condition and significant comorbidities, and is selected for 1-10% of patients. When a UCS is formed, diversions through a single stoma connecting to a single bag can be created. This is achieved with transuretero-ureterostomy by end-to-side anastomosis of the thin ureter to the other ureter and UCS of this single ureter. Another option is to join the medial edges of the ureter ends and pass them through an opening in the anterior abdominal wall to create a single stoma with a double-end appearance. In this study, we analyzed the long-term results of patients for whom we preferred the UCS method.

Patient age is important when determining the diversion method. Particularly at advanced ages, compromised intestinal integrity and segment excision from the GIS result in impaired intestinal absorption and secretion, and these patients become more susceptible to metabolic disorders (11). In a study by Kozacıoğlu et al. (12) presenting the data of 27 patients who underwent UCS, the patients' ages ranged from 58 to 78 years. Similarly, in our study, the age range was between 54 and 81 years. It is known that age is among the main factors determining quality of life of patients after UD (13). However, conflicting results have been reported on the relationship between age and the quality of life expected after cystectomy. Saika et al. (14) compared health-related quality of life after radical cystectomy in patients aged 75 years and older who underwent IC, UCS, and orthotopic UD (OUD) procedures. They determined that there were no significant differences in the quality of life questionnaire results between the three groups and concluded that OUD is a method that can be utilized in elderly patients (14). We did not use a questionnaire that assessed the quality of life of our patients, but we did not encounter any substantial complaints regarding quality of life after UCS. Limitations in the social activities of our patients due to their comorbidities and advanced age may be an important factor in this.

UCS is a technique that is often preferred for patients with significant comorbidities. In diversion types that involve taking a segment from the GIS, it is expected that comorbidities would increase the risk of complications (15). Furthermore, the presence of serious comorbidities is one of the accepted indications for UCS (6). UD method should be discussed in detail with each patient and factors influencing UD selection, including the patient's preference, age, comorbidities, and the oncological characteristics of the tumor, should be considered. Being relatively easy to perform and having a low risk of complications makes UCS a first-line choice, especially for patients with multiple comorbidities. Kozacıoğlu et al. (12) reported that important comorbidities such as hypertension, chronic obstructive pulmonary disease, and diabetes were common among the patients in their study. We found that UCS was most commonly performed on high-risk patients with major comorbidities, and for this reason the operation was done under a combination of spinal and epidural anesthesia in 66.6% of patients.

The ASA score is a scoring system established by the ASA to predict patients' operative risk. It has been shown that UCS, the simplest incontinent diversion method, can reduce the risk of postoperative ileal and pulmonary complications, especially in patients with an ASA score of 3 or higher (16). Our patients had a mean ASA score of 3.25 and were at high anesthesia risk. For this reason, regional anesthesia was preferred for a large proportion of our patients. Longo et al. (17) compared the perioperative and quality of life outcomes of UCS and IC in patients over 75 years of age with ASA scores greater than 2 who underwent radical cystectomy, and reached the conclusion that UCS is a valid alternative that reduces perioperative complications and does not significantly affect quality of life in patients with significant comorbidities. Although the ASA scores of our patients were high, this method was considered relatively safer due to the short operation time, the use of regional anesthesia in most patients, and our desire to avoid the morbidity caused by alternative treatment methods such as RT and chemotherapy.

Prior or planned RT is a major obstacle to the use of the rectum segment for diversion, and may also warrant a UCS indication. One of the underlying causes of poor functional outcomes in elderly patients who undergo continent UD is a history of RT.

UD is not only performed for bladder malignancies or as a post-cystectomy procedure, but can also be done for neurogenic

bladder and congenital bladder anomalies. However, UCS is often performed in cases where intraoperative survival may be affected because of complications associated with locally advanced bladder tumor and intestinal and general health problems. OUD is not suitable in cases where the bladder tumor involves the bladder neck or for patients with renal dysfunction (creatinine clearance <50 mg/dL) and heart failure (ejection fraction <45%), and UCS or IC is often preferred for these patients (18). The incidence of bladder tumor is increasing across the world, leading to more radical cystectomy and UD procedures. UCS was performed for various reasons on our patients, but the most common reason was for UD after radical cystectomy due to muscle-invasive bladder tumor. When all stages of bladder tumor are taken into account, the 5-year survival rate is around 77% and the 10-year survival rate is around 70%. The 5-year survival rate falls to approximately 47% for localized muscle-invasive bladder tumors, which account for 35% of cases (19). In our patients, the 10-year survival rate was 75%. The main reasons for this were that the operation was performed for reasons unrelated to cancer in 25% of patients, and in those patients operated due to tumors, the procedure was performed within 90 days, which is a critical period for these patients.

In patients with solitary kidneys who have comorbidities and are in poor general condition, UCS may be a suitable method in order to avoid subjecting the patient to additional bowel surgery. The UCS procedure was performed bilaterally in the majority of our patients, but unilateral UCS was preferred in 9 patients with multiple comorbidities and poor general condition. The operation time can also be an important factor contributing to complication rates in these patients. The mean operation time was 89.4 minutes in our study.

Continent diversion methods offer certain advantages in terms of function and quality of life, but they are technically difficult to perform and the operation time is long, both of which contribute to high complication rates. They are also associated with high rates of reoperation, which may be needed in the long term. Compared to these procedures, UCS is technically easier to perform and is especially safer for patients with high anesthesia risk, and has lower complication rates. However, stoma problems are an important issue with UCS, and therefore, the IC method introduced in 1952 has largely replaced UCS. Nevertheless, UCS seems to cause less morbidity than IC. Kilciler et al. (20) reported that UCS was associated with shorter hospitalization time, less perioperative blood loss, and lower late complication rate compared to IC. However, another study showed that the type of diversion did not affect length of hospital stay (21). Furthermore, with the use of new stents, stoma problems have mostly been overcome. Some clinics attempt to prevent stomal obstruction by inserting a mono-j catheter into the ureter and replacing it every 2-3 months using a guidewire. However, serious stomal problems may occur despite this, and may require stomal reconstruction with open surgery. In a study analyzing 16 months of follow-up for incontinent diversion methods, UCS was found to be more advantageous than ileal and colonic conduits (22). There is consensus in the literature that UD types cannot be recommended randomly to patients and that of all types of UD, UCS has the lowest surgical complication rate. Two large reviews emphasized that there is no scientific evidence that any diversion type is superior to others in terms of quality of life (23,24). However, there is a need for large-scale, randomized, prospective studies in this area. Ureterocutaneous anastomotic stricture and pyelonephritis attacks were two major surgery-related complications in our patients, but these occurred at low rates (8.33% and 16.66%, respectively). Although different techniques have been modified, high rates of stomal stenosis have been reported in the literature (25). Toyoda (26) emphasized that with the technique they developed, the high rate of stenosis can be overcome by spatulating the ureter and implanting the stoma to skin separated from the epidermis and dermis. Kim et al. (27) reduced stenosis rates with a modified version of this technique in which they fixed the tunnel inside the abdominal wall between the anterior and posterior sheaths of the rectus fascia, and suggested that the main cause of stenosis is compression of the ureter by the tunnel in the abdominal wall. Our technique was similar to both of these methods, and we believe that ureteral spatulation and fixation of the tunnel to the abdominal wall contributed to our low rate of stomal stenosis. In addition, it has been speculated that obesity may contribute to stomal stenosis (28) and the mean body mass index of our patient group was 23.8 (normal weight). We detected stomal necrosis in one patient at postoperative 122 months. This patient was a 78-year-old man with uncontrolled diabetes and severe peripheral vascular disease. In this patient, ischemia at the microvascular level due to his comorbidities may have led to the development of this destructive complication.

Study Limitations

The drawbacks of our study are its retrospective nature, the fact that the surgical procedures were performed by different surgeons, and the lack of a comparative control group. However, we believe that the long follow-up period and the large patient group are strengths of our study because of the limited data in the literature about UCS, which is a rarely performed type of UD.

Conclusion

UCS should not be considered as a first option for patients who will undergo UD. However, diversion with UCS should still be kept in mind in the 21st century for selected patients with low life expectancy and significant comorbidities, those with a contraindication for obtaining a GIS segment, and those who cannot tolerate postoperative complications.

Ethics

Ethics Committee Approval: Because the study was retrospective, ethics committee approval was not obtained.

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.K., A.Ş., İ.C., Ç.Ç. Concept: F.K., A.Ş., Design: F.K., A.Ş., Data Collection or Processing: F.K.,

A.Ş., Analysis or Interpretation: F.K., A.Ş., İ.C., Ç.Ç., Literature Search: F.K., A.Ş., Writing: F.K., A.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

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Orijinal Makale / *Original Article*

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Üreterokutanostomi Uygulanan Hastaların Uzun-Dönem Sonuçları

Long-Term Outcomes of Patients Who Underwent Ureterocutaneostomy

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Öz

Amaç: Üreterokutanostomi (ÜKS), seçilmiş hasta grubunda nadir olarak uygulanan bir üriner diversiyon (ÜD) yöntemidir. Bu çalışmada, kliniğimizde ÜKS tedavisi uygulanan hastaların verilerini ve uzun dönem sonuçlarını sunmayı amaçladık.

Gereç ve Yöntem: Ocak 2000 ve Aralık 2017 arasında ÜKS uygulanan toplam 36 hasta, çalışmaya dahil edildi. Tüm hastalara unilateral veya bilateral üreter deri anostomozu uygulandı. Hastane kayıt sisteminden hastaların demografik verileri, tanıları, ek hastalıkları, ÜKS tarafı (unilateral-bilateral), anestezi yöntemi, operasyon süreleri ve komplikasyonları kaydedildi. Hastaların çalışma tarihine kadar olan takip süreleri içerisindeki komplikasyonları ve sağkalım durumları değerlendirildi. Çalışma verileri, ortalama (minimum-maksimum) ve sayı (yüzde) olarak ifade edildi.

Bulgular: Ortalama takip süresi 128,5 (8-192) aydı. Ortalama Amerikan Anesteziyolojistleri Derneği skoru 3,25'di. Hastaların başlıca, hipertansiyon, kronik obstrüktif akciğer hastalığı ve koroner arter hastalığı olmak üzere önemli komorbiditeleri mevcuttu. ÜKS, en sık kasa-invaziv mesane tümörü nedeniyle yapılan radikal sistektomi sonrasında uygulandı (%75) ve sıklıkla bilateral uygulandı (%75). En sık ÜKS endikasyonu, önemli komorbiditelerdi (%55,5). Takip sürecinde yalnızca 3 (%8,33) hastada üreter deri anostomoz darlığı, 6 (%16,66) hastada piyelonefrit gelişti ve 9 hasta takip süresinde eksitus oldu.

Sonuç: Her ne kadar ÜKS, ÜD planlanan hastalarda ilk planda düşünülmesi gereken bir diversiyon yöntemi olmasa da komorbiditeleri nedeniyle gastrointestinal sistemden segment alınmasını ve postoperatif komplikasyonları tolere edemeyecek hastalarda, 21. yüzyılda da hala akılda bulundurulmalıdır.

Anahtar Kelimeler: Üreterokutanostomi, üriner diversiyon, mesane tümörü, sağkalım, komplikasyon

Abstract

Objective: Ureterocutaneostomy (UCS) is a urinary diversion (UD) method which is used rarely in a carefully selected patient group. In this study, we aimed to present the data and long-term outcomes of patients who underwent UCS treatment in our clinic.

Materials and Methods: A total of 36 patients who underwent UCS between January 2000 and December 2017 were included in the study. All patients had unilateral or bilateral ureteral-skin anastomosis. The demographic data, diagnoses, comorbidities, side of UCS (unilateral-bilateral), anesthesia method, operation time, and complications of the patients were recorded from the hospital registry system. The complications and survival status of the patients until the study date were evaluated. The study data were presented as mean (minimum-maximum) and number (percent).

Results: Mean follow-up time was 128.5 (8-192) months. The mean American Society of Anesthesiologists score was 3.25. The patients had significant comorbidities, mainly hypertension, chronic obstructive pulmonary disease, and coronary artery disease. UCS was performed most frequently after radical cystectomy due to muscle-invasive bladder tumour (75%) and was usually bilateral (75%). The most common indications for UCS were significant comorbidities (55%). Only 3 (8.33%) patients developed ureteral-skin anastomosis, 6 (16.66%) patients developed pyelonephritis, and 9 patients died during the follow-up period.

Conclusion: Although UCS is not a first-line UD method, it should still be kept in mind in the 21st century for patients unable to tolerate segment excision from the gastrointestinal tract and postoperative complications due to comorbidities.

Keywords: Ureterocutaneostomy, urinary diversion, bladder tumour, survival, complication

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Giriş

Üreterokutanostomi (ÜKS), ilk olarak Johnston (1) tarafından 40 yıl önce bir üriner diversiyon (ÜD) yöntemi olarak, bilateral yan-yan kutanöz üreterostomi şeklinde tanımlanmıştır. Johnston bu tanımlamayı, ilk olarak, konjenital üriner obstrüksiyonlu çocuklarda bir diversiyon yöntemi olarak tariflemiştir; daha sonradan bu yöntem, pelvik maligniteli erişkinlerde kullanılmaya başlanmıştır.

Mesane tümörü, erkeklerde en sık görülen dördüncü, tüm genitoüriner sistem tümörleri arasında ikinci en sık prevalans oranına sahip tümördür. Tanı anında olguların %20-25'i kasa-invaziv tümörlerdir. Kasa-invaziv tümörlerin altın standart tedavisi radikal sistektomi, genişletilmiş lenf nodu diseksiyonu ve ÜD'dir (2). İnvaziv mesane tümörü tedavisinde cerrahinin amacı küratif ya da palyatif olabilir. Eğer palyatif bir girişim planlanıyorsa en basit ve en kısa sürede uygulanabilecek bir diversiyon yöntemi, en iyisidir.

ÜD ise ilk olarak Simon (3) tarafından 1852'de tanımlanmış ve 1950'de Bricker (4) tarafından ileal konduit (İK) tekniğinin polülarize edilmesinden sonra, bu teknik, standart bir tedavi yöntemi haline gelmiştir. ÜD, yalnızca sistektomi sonrasında uygulanan bir yöntem değildir; nörojenik mesanede veya mesanenin konjenital anomalilerinden sonra da uygulanmaktadır. Tüm bu nedenlerden dolayı uygulanan ÜD işleminde sistektomi yapılması da zorunlu değildir. Abdominal duvar, üretra ve rektosigmoid kolon ÜD için kullanılan başlıca lokasyonlardır (5). ÜD tipine karar vermek için değerlendirilen faktörler; hastanın genel sağlık durumu, hastalık-spesifik sağlık durumu, hastanın operasyon sonrası yaşam kalitesi beklentisi ve hastanın renal fonksiyonlarıdır. Ortotopik ileal yeni mesane substitüsyonu, fizyolojik anatomiye en iyi uyan ve gerek yaşam kalitesi, gerek kozmetik açıdan hastaya en iyi sonucu sağlayan yöntem gibi gözükmektedir. Ancak bu yöntemin bazı sakıncaları vardır. Lokal-ileri mesane tümörü bulunması ve üretra veya mesane boynu tutulumu olması, uzun dönem komplikasyon oranları, temiz aralıklı kateterizasyon gerektirebilmesi, teknik açıdan zor ve uzun bir cerrahi prosedür olması ortotopik substitüsyonun başlıca dezavantajlarıdır. Bu durumda, İK ve ÜKS gibi inkontinan ÜD tipleri, alternatif yöntemler olarak ön plana çıkmaktadır. ÜKS, gastrointestinal sistemden (GİS) segment alınarak yapılması planlanan bir diversiyon yöntemi olmadığı için hastalar bu ek girişimin potansiyel yan etkilerinden korunabilmektedir. Özellikle; palyatif tedavi amacıyla, önemli komorbiditelerin eşlik ettiği, yaşam beklentisinin kısıtlı olduğu, barsağa radyoterapi (RT) öyküsünün olduğu veya planlandığı ve barsak patolojilerinin (ülseratif kolit, Crohn hastalığı) eşlik ettiği durumlarda ÜKS tercih edilmelidir (6). Bu çalışmada, 2000-2016 yılları arasında kliniğimizde ÜKS uyguladığımız hastalardaki uzun dönem sonuçlarımızı değerlendirmeyi amaçladık.

Gereç ve Yöntem

Hasta Seçimi ve Veri Toplanması

Ocak 2000 ve Aralık 2017 arasında ÜKS uygulanan toplam 36 hasta çalışmaya dahil edildi. Hastaların demografik verileri, tanıları, ek hastalıkları, ÜKS tarafı (unilateral-bilateral), anestezi yöntemi, operasyon süreleri ve komplikasyonlar hastane kayıt sisteminden kaydedilerek değerlendirildi. Tüm hastalardan ÜKS prosedürü için operasyon öncesi imzalı bilgilendirilmiş onam formu alındı. Hastaların çalışma tarihine kadar olan takip süreleri içerisindeki komplikasyonları ve sağkalım durumları kaydedildi. Çalışmamız Helsinki Bildirgesi'ne uygun şekilde yürütüldü, retrospektif bir çalışma olması nedeniyle etik kurul onayı alınmadı.

Üreterokutanostomi Operasyonu

Hastalar, epidural ve spinal anestezi kombinasyonu veya genel anestezi eşliğinde, supin pozisyonda opere edildi. Medyan kesi uygulandı. Üreterler, bilateral (veya unilateral) üreterovezikal bileşkeye kadar diseke edildi ve bu noktadan sonra kesilerek spatüle edildi. Üreter lümenine 4 Fr üreter kateteri yerleştirilerek üreter orta kısmından 2/0 Vicryl Rapide sütürler ile tespit edildi. Ardından üreterler rektus kası lateralinden deri dışarısına alındı ve sonlanım noktasının yaklaşık 3,5 cm proksimalinden saat 12, 3, 6 ve 9 hizasından 4/0 Vicryl sütürler ile rektus abdominis fasyasına tespit edildi. Üreter distal ucu deriye yine 4 kadrandan 4/0 Vicryl sütürler ile tespit edildi. Operasyondan hemen sonra, operasyon odasında ÜKS ağızları stoma içerisine alındı. Postoperatif 10. gün üreter kateterleri alındı.

Çalışma verileri, ortalama (minimum-maksimum) ve sayı (yüzde) olarak ifade edildi.

Bulgular

Hastaların ortalama yaşı 74,4'tü ve büyük çoğunluğu erkekti (%66,7). Hastaların ortalama takip süresi 128,5 (8-192 aralığı) aydı. Hastalar, anestezi açısından orta-yüksek riskliydi ve ortalama Amerikan Anesteziyolojistleri Derneği (ASA) skoru 3,25'ti (2-5 aralığı). Hastaların 24'ünde (%66,6) epidural ve spinal anestezi kombinasyonu, 12'sinde (%33,4) ise genel anestezi eşliğinde cerrahi işlem uygulandı. Ortalama operasyon süresi 89,4 dakikaydı. ÜKS, en sık kasa-invaziv mesane tümörü nedeniyle yapılan radikal sistektomi sonrasında uygulandı (%75). ÜKS endikasyonları 20 (%55,5) hastada önemli komorbiditelerin eşlik etmesi, 12 (%33,3) hastada pelvik RT öyküsü olması ve 4 (%11,1) hastada enflamatuvar barsak hastalığı olmasıydı. Hastalarımızda ÜKS, sıklıkla bilateral uygulanmıştı (%75). Unilateral ÜKS uygulanan 9 hastanın 6'sının soliter böbreği vardı ve bu hastalar 70 yaşından büyük, çoklu komorbiditeleri olan hastalardı. Hastaların demografik verileri ve ÜKS uygulaması karakteristikleri Tablo 1'de özetlenmiştir.

Takip sürecinde yalnızca 3 (%8,33) hastada operasyondan ortalama 98 ay sonra üreter deri anostomoz darlığı gelişti ve üreteral dilatasyon ve 3 aylık 6 Fr double j stent uygulaması sonrası darlık tedavi edildi. Altı hastada piyelonefrit gelişti ve 9 hasta takip süresinde eksitus oldu. Beş hastada mortalite nedeni, mesane tümörü rekürrensine bağlı sistemik metastazlar, 4 hastada ise miyokard enfarktüsüydü. Hastaların uzun dönem takip verileri ve komplikasyonları Tablo 2'de gösterilmiştir.

Tablo 1. Üreterokutanostomi yapılan hastaların demografik özellikleri

Değişken	**Değer***
Hasta sayısı	36
Yaş	74,4 (54-81)
VKİ (kg/m²)	23,8 (21,2-27,5)
Cinsiyet	
Kadın	12 (33,3)
Erkek	24 (66,7)
Ek hastalıklar	
Diabetes mellitus	15
Hipertansiyon	27
Kronik obstrüktif akciğer hastalığı	24
Koroner arter hastalığı	24
Kronik böbrek yetmezliği	14
Crohn hastalığı	12
ÜKS endikasyonları	
Önemli komorbiditeler	20 (55,5)
Pelvik RT öyküsü	12 (33,3)
Enflamatuvar barsak hastalığı	4 (11,1)
ASA skoru	3,25 (2-5)
Anestezi yöntemi	
Genel anestezi	12 (%33,4)
Spinal + epidural anestezi	24 (%66,6)
ÜKS'ye eşlik eden patolojiler (%)	
Kasa-invaziv mesane tümörü	27 (75)
Nörojen mesane	9 (25)
ÜKS uygulaması	
Unilateral	9 (25)
Bilateral	27 (75)
Operasyon süresi (dk)	89,4 (30-150)

VKİ: Vücut kitle indeksi, RT: Radyoterapi, ASA: Amerikan Anesteziyolojistleri Derneği, ÜKS: Üreterokutanostomi
*Değerler, ortalama (minimum-maksimum) veya sayı (yüzde) olarak verilmiştir

Tablo 2. Üreterokutanostomi yapılan hastaların uzun dönem takip verileri

Komplikasyonlar	**Değer***	**Süre****
Üreter deri anostomoz darlığı	3 (8,33)	98 (76-112)
Piyelonefrit	6 (16,66)	63,5 (58-69)
Üreteral retraksiyon	1 (2,77)	110,4
Stoma nekrozu	1 (2,77)	122,8
Eksitus	9 (25)	76,33 (68-82)

*Değerler, sayı (yüzde) olarak verilmiştir
**Süreler, ay cinsinden ortalama (minimum-maksimum) olarak verilmiştir

Tartışma

ÜD seçiminde rol oynayan faktörler; hastanın yaşı, el becerisi, vücut yapısı, fiziksel ve mental durumu, böbrek fonksiyonları, primer hastalığının prognozu, varsa mevcut barsak patolojisi, hastanın beklentileri, tercihleri ve korkuları, doktorun eğitimi, deneyimi ve becerisidir. Bunlara ek olarak işlemin maliyeti de göz önünde bulundurulması gereken bir faktördür (7). Her hastaya uygun, tek bir seçenekten söz edilemeyeceği için farklı diversiyon yöntemlerinin bilinmesi ve göz önünde bulundurulması büyük önem taşımaktadır. Üreterlerin deriye implantasyonu (üreterokutanostomi), ÜD'nin en kolay yöntemidir ve GİS'den segment alınmasını gerektirmeyen tek diversiyon yöntemidir. ÜKS için kabul edilen endikasyonlar başlıca; palyatif tedavi planlanması, önemli komorbiditeler olması, yaşam beklentisinin az olması, barsaklara RT öyküsü olması veya planlanması ve barsak segmentinin kullanılmasının uygun olmadığı patolojilerdir (ülseratif kolit, Crohn hastalığı) (6). Özellikle stoma nekrozu, stenozu ve darlığı olmak üzere, yüksek komplikasyon oranları mevcuttur ve hastalar sıklıkla üreteral kateterizasyon uygulamasına maruz kalabilmektedir. Bu nedenle İK, en sık tercih edilen ÜD yöntemidir (%33-63) (8,9,10). Üreterin deriye anostomozu ile oluşturulan ÜKS, palyatif amaçlı ve genel durumu düşkün olan ve önemli komorbiditeleri olan hastalarda endikedir ve hastaların %1-10'unda tercih edilen diversiyon yöntemidir. ÜKS oluşturulurken tek stomalı, tek bir torbanın bağlanacağı diversiyonlar uygulanabilir. İnce olan üreter, diğer üretere uç-yan anastomoz ile transüretero-üreterostomi ve tek üreterin deriye ağızlaştırılmasıyla oluşturulur. Diğer bir seçenek de üreterlerin uçlarında medyal sınırları birleştirerek, karın ön duvarındaki bir açıklıktan çıkartarak, çift uç görünümlü tek stoma oluşturmaktır. Bu çalışmada, ÜKS yöntemini tercih ettiğimiz hastalarımızın uzun dönemli sonuçlarını analiz ettik.

Hastaların yaşı, diversiyon yönteminin belirlenmesinde önemli yere sahiptir. Özellikle ileri yaşlarda barsak bütünlüğü bozulur; GİS'den segment eksizyonu ile birlikte barsağın absorpsiyon ve sekresyon yetenekleri bozulur ve ortaya çıkan metabolik bozukluklara bu hastalar daha duyarlı hale gelir (11). Kozacıoğlu ve ark. (12) ÜKS uyguladıkları 27 hastanın verilerini sundukları çalışmalarında hastaların yaşlarının 56-78 arasında değiştiğini belirtmiştir. Bizim çalışmamızda yaş aralığı benzer şekilde 54 ile 81 arasında değişmekteydi. ÜD sonrası hastaların yaşam kalitesini belirleyen önemli faktörlerden birisinin de yaş olduğu bilinen bir gerçektir (13). Ancak, yaş ile sistektomi sonrasında beklenen yaşam kalitesi arasındaki ilişki üzerinde çelişkili sonuçlar da bildirilmiştir. Saika ve ark. (14) İK, ÜKS ve ortotopik ÜD (OÜD) uygulanan 75 yaş ve üzeri hastalarda radikal sistektomi sonrasında sağlıkla ilişkili yaşam kalitesini karşılaştırmıştır. Üç grup arasında yaşam kalitesi sorgulama formları sonucunda önemli bir farklılık olmadığını saptamışlardır ve OÜD'nin yaşlı hastalarda

uygulanabilir bir yöntem olduğu sonucuna varmışlardır (14). Hastalarımızda yaşam kalitesini değerlendiren bir sorgulama formu kullanmadık, ancak ÜKS sonrasında yaşam kalitesine yönelik belirgin bir yakınmayla karşılaşmadık. Hastalarımızın komorbiditeleri olan, ileri yaşlı hastalar olması nedeniyle sosyal aktivitelerinin kısıtlı olmasının bunda önemli bir etken olduğu düşüncesindeyiz.

ÜKS, sıklıkla önemli komorbiditeleri olan hastalarda tercih edilen bir tekniktir. GİS'den segment alınarak uygulanan diversiyon tiplerinde komorbiditelerin, komplikasyon riskini artırması beklenen bir sonuçtur (15). Hastanın ciddi komorbiditelerinin olmasının, ÜKS için kabul gören endikasyonlardan birisi olduğu da bilinen bir gerçektir (6). ÜD yöntemi, her hastayla ayrıntılı şekilde tartışılmalıdır ve yöntemin seçilmesinde etkili faktörler olan hastanın tercihi, yaşı, komorbiditeleri ve tümörün onkolojik özellikleri göz önünde bulundurulmalıdır. Nispeten uygulanması kolay bir teknik olması ve düşük komplikasyon riski, ÜKS'yi özellikle çoklu komorbiditeleri olan hastalarda ilk planda düşünülen bir yöntem haline getirmektedir. Kozacıoğlu ve ark. (12) çalışmalarında hastalarında sıklıkla hipertansiyon, kronik obstrüktif akciğer hastalığı ve diyabet olmak üzere önemli komorbiditeler saptamışlardır. Hastalarımızda ÜKS'nin en sık, önemli komorbiditeleri olan yüksek riskli hastalarda uygulandığını saptadık ve bu nedenle operasyon, hastaların %66,6'sında spinal ve epidural anestezi kombinasyonuyla gerçekleştirilmiştir.

ASA skoru, ASA tarafından hastanın operatif riskini öngörmek için oluşturulmuş bir skorlama sistemidir. Özellikle ASA skoru 3 ve üzerinde olan hastalarda en basit inkontinan diversiyon yöntemi olan ÜKS'nin postoperatif dönemde artmış ileus ve pulmoner komplikasyon riskini azaltabileceği gösterilmiştir (16). Hastalarımızın ortalama ASA skoru 3,25 olup, yüksek anestezik riske sahip hastalardı ve bu nedenle, hastalarımızın büyük kısmında rejyonel anestezi tercih edilmiştir. Longo ve ark. (17) 75 yaşından büyük, ASA skoru 2'den fazla olan ve radikal sistektomi uygulanan hastalarda ÜKS ve İK'nin perioperatif ve yaşam kalitesi sonuçlarını karşılaştırmışlar ve ÜKS'nin, önemli komorbiditeleri olan hastalarda, perioperatif komplikasyonları azaltan ve yaşam kalitesini önemli ölçüde etkilemeyen geçerli bir alternatif olduğu sonucuna varmışlardır. Her ne kadar hastalarımızın ASA skoru yüksek olsa da kısa operasyon süresi, çoğunlukla rejyonel anestezinin tercih edilmesi ve alternatif tedavi yöntemi olan RT ve kemoterapinin morbiditesinden kaçınmak istememiz, bu yöntemi hastalarımızda nispeten daha güvenli hale getirmiştir.

RT yapılmış olması veya planlanması, rektum segmentinin diversiyon amaçlı kullanımı için önemli bir engel oluşturmaktadır ve tam tersi RT öyküsü veya planlanması, ÜKS endikasyonunu gerektirebilen bir durumdur. Kontinan ÜD uygulanan yaşlı hastalarda kötü fonksiyonel sonuçların altında yatan nedenlerden birisi de hastanın RT öyküsü olmasıdır.

ÜD yalnızca mesane malignitelerinde ve postsistektomi bir prosedür olarak uygulanmaz, nörojenik mesane ve konjenital mesane anomalileri için de uygulanabilir. Ancak ÜKS; sıklıkla lokal-ileri mesane tümörü, intestinal ve genel sağlık problemleri nedeniyle, ciddi komplikasyonlar nedeniyle intraoperatif sağkalımın etkilenebileceği durumlarda uygulanmaktadır. Mesane tümörünün mesane boynunu tuttuğu durumlarda, renal disfonksiyonda (kreatinin klirensi <50 mg/dL) ve kalp yetmezliği (ejeksiyon fraksiyonu <%45) olan hastalarda OÜD uygun bir yöntem değildir ve bu hastalarda ÜKS veya İK sıklıkla tercih edilen yöntemlerdir (18). Dünyada mesane tümörü insidansı artmaktadır, buna bağlı olarak da daha çok sayıda radikal sistektomi ve ÜD operasyonu uygulanmaktadır. Bizim hastalarımızda farklı nedenlerle ÜKS uygulanmıştır; ancak en sık neden, kasa-invaziv mesane tümörü nedeniyle yapılan radikal sistektomi sonrası gereken diversiyon gerekliliğiydi. Mesane tümörünün tüm evreleri göz önüne alındığında 5 yıllık sağkalım %77 ve 10 yıllık sağkalım %70 civarındadır. Hastaların %35'ini oluşturan lokalize-kasa invaziv mesane tümörleri için ise 5 yıllık sağkalım %47'lere gerilemektedir (19). Bizim hastalarımızda 10 yıllık sağkalım %75 olarak saptandı. Bunun başlıca nedenleri hastaların %25'inde nontümöral nedenlerle operasyonun uygulanması ve tümör nedeniyle uygulanan hastalarda operasyonun kritik süre olan 90 günden fazla geciktirilmemesiydi.

Soliter böbrekli hastalarda, eşlik eden komorbiditeler mevcutsa ve hastaların genel durumu düşkünse hastayı ek barsak cerrahisi morbiditesine maruz bırakmamak için ÜKS, uygun bir yöntem olabilir. Hastalarımızın çoğunluğunda ÜKS prosedürü bilateral uygulanmıştı, ancak çoklu komorbiditeleri olan genel durumu düşkün 9 hastada unilateral ÜKS tercih edilmiştir. Operasyon süresi de bu hastalarda komplikasyon oranlarına katkıda bulunan önemli bir faktör olabilir. Çalışmamızda ortalama operasyon süresi, 89,4 dakikaydı.

Kontinan diversiyon yöntemlerinin fonksiyonel ve yaşam kalitesi ile ilişkili avantajları mevcuttur; ancak uygulanması teknik olarak zordur, operasyon süresi uzundur ve bunlara bağlı olarak da komplikasyon oranı yüksektir. Ayrıca geç dönemde de gerekebilen önemli oranda reoperasyon oranlarına sahiptir. Bunun yanında ÜKS, uygulanması teknik olarak daha kolaydır ve özellikle anestezik riski yüksek hastalarda daha güvenli ve daha az komplikasyon oranlarına sahip bir yöntemdir. Ancak ÜKS ile görülebilen önemli bir problem stoma problemleridir ve bu nedenle 1952 yılında uygulanmaya başlanan İK, büyük oranda ÜKS'nin yerini almıştır. Ancak ÜKS, İK'ye göre daha az morbiditeye sahip gibi gözükmektedir. Kilciler ve ark. (20) İK'ye göre ÜKS'nin daha az hospitalizasyon süresi, perioperatif kan kaybı ve geç komplikasyon oranına sahip olduğunu bildirmiştir. Ancak bir çalışmada diversiyon tipinin, hastanede kalış süresi üzerinde belirleyici olmadığı gösterilmiştir (21). Yeni stentlerin

kullanımıyla stoma problemleri de büyük oranda aşılmıştır. Bazı kliniklerde üreter içerisine mono-j kateter yerleştirilmektedir ve kılavuz tel üzerinden 2-3 ayda bir değiştirilerek stomal obstrüksiyon önlenmeye çalışılmaktadır. Buna rağmen, önemli stomal problemler ortaya çıkabilir ve açık cerrahi ile stomal rekonstrüksiyon gerekebilmektedir. İnkontinan diversiyon yöntemlerinin 16 aylık takiplerini analiz eden bir çalışmada, ÜKS ileal ve kolonik konduite göre daha avantajlı bulunmuştur (22). Herhangi bir ÜD tipinin her hastaya rastgele önerilemeyeceği ve tüm ÜD tipleri arasında ÜKS'nin en az cerrahi komplikasyon oranına sahip olduğu konusunda literatürde fikir birliği vardır. İki büyük derlemede yaşam kalitesi açısından diversiyon tiplerinin birbirine daha üstün olduğuna yönelik bir bilimsel kanıt olmadığı vurgulanmıştır (23,24). Ancak bu konuda büyük ölçekli, randomize, prospektif çalışmalara ihtiyaç vardır. Hastalarımızda işleme bağlı görülen iki önemli komplikasyon üreter deri anostomoz darlığı ve piyelonefrit atağıydı; ancak bunlar oldukça düşük oranlarda, sırasıyla %8,33 ve %16,66 oranında görüldü. Farklı teknikler modifiye edilmesine rağmen literatürde yüksek stoma stenoz oranları bildirilmiştir (25). Toyoda (26) geliştirdiği teknikte, üreterin spatüle edilmesi ve stomanın epidermis ve dermisten arındırılmış deriye implante edilmesinin, yüksek stenoz oranının üstesinden gelebileceğini vurgulamıştır. Kim ve ark. (27) bu tekniği modifiye ederek abdominal duvar içerisindeki tüneli rektus fasyasının ön ve arka kılıfı arasında sabitleyerek stenoz oranlarını azaltmışlar ve stenozun esas nedeninin üreterin abdominal duvar içerisindeki tünelin kompresyonu olduğunu ileri sürmüşlerdir. Bizim tekniğimiz bu iki yönteme de benzemekteydi; üreteral spatülasyon ve tünelin abdominal duvarda sabitlenmesinin düşük stomal stenoz oranımıza katkıda bulunduğunu düşünmekteyiz. Ayrıca obezitenin stoma stenozuna katkıda bulunabileceği speküle edilmiştir (28) ve bizim hasta grubumuzun ortalama vücut kitle indeksi 23,8'di (normal kilolu). Bir hastamızda postoperatif 122. ayda stoma nekrozu saptadık. Bu hasta 78 yaşında, kontrolsüz diyabeti ve ciddi periferik damar hastalığı olan bir erkekti. Komorbiditelerine bağlı mikrovasküler düzeyde gerçekleşen doku iskemisinin, hastada bu yıkıcı komplikasyonun gelişmesine neden olduğunu düşünmekteyiz.

Çalışmanın Kısıtlılıkları

Çalışmamızın eksik yönleri retrospektif yapısı, cerrahi prosedürlerin farklı cerrahlar tarafından uygulanmış olması ve karşılaştırmalı bir kontrol grubu olmamasıdır. Ancak nadir uygulanan bir ÜD tipi olan ÜKS hakkında literatürde kısıtlı veri olması nedeniyle, uzun takip süresinin ve geniş hasta grubunun çalışmamızın güçlü yönleri olduğunu düşünmekteyiz.

Sonuç

ÜKS, ÜD planlanan hastalarda ilk planda düşünülmesi gereken bir diversiyon yöntemi değildir. Ancak özellikle yaşam beklentisi az olan, önemli komorbiditeleri olan ve GİS'den segment alınmasının uygun olmadığı, postoperatif komplikasyonları tolere edemeyecek seçilmiş hastalarda ÜKS ile diversiyon, 21. yüzyılda da hala akılda bulundurulmalıdır.

Etik

Etik Kurul Onayı: Çalışmamız Helsinki Bildirgesi'ne uygun şekilde yürütülmüştür, ancak retrospektif bir çalışma olması nedeniyle etik kurul belgesi yoktur.

Hasta Onayı: Hastaların uygulanan işlemle ilgili yazılı onamları alınmıştır.

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Assessment of the Relationship Between Serum Prostate-Specific Antigen Level and Serum Fasting Glucose, Total Cholesterol and Neutrophil-Lymphocyte Ratio in Men Aged 50-70 Years with Prostate-Specific Antigen Level 0-10 ng/mL without Prostate Cancer Diagnosis

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Abstract

Objective: To evaluate the relationship between serum prostate-specific antigen (PSA) level and total cholesterol, fasting blood glucose, and neutrophil-lymphocyte ratio (NLR) in men without prostate cancer.

Materials and Methods: Between 2010 and 2017, 2631 male participants aged 50-70 years with a serum PSA level of 0-10 ng/mL were included from a population of 4643 healthy males who participated in a health screening program conducted by the İzmir Metropolitan Municipality Eşrefpaşa Hospital in the district villages of İzmir. Participants' serum PSA, fasting blood glucose, total cholesterol levels, and NLR were retrospectively assessed. Participants were grouped as those with high and low serum PSA levels, high and low glucose levels, and high and low cholesterol levels. Differences between the groups in terms of serum PSA levels, serum total cholesterol, glucose, and NLR were analyzed.

Results: The mean age of the participants was 60.2±5.4 years and the mean serum PSA level was 1.28±1.20 ng/mL. The mean PSA value was higher in the high cholesterol group (1.36±1.33 vs 1.19±1.02, p<0.001) compared to the low cholesterol group, and the mean PSA value in the high glucose group was lower than in the low glucose group (1.08±0.86 vs 1.32±1.25, p<0.001). Compared to the normal PSA group, the high PSA group had higher mean cholesterol level (208.6±39.9 vs 203.3±41.8, p<0.001) and NLR (2.17±1.00 vs 2.06±0.89, p=0.039), but lower glucose level (108.5±32.5 vs 117.2±51.0, p=0.004). Serum PSA level was positively correlated with total cholesterol and NLR (r=0.074 and p<0.001, r=0.050 and p=0.011), and negatively with glucose level (r=-0.084 and p<0.001).

Conclusion: Evaluation of total cholesterol, fasting glucose, and NLR, which may be associated with serum PSA levels, may help urologists when investigating elevated serum PSA levels in asymptomatic men aged 50-70 years who have not been diagnosed with prostate cancer.

Keywords: Prostate-specific antigen testing, prostate cancer, screening

Introduction

Globally, prostate cancer is the second leading cause of cancer-related mortality in males (1,2). The incidence of prostate cancer has risen in many countries over the past two decades due to prostate cancer screening utilizing the serum prostate-specific antigen (PSA) test (3,4,5). Although PSA testing is not currently recommended as a routine screening tool for prostate cancer

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(6,7,8), it is commonly used as a preliminary test for men who present to urology outpatient clinics with complaints regarding urination or in patients over 40 years of age upon their request. The PSA glycoprotein, which is secreted from the prostate gland, has no definitive threshold value for prostate cancer, and high serum PSA levels can occur in benign prostatic hypertrophy (BPH), prostatitis, and following procedures performed on the prostate (prostate massage, prostate biopsy, and urethroscopy) (9).

Serum PSA levels may be affected by a number of factors other than prostate disorders in men who have not been diagnosed with prostate cancer. Although there are studies in the literature investigating the effects of obesity, serum glucose, total cholesterol, and triglyceride levels on serum PSA levels, the results of these studies are contradictory (10,11,12,13). Today, many men aged 50-70, despite not being diagnosed with diabetes or hypercholesterolemia, are found to have high blood glucose or total cholesterol level when tested for PSA.

In addition to numerous other parameters, neutrophil-lymphocyte ratio (NLR) has recently been studied as a marker of the inflammatory response in solid organ tumors because it is easily determined. NLR is an established marker of progression and poor prognosis in lung, pancreatic, colorectal, ovarian, and prostate cancer (14). Although there are many studies demonstrating a relationship between NLR and the risk of prostate cancer diagnosis, recurrence, and progression (15,16), few studies have shown a relationship between serum PSA levels and NLR in patients without prostate cancer (14).

The aim of this study was to determine the relationship between serum PSA level and fasting blood glucose, total cholesterol, and NLR in men aged 50-70 years without prostate cancer.

Materials and Methods

Of 4643 healthy males who presented for health screening conducted by the İzmir Metropolitan Municipality Eşrefpaşa Hospital in the district villages of İzmir between 2010 and 2017, 2631 participants aged 50-70 with a serum PSA level of 0-10 ng/mL were included in the study. The participants' serum PSA, fasting blood glucose, total cholesterol levels, and NLR were retrospectively evaluated. Patients with prostate cancer and patients receiving medical treatment for urinary tract infections, BPH, diabetes, and hyperlipidemia were excluded from the study. Relationships between serum PSA level and fasting glucose, total cholesterol, and NLR were assessed. Participants were grouped as those with and without high glucose (>126 mg/dL) (17) and high cholesterol (>200 mg/dL) (18), and the differences between groups and their association with serum PSA levels were assessed. In addition, differences in serum total cholesterol, glucose, and NLR between participants with and without serum PSA level over 2.5 ng/mL (8) were evaluated.

Because the study was designed as a retrospective chart review, ethics committee approval and informed consent were not obtained. However, the participants provided informed consent during the health screening.

Results

The mean age of the 2631 male participants included in the study was 60.2±5.4 years and their mean serum PSA level was 1.28±1.20 ng/mL. The participants' demographic data, serum glucose and total cholesterol levels, and NLR are shown in Table 1. Men with high cholesterol had significantly higher mean serum PSA levels than men without high cholesterol ($p<0.001$). However, mean serum PSA level was significantly lower in participants with high serum glucose levels when compared to those without high serum glucose ($p<0.001$) (Table 2). Comparison of groups with and without elevated PSA revealed higher total cholesterol and NLR and lower mean fasting glucose levels among men with elevated serum PSA levels ($p<0.001$, $p=0.039$, and $p=0.004$, respectively) (Table 3). There were statistically significant but weak positive correlations between serum PSA level and total cholesterol and NLR ($r=0.074$ and $p<0.001$; $r=0.050$ and $p=0.011$). However, there was a significant but weak negative correlation between serum PSA level and fasting blood glucose ($r=-0.084$ and $p<0.001$).

Table 1. Demographic data of the participants

Number of participants	2631
Mean age (range), years	60.2±5.4 (50-69)
Mean PSA (range), ng/mL	1.28±1.20 (0.10-9.32)
Mean cholesterol (range), mg/dL	203.9±41.6 (83-437)
Mean glucose (range), mg/dL	116.2±49.3 (46-554)
Mean neutrophil/lymphocyte ratio	2.07±0.91
Elevated glucose (>126 mg/dL), (n, %) **No** **Yes**	 2153, 81.8% 237, 11.3%
Elevated cholesterol (>200 mg/dL), (n, %) **No** **Yes**	 1263, 48.0% 1368, 52.0%

PSA: Prostate-specific antigen

Table 2. Comparison of age and serum prostate-specific antigen level between groups

	Elevated glucose			**Elevated cholesterol**		
	Yes n=237	**No n=2153**	**p value**	**Yes n=1368**	**No n=1263**	**p value**
Age, years (mean ± SD)	61.2±5.1	60.0±5.5	<0.001	60.3±5.5	60.2±5.4	0.236
PSA, ng/mL (mean ± SD)	1.08±0.86	1.32±1.25	<0.001	1.36±1.33	1.19±1.02	<0.001

PSA: Prostate-specific antigen, SD: Standard deviation

Table 3. Comparison of serum cholesterol, serum glucose, and neutrophil/lymphocyte ratio between groups with and without elevated prostate-specific antigen (>2.5 ng/mL)

	PSA >2.5 ng/mL n=297	PSA <2.5 ng/mL n=2334	p value
Age	63.1±4.6	59.9±5.4	<0.001
PSA	4.01±1.46	0.93±0.52	<0.001
Cholesterol	208.6±39.9	203.3±41.8	<0.001
Glucose	108.5±32.5	117.2±51.0	0.004
Neutrophil/lymphocyte ratio	2.17±1.00	2.06±0.89	0.039

PSA: Prostate-specific antigen

Discussion

PSA is a glycoprotein tumor marker that is now commonly used in prostate cancer diagnosis and follow-up. Although it is secreted from normal prostate cells, prostate cancer cells secrete 10 times more PSA than normal (19). In addition to prostate cancer, PSA levels have also been observed in benign prostate diseases such as BPH and prostatitis, and interventions involving the prostate such as prostate biopsy, prostate resection, rigid cystoscopy, and transrectal ultrasonography (19). Although not currently recommended for routine prostate cancer screening (6,7,8), it is widely used in urology outpatient clinics for those over 40 years of age upon patient request. Tawfik (20) argued that PSA testing creates high costs for the health care system, both due to the test itself and expenses associated with staging and treatment of detected prostate cancers. Based on these concerns, various studies were designed to determine when and for whom PSA testing should be conducted, which PSA value should be used as an indication for biopsy, and what factors affect serum PSA levels, but no definitive conclusions have been reached.

Despite numerous studies investigating associations between prostate cancer and hypercholesterolemia and statin use (21,22,23), there have been relatively few studies aiming to correlate hypercholesterolemia with serum PSA levels in men without prostate cancer (12). Similar to the results of our study, Mondul et al. (12) investigated the relationship between serum total cholesterol and serum PSA levels in 2574 men over 40 years of age who did not have prostate cancer, and found that low PSA levels corresponded to low cholesterol levels. In addition, patients who achieved low cholesterol levels using statins also had low serum PSA levels. Higher cholesterol content and reduced cholesterol bioavailability in prostate tissue have been shown to alter the structure of cell membrane signaling sites and increase apoptosis in prostate cells (24,25). Furthermore, these changes may also increase the inflammatory response against prostate cells. Therefore, both prostate cell apoptosis and the resulting inflammation can increase PSA release from prostate cells. Cholesterol is an important precursor for androgen synthesis (26). Androgens are shown to have a role in the proliferation of prostate cells and the development of prostate cancer, and PSA secretion has been associated with androgens (26). The cholesterol-androgen relationship may explain the association between elevated serum PSA and high cholesterol.

In this study, we showed that serum PSA levels were inversely correlated with fasting blood glucose and that glucose levels were lower in those with elevated PSA. Werny et al. (27) reported lower PSA levels in diabetic patients compared to non-diabetic patients. Müller et al. (10) showed that greater diabetes severity was associated with larger decreases in PSA. Similarly, Sun et al. (28) showed that patients with type 2 diabetes had lower PSA levels and that prediabetes was associated with higher PSA levels. Although the participants in the present study were not diagnosed with diabetes, the results were similar to those of previous studies. In addition, we found that participants with elevated PSA had lower fasting blood glucose levels. In the literature, molecular studies describing this inverse relationship between PSA and fasting blood glucose have shown a decline in blood testosterone level and increase in estrogen level in diabetes, which may result in a decrease in androgen-dependent PSA synthesis and secretion (29,30).

Some previous studies have shown that systemic inflammation plays a role in the development and progression of cancer and that prostate cancer is associated with infectious agents, chronic infections, and dietary and hormonal inflammatory factors (31,32). NLR is one of the markers of systemic inflammation and has been shown to correlate with the diagnosis, prognosis, and progression of prostate cancer (15,16); however, the relationship between systemic inflammation and serum PSA levels in men without prostate cancer remains unclear. McDonald et al. (14) demonstrated in their study that NLR was associated with elevated serum PSA. In our study, there was a positive correlation between elevated serum PSA and NLR, and NLR was higher in the group with PSA elevation. NLR elevation is associated with higher concentrations of many pro-inflammatory cytokines. These pro-inflammatory cytokines cause cellular DNA damage which can lead to cell death or cancer development (32).

Study Limitations

The main limitations of this study are its retrospective nature, the lack of advanced testing to establish other possible etiologies of PSA elevation, and the lack of follow-up results for the participants.

Conclusion

The results of this study indicate that serum PSA elevation may be associated with high total cholesterol level, high NLR, and low fasting blood glucose level. Taking total cholesterol level, fasting glucose level, and NLR into account may help urologists when evaluating elevated serum PSA in asymptomatic men aged 50-70 who have never been diagnosed with prostate cancer. However, better planned studies that analyze the results of patient follow-up are needed to establish the exact relationship between these factors and serum PSA levels in asymptomatic men.

Ethics

Ethics Committee Approval: Because the study was designed as a retrospective chart review, ethics committee approval was not obtained.

Informed Consent: Informed consent was obtained during the health screening in which the data analyzed in the study were collected. Separate informed consent was not sought for this retrospective chart review study.

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Orijinal Makale / *Original Article*

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Prostat Kanseri Tanısı Almamış, Prostat Spesifik Antijen Değeri 0-10 ng/mL Olan 50-70 Yaş Arası Erkeklerde Serum Prostat Spesifik Antijen Seviyesi ile Serum Açlık Glikoz, Total Kolesterol ve Nötrofil-Lenfosit Oranı Arasındaki İlişkisinin Değerlendirilmesi

Assessment of the Relationship Between Serum Prostate-Specific Antigen Level and Serum Fasting Glucose, Total Cholesterol and Neutrophil-Lymphocyte Ratio in Men Aged 50-70 Years with Prostate-Specific Antigen Level 0-10 ng/mL without Prostate Cancer Diagnosis

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Öz

Amaç: Prostat kanseri tanısı olmayan erkelerde, serum prostat spesifik antijen (PSA) düzeyinin total kolesterol, açlık kan glikozu ve nötrofil-lenfosit oranı (NLO) ile olan ilişkisinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Çalışmaya 2010-2017 yılları arasında, İzmir Büyükşehir Belediyesi Eşrefpaşa Hastanesi'nin İzmir'in ilçe köylerinde yaptığı sağlık taramasına başvuran sağlıklı 4643 erkek katılımcı arasından serum PSA seviyesi 0-10 ng/mL olanlar ve yaşları 50-70 arasında olan 2631 erkek katılımcı dahil edildi. Katılımcıların serum PSA, açlık kan glikozu, total kolesterol seviyeleri ve NLO'ları retrospektif olarak değerlendirildi. Katılımcılar serum PSA düzeyi yüksek olan ve olmayan, glikoz yüksekliği olan ve olmayan, kolesterol yüksekliği olan ve olmayan olarak gruplandırıldı. Gruplar arasında serum PSA düzeyi, serum total kolesterol, glikoz ve NLO arasında farklılığın varlığı gösterilmeye çalışıldı.

Bulgular: Katılımcıların yaş ortalaması 60,2±5,4 yıl ve ortalama serum PSA düzeyi 1,28±1,20 ng/mL olarak bulundu. Kolesterol yüksekliği olan grupta olmayan gruba göre ortalama PSA değeri daha yüksek (1,36±1,33-1,19±1,02 ve p<0,001); glikoz yüksekliği olan grupta ortalama PSA değeri, olmayan gruba göre ise daha düşüktü (1,08±0,86-1,32±1,25 ve p<0,001). PSA yüksekliği olan grupta ortalama kolesterol seviyesi (208,6±39,9-203,3±41,8 ve p<0,001) ve NLO daha yüksek (2,17±1,00-2,06±0,89 ve p=0,039), glikoz seviyesi normal PSA grubuna

Abstract

Objective: To evaluate the relationship between serum prostate-specific antigen (PSA) level and total cholesterol, fasting blood glucose, and neutrophil-lymphocyte ratio (NLR) in men without prostate cancer.

Materials and Methods: Between 2010 and 2017, 2631 male participants aged 50-70 years with a serum PSA level of 0-10 ng/mL were included from a population of 4643 healthy males who participated in a health screening program conducted by the İzmir Metropolitan Municipality Eşrefpaşa Hospital in the district villages of İzmir. Participants' serum PSA, fasting blood glucose, total cholesterol levels, and NLR were retrospectively assessed. Participants were grouped as those with high and low serum PSA levels, high and low glucose levels, and high and low cholesterol levels. Differences between the groups in terms of serum PSA levels, serum total cholesterol, glucose, and NLR were analyzed.

Results: The mean age of the participants was 60.2±5.4 years and the mean serum PSA level was 1.28±1.20 ng/mL. The mean PSA value was higher in the high cholesterol group (1.36±1.33 vs 1.19±1.02, p<0.001) compared to the low cholesterol group, and the mean PSA value in the high glucose group was lower than in the low glucose group (1.08±0.86 vs 1.32±1.25, p<0.001). Compared to the normal PSA group, the high PSA group had higher mean cholesterol level (208.6±39.9 vs 203.3±41.8, p<0.001) and NLR (2.17±1.00 vs 2.06±0.89, p=0.039), but

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göre daha düşüktü (108,5±32,5-117,2±51,0 ve p=0,004). Serum PSA seviyesi ile total kolesterol ve NLO arasında pozitif korelasyon (r=0,074 ve p<0,001, r=0,050 ve p=0,011), glikoz seviyesi ile ters korelasyon bulundu (r=-0,084 ve p<0,001).

Sonuç: Serum PSA düzeyi ile ilişkili olabilecek olan total kolesterol, açlık glikoz düzeyleri ve NLO'nun da değerlendirilmesi; prostat kanseri tanısı olmayan asemptomatik 50-70 yaşlarındaki hastalarda serum PSA düzeyi yüksekliğinin araştırılması sırasında üroloji uzmanına yardımcı olabilir.

Anahtar Kelimeler: Prostat spesifik antijen testi, prostat kanseri, tarama

lower glucose level (108.5±32.5 vs 117.2±51.0, p=0.004). Serum PSA level was positively correlated with total cholesterol and NLR (r=0.074 and p<0.001, r=0.050 and p=0.011), and negatively with glucose level (r=-0.084 and p<0.001).

Conclusion: Evaluation of total cholesterol, fasting glucose, and NLR, which may be associated with serum PSA levels, may help urologists when investigating elevated serum PSA levels in asymptomatic men aged 50-70 years who have not been diagnosed with prostate cancer.

Keywords: Prostate-specific antigen testing, prostate cancer, screening

Giriş

Dünyada erkeklerde kansere bağlı ölüm nedenleri arasında ikinci sırada prostat kanseri yer almaktadır (1,2). Serum prostat spesifik antijen (PSA) testi kullanılarak prostat kanseri taraması yapılması nedeniyle, son 20 yılda birçok ülkede prostat kanseri insidansında artış görülmüştür (3,4,5). PSA testi halen prostat kanseri için rutin bir tarama aracı olarak önerilmemekle birlikte (6,7,8), işeme yakınmaları ile üroloji polikliniklerine başvuran erkeklerde ön test olarak veya 40 yaş üstü hastalarda, hastanın talebi üzerine yaygın olarak yapılmaktadır. Prostat bezinden salgılanan glikoprotein yapısındaki PSA'nın, prostat kanseri tanısında kesinleşmiş bir eşik değeri yoktur ve benign prostat hipertrofisi (BPH), prostatit ve prostata uygulanmış işlemlerden sonra (prostat masajı, prostat biyopsisi ve üretroskopi) yüksek serum PSA düzeylerine rastlanabilir (9). Serum PSA seviyeleri prostat kanseri tanısı almamış kişilerde prostat hastalıkları dışında da birtakım faktörlerden etkilenebilir. Literatürde obezitenin, serum glikoz, total kolesterol ve trigliserig düzeylerinin serum PSA düzeylerine etkisini araştıran çalışmalar bulunsa da bu çalışmalardan çıkan sonuçlar birbirleri ile çelişki göstermektedirler (10,11,12,13). Günümüzde 50-70 yaş arasında birçok erkek diyabet ve hiperkolesterolemi tanısı almamasına rağmen, yüksek kan glikozu ya da total kolesterol seviyesi ile PSA testine tabi tutulmaktadır.

Son yıllarda solid organ tümörlerinde enflamatuvar yanıtın göstergesi olarak birçok parametrenin yanında, kolay ulaşılabilir olması nedeniyle nötrofil-lenfosit oranı (NLO) araştırılmaya başlanmıştır. NLO akciğer, pankreas, kolorektal, over ve prostat kanserinde progresyon ve kötü prognoz göstergesi olarak tespit edilmiştir (14). Özellikle NLO ile prostat kanserinin tanı, nüks ve progresyon gösterme riski arasındaki ilişkiyi ortaya koyan birçok çalışma varken (15,16), prostat kanseri tanısı almayan hastalarda serum PSA düzeyleri ile NLO arasındaki ilişkiyi gösteren çalışma sayısı çok azdır (14).

Bu çalışmada prostat kanseri tanısı olmayan 50-70 yaş arası erkeklerde açlık kan glikoz, total kolesterol ve NLO'nun serum PSA düzeyi ile ilişkisinin ortaya konulması amaçlandı.

Gereç ve Yöntem

Çalışmaya 2010-2017 yılları arasında, İzmir Büyükşehir Belediyesi Eşrefpaşa Hastanesi'nin İzmir'in ilçe köylerinde yaptığı sağlık taramasına başvuran sağlıklı 4643 erkek katılımcı arasından serum PSA seviyesi 0-10 ng/mL olanlar ve yaşları 50-70 arasında olan 2631 erkek katılımcı dahil edildi. Katılımcıların serum PSA, açlık kan glikozu, total kolesterol seviyeleri ve NLO'ları retrospektif olarak değerlendirildi. Prostat kanseri tanısı olan hastaların ve idrar yolları enfeksiyonu, BPH, diyabet ve hiperlipidemi nedeniyle ilaç tedavisi alan hastaların sonuçları çalışma dışı bırakıldı. Serum PSA düzeyi ile açlık glikoz, total kolesterol ve NLO arasındaki ilişkinin varlığı değerlendirildi. Katılımcılar glikoz yüksekliği (>126 mg/dL) (17) olan ve olmayan, kolesterol yüksekliği (>200 mg/dL) (18) olan ve olmayan olarak gruplandırıldı ve gruplar ile serum PSA düzeyi arasındaki ilişki ve farklılık değerlendirildi. Ayrıca serum PSA düzeyi 2,5 ng/mL'den yüksek olan (8) ve olmayan katılımcıların serum total kolesterol, glikoz ve NLO'ları arasında farklılığın olup olmadığı gösterilmeye çalışıldı.

Çalışma retrospektif dosya tarama çalışması olarak dizayn edildiği için etik kurul onayı ve hasta onamı alınmadı. Ancak sağlık taraması sırasında katılımcıların bilgilendirilmiş onamı alındı.

Bulgular

Bu çalışmada sonuçları değerlendirilen 2631 erkek katılımcının yaş ortalaması 60,2±5,4 yıl ve ortalama serum PSA düzeyi 1,28±1,20 ng/mL olarak bulundu. Tablo 1'de katılımcı erkeklerin demografik verileri ve serum glikoz, total kolesterol düzeyleri ve NLO'ları gösterilmiştir. Kolesterol yüksekliği olan hastaların ortalama serum PSA değerleri, kolesterol yüksekliği olmayan hastaların serum PSA değerlerine göre istatistiksel olarak anlamlı bir şekilde yüksek olduğu gözlendi (p<0,001). Ancak, serum glikoz yüksekliği olan ve olmayan gruplar arasında serum PSA değerleri karşılaştırıldığında serum glikoz düzeyi yüksek olan grupta ortalama serum PSA seviyesi diğer gruba göre istatistiksel olarak anlamlı bir şekilde daha düşük saptandı (p<0,001) (Tablo 2). Serum PSA yüksekliği olan grupta ortalama total kolesterol ve NLO PSA yüksekliği olmayan grupla karşılaştırıldığında daha

Tablo 1. Katılımcıların demografik verileri

Katılımcı sayısı	2631
Ortalama yaş (aralık), yıl	60,2±5,4 (50-69)
Ortalama PSA (aralık), ng/mL	1,28±1,20 (0,10-9,32)
Ortalama kolesterol (aralık), mg/dL	203,9±41,6 (83-437)
Ortalama glikoz (aralık), mg/dL	116,2±49,3 (46-554)
Ortalama nötrofil/lenfosit oranı	2,07±0,91
Glikoz yüksekliği (>126 mg/dL) (n, %) **Yok** **Var**	 2153 %81,8 237 %11,3
Kolesterol yüksekliği (>200 mg/dL) (n, %) **Yok** **Var**	 1263 %48,0 1368 %52,0

PSA: Prostat spesifik antijen

Tablo 2. Gruplara göre yaş ve serum prostat spesifik antijen düzeyinin karşılaştırılması						
	Glikoz yüksekliği			Kolesterol yüksekliği		
	Var n=237	Yok n=2153	p değeri	Var n=1368	Yok n=1263	p değeri
Yaş, yıl (Ort ± SS)	61,2±5,1	60,0±5,5	<0,001	60,3±5,5	60,2±5,4	0,236
PSA, ng/mL (Ort ± SS)	1,08±0,86	1,32±1,25	<0,001	1,36±1,33	1,19±1,02	<0,001
PSA: Prostat spesifik antijen, Ort: Ortalama, SS: Standart sapma						

yüksek, ortalama açlık glikoz seviyesi daha düşük olarak bulundu (sırasıyla p<0,001, p=0,039 ve p=0,004) (Tablo 3). Serum PSA düzeyi ile total kolesterol ve NLO arasında pozitif yönde istatistiksel olarak anlamlı fakat zayıf bir kolerasyon bulunurken (r=0,074 ve p<0,001, r=0,050 ve p=0,011), serum PSA düzeyi ile açlık kan glikozu arasında ters yönde istatistiksel olarak anlamlı fakat zayıf bir kolerasyon olduğu gösterildi (r=-0,084 ve p<0,001).

Tablo 3. Prostat spesifik antijen yüksekliği >2,5 ng/mL olan ve olmayan gruplar arasında serum kolesterol, serum glikoz ve nötrofil/lenfosit oranının karşılaştırılması			
	PSA >2,5 ng/mL n=297	PSA <2,5 ng/mL n=2334	p değeri
Yaş	63,1±4,6	59,9±5,4	<0,001
PSA	4,01±1,46	0,93±0,52	<0,001
Kolesterol	208,6±39,9	203,3±41,8	<0,001
Glikoz	108,5±32,5	117,2±51,0	0,004
Nötrofil/Lenfosit	2,17±1,00	2,06±0,89	0,039
PSA: Prostat spesifik antijen			

Tartışma

PSA, günümüzde prostat kanserinin tanısında ve tedavi takibinde yaygın olarak kullanılan glikoprotein yapıda bir tümör belirtecidir. Normal prostat hücrelerinden de salgılanmasına rağmen, prostat kanseri hücreleri normalden 10 kat daha fazla PSA salgılamaktadırlar (19). Prostat kanserinin dışında, BPH ve prostatit gibi benign prostat hastalıklarında ve prostat biyopsisi, prostat rezeksiyonu, rijit sistoskopi ve transrektal ultrasonografi gibi prostata yapılan uygulamalardan sonra da PSA seviyesinde artışlar gözlenmektedir (19). Günümüzde prostat kanserinin rutin taramasında önerilmese de (6,7,8), üroloji polikliniklerinde hasta talebi üzerine 40 yaş üstü erkeklerde yaygın olarak kullanılmaktadır. Tawfik (20) PSA testinin kendisinin ve sonuçta tanı konan prostat kanserinin evreleme ve tedavi masraflarının da göz önüne alındığında, sağlık sistemi için yüksek maliyetlere yol açtığını belirtmiştir. Bu tür endişelerle kimlere ne zaman PSA istenmesi gerektiğiyle, biyopsi için hangi PSA değerinin doğru olduğuyla ve serum PSA düzeyini etkileyen faktörlerle ilgili birçok çalışma dizayn edilmiş ve net sonuçlara varılamamıştır.

Hiperkolesteroleminin ve statin türü ilaç kullanımının prostat kanseri ile ilişkisini araştıran birçok çalışma varken (21,22,23), prostat kanseri olmayan erkelerde hiperkolesterolemi ile serum PSA düzeyi arasında ilişki kurmaya çalışan çalışma sayısı oldukça azdır (12). Bu çalışmanın sonuçlarına benzer şekilde, Mondul ve ark. (12), prostat kanseri tanısı almamış 40 yaş üstü 2574 erkekte serum total kolesterol düzeyi ile serum PSA düzeyi arasındaki ilişkiyi incelemişler ve kolesterol düzeyi düşük olanlarda PSA düzeylerinin de düşük olduğunu saptamışlardır. Ek olarak statin türevi ilaçlar kullanarak düşük kolesterol düzeylerine ulaşılan hastalarda da düşük serum PSA düzeylerine rastlamışlardır. Prostat dokusunda artmış kolesterol içeriğinin ve kolesterol biyoyararlanımının azalmasının hücre zarındaki sinyalizasyon alanlarının yapısını değiştirdiği ve prostat hücrelerinde apoptozu artırdığı bulunmuştur (24,25). Ayrıca bu değişimler prostat hücrelerine karşı enflamatuvar yanıtı da artırabilir. Bu sebeple hem prostat hücrelerinin apoptozu hem de oluşan enflamasyon prostat hücrelerinden PSA salınımını artırabilir. Kolesterol androjen oluşumu için önemli bir prekürsör maddedir (26). Prostat hücrelerinin çoğalmasında ve prostat kanserinin gelişiminde androjenlerin rolü ortaya konmuş ve PSA'nın sekresyonunun androjenlerle ilişkisi gösterilmiştir (26). Kolesterol-androjen ilişkisi de serum PSA yüksekliği ile kolesterol yüksekliği arasındaki ilişkiyi açıklayabilir.

Bu çalışmada, serum PSA düzeyi ile açlık kan glikozunun ters ilişkili olduğunu ve PSA yüksekliği olanlarda glikoz seviyelerinin daha düşük olduğunu gösterdik. Werny ve ark. (27), diyabetik hastalarda diyabetik olmayan hastalara göre daha düşük PSA düzeyleri saptamışlardır. Müller ve ark. (10) diyabetin şiddeti arttıkça PSA'daki düşüşün daha fazla olduğunu ortaya koymuşlardır. Aynı şekilde Sun ve ark. (28) da tip 2 diyabetli hastaların daha düşük PSA seviyelerine sahip olduklarını ve pre-diyabetin ise yüksek PSA seviyesi ile ilişkili olduğunu göstermişlerdir. Bu çalışmada katılımcıların diyabet tanısı olmamasına rağmen, sonuçlar önceki çalışmalarla benzer olarak saptandı. Ayrıca PSA yüksekliği olan katılımcıların açlık kan glikoz seviyeleri daha düşük olarak gözlendi. Literatürde PSA ile açlık kan glikozu arasındaki bu ters ilişkiyi açıklayan moleküler çalışmalarda, diyabet ortaya çıktığında kan testosteron düzeyinin düştüğü, östrojen seviyesinin yükseldiği ve bu sebeple sentezi ve sekresyonu androjen bağımlı olan PSA seviyesinde azalma olabileceği gösterilmiştir (29,30).

Literatürde sistemik enflamasyonun kanser gelişiminde ve progresyonunda rol aldığını ve prostat kanseri ile enfeksiyöz ajanların, kronik enfeksiyonların, diyetsel ve hormonal inflamatuvar faktörlerin ilişkili olduğunu gösteren çalışmalar bulunmaktadır (31,32). Sistemik enflamasyonun göstergelerinden biri olan NLO'nun prostat kanserinin tanı, prognoz ve progresyonu ile ilişkisi ortaya konmasına rağmen (15,16), prostat kanseri tanısı almamış erkeklerde sistemik enflamasyon ile serum PSA düzeyleri arasındaki ilişki net değildir. McDonald ve ark. (14) çalışmalarında NLO'nun serum PSA yüksekliği ile ilişkili olduğunu göstermişlerdir. Bu çalışmada da serum PSA yüksekliği ile NLO arasında pozitif ilişki olduğu, PSA yüksekliği olan grupta NLO'nun daha yüksek çıktığı tespit

edildi. NLO'nun yüksekliği, birçok pro-enflamatuvar sitokinin konsantrasyonunun yüksekliği ile ilişkilidir. Bu pro-enflamatuvar sitokinler hücresel DNA hasarına neden olurlar ve sonuçta hücre ölümü ya da kanser gelişimi ortaya çıkabilir (32).

Çalışmanın Kısıtlılıkları

Çalışmamızın retrospektif olması ve çalışmaya katılan katılımcıların PSA yüksekliğini açıklayacak ileri tetkik yapılmamış olması ve takip sonuçlarının olmaması başlıca kısıtlılıklar olarak sıralanabilir.

Sonuç

Sonuç olarak bu çalışmada serum PSA yüksekliği ile total kolesterol seviyesinin ve NLO'nun yüksekliğinin ve açlık kan glikoz seviyesinin düşüklüğünün ilişkili olabileceği gösterilmiştir. Prostat kanseri tanısı almamış asemptomatik 50-70 yaş arası erkelerde serum PSA yüksekliği değerlendirilirken; total kolesterol, açlık glikoz seviyelerinin ve NLO'nun da göz önünde bulundurulması üroloji uzmanına yardımcı olabilir. Ancak bu faktörlerin asemptomatik erkeklerde serum PSA seviyesi ile net ilişkisini ortaya koymak için daha iyi planlanmış ve katılımcıların takip sonuçlarının da olduğu çalışmalara ihtiyaç vardır.

Etik

Etik Kurul Onayı: Retrospektif çalışma olması nedeniyle etik kurul onayı alınmamıştır.

Hasta Onayı: Retrospektif dosya tarama çalışması olduğu için alınmamıştır. Ancak sağlık taraması sırasında katılımcılardan kan alımı için bilgilendirilmiş onam formu alınmıştır.

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Kaynaklar

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Review
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Organ-Preserving Approach in Bladder Cancer: Assessment of the Current Situation

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Abstract

Intravesical bacillus Calmette-Guerin (BCG) therapy is the gold standard treatment option in high-risk non-invasive bladder cancer. However, BCG is a very toxic agent. A significant proportion of patients have BCG intolerance after beginning intravesical treatment. Radical cystectomy is the recommended approach for patients with either BCG failure or BCG intolerance. Alternative intravesical salvage treatments are needed for patients who cannot tolerate radical cystectomy due to comorbidities or who refuse surgery.

In this review, current intravesical treatment alternatives to radical cystectomy in intravesical BCG failure are discussed with oncologic outcomes.

Keywords: Bladder cancer, bacillus Calmette-Guérin failure, intravesical salvage therapy

Introduction

Bladder cancer is the seventh most common type of cancer among males and eleventh among both genders combined (1). In 2016 alone, 76,960 new cases were diagnosed and 16,390 cancer-related deaths were reported in the United States of America (2). Cancer staging and treatment planning can be achieved with a successful endoscopic resection and when necessary, metastatic evaluation. Although 70% of cases are non-muscle invasive superficial cancers (NMIBC) at the time of diagnosis, about 20% of these are grade Ta and T1 tumors including carcinoma *in situ* (CIS), which form a special group associated with high risk of cancer progression and relapse (3). Intravesical bacillus Calmette-Guérin (BCG) therapy is the primary treatment method for these high-risk NMIBCs (4). For non-metastatic muscle-invasive bladder cancer, radical cystectomy is considered the gold standard treatment option that provides the longest survival. With a goal of complete tumor elimination, grade 3-4 complication rate of 13% and mortality rate of 2.5-5.2% are considered acceptable (5).

Although NMIBC patients can be successfully treated with intravesical BCG, they exhibit relapse and progression rates of 80% and 40% respectively at 5-year follow-up. As described in a 2000 study by the Southwestern Oncological Group (SWOG), the intravesical BCG regimen is administered as a 6-week induction course followed by 3 years of maintenance therapy if there are no signs of tumor in follow-up endoscopic examinations (6). However, in the presence of persistent or recurrent NMIBC, a substantial proportion of patients may benefit from an additional 6-week induction course with or without interferon (IFN) alpha (3). Findings indicating BCG resistance during therapy include high-grade NMIBC in the first cystoscopic examination, CIS in the first or second cystoscopic examination, and high-grade cancer in follow-up cystoscopic examinations during or after completing the intravesical BCG protocol (7). The occurrence of adverse effects that prevent continuation of treatment is referred to as BCG intolerance (7,8). NMIBC patients exhibiting BCG resistance or intolerance are candidates for radical cystectomy (9). However, the various comorbidities in elderly patients and the reluctance of younger patients to risk undergoing such a

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procedure have led to a search for local therapeutic alternatives to radical cystectomy (5).

Mitomycin C

Thiotepa, adriamycin, and mitomycin C (MMC) were initially the preferred first-line agents for patients who were sensitive to BCG but could not undergo BCG therapy (9). Today, only MMC still holds this position (10). MMC has an important place among chemotherapeutic agents. It is an alkylating agent that disrupts DNA synthesis (4). It is used perioperatively in NMIBC treatment due to its ability to block tumor seeding in particular (4). However, maintenance therapy does not yield satisfactory outcomes when BCG fails (10). To that end, it seems that advances in intravesical drug administration techniques are starting to provide favorable outcomes. Chemohyperthermia (CHT) and electromotive drug administration (EMDA) are two methods developed to achieve this aim. In CHT, a specialized urethral catheter is used to deliver radiofrequency waves inside the bladder, thus raising the temperature. This increases cell permeability to MMC and promotes apoptosis by inducing stress in tumor cells (11). After using this technique in 111 patients with failed BCG, Nativ et al. (12) reported recurrence-free rates of 85% at 1 year and 56% at 2 years. In another study including 51 patients with failed BCG from 15 centers in Europe, Witjes et al. (13) reported complete response rates of 92% initially and 50% after 2 years. Although CHT is recognized by many authorities, it is still in the Food and Drug Administration (FDA) review process. EMDA aims to create an electromagnetic field to increase bladder surface epithelial cell permeability to MMC (14). Like CHT, EMDA was designed to increase the efficacy of MMC in moderate and high-risk NMIBC, but was unable to provide satisfactory results when applied after resistance to BCG. Sockett et al. (15) reported 31% relapse at 15 months in 13 patients with failed BCG who were given MMC by EMDA.

Gemcitabine

Gemcitabine (GC) is a nucleotide antimetabolite that disrupts DNA synthesis in tumor cells by inhibiting ribonucleotide reductase and cystine diaminase (4). In a randomized controlled study, Addeo et al. (16) determined that GC was more effective and less toxic than MMC. In their phase 2 trial, Skinner et al. (17) reported a recurrence-free rate of 28% after 1 year of treatment with intravesical GC. Prasanna et al. (18) also reported in their study that intravesical GC provided a similar disease-free survival to intravesical BCG and caused less toxicity. Although intravesical BCG is currently the gold standard treatment for high-risk NMIBC, GC may be recommended as an alternative first-line intravesical therapy for BCG-resistant patients not suitable for cystectomy and patients who cannot tolerate the toxicity of BCG (18).

Valrubicin

Valrubicin is a synthetic anthracycline analogue that exerts a toxic effect by penetrating nucleic acid sequences and arresting the cell cycle (19). Steinberg et al. (19), who comprise the valrubicin study group, reported a complete response rate of 21% and disease-free rate of 8% at the end of 18 months follow-up in 90 patients with BCG-refractory CIS. As a result of this study, intravesical valrubicin therapy is the only chemotherapeutic agent approved by the FDA for BCG-refractory CIS (20).

Taxanes (Docetaxel and Paclitaxel)

Agents in the taxane group act by disrupting microtubule function and halting cell division at M-phase (21). Preclinical studies have shown that taxane chemotherapeutics are highly effective on bladder cancer cells (22). Laudano et al. (22) conducted a phase 1 trial in which intravesical docetaxel (DTX) was administered to 18 patients who did not respond to intravesical BCG, and reported a complete response rate of 22%, partial response rate of 17%, and non-response rate of 61% during a mean follow-up of 48 months (22). In another study by Barlow et al. (23) 54 non-responders to BCG where administered intravesical DTX, and recurrence-free rates at 1 and 3 years were 40% and 25%, respectively.

Intravesical agents must remain in the bladder for 2 hours to achieve maximum efficacy (24). However, due to reasons such as bladder irritability or low bladder capacity, this waiting period is often unachievable (24). Since paclitaxel (PTX) was first introduced in 1967, many carrier agents have been investigated to increase the efficacy of taxanes due to their lipophilic properties and low cell penetration (4). In the phase 1 study by McKiernan et al. (25) using PTX bound to intravesical nanoparticle albumin (NPA), the complete response rate at 6 weeks was 28% and only grade 1 toxicity occurred in 10 of the 18 patients. In a subsequent phase 2 study, the complete response rate was 35.7% and toxicity rate was 32.1% at 1 year (26). Robins et al. (27) recently reported a disease-free rate of 18% and a cancer-specific survival rate of 9% at the end of 41 months follow-up in patients treated with NPA-bound PTX after BCG failure.

Interferon

IFN is a cytokine with immunomodulatory, antiproliferative, and antiviral properties (28). Earlier research established that IFN monotherapy had no utility in the treatment of NMIBC (28). The first of these studies was a 1990 prospective randomized study by Glashan (29) including 87 patients who were treated with either low-dose (10 million U) or high-dose (100 million U) intravesical IFN monotherapy and followed for 12 months. After 1 year, complete response rate was 43% in the high-dose arm and 5% in the low-dose arm (29). The most common side effects were influenza-like symptoms, which occurred in 17% of patients in the high-dose arm and 8% of those in the low-dose arm (29). However, in 1995, Hudson and Ratliff (30) conducted a prospective study with 12 patients who were treated with intravesical IFN (100 million U) after non-response to previous BCG treatment, and they reported a complete response rate of 8% at the end of 24 months. In a multi-center randomized phase 2 trial of intravesical BCG and IFN combined therapy conducted by Joudi et al. (31) a cancer-free survival rate of 13% was reported at the end of 24 months follow-up. In another prospective study including 50 patients treated

with a combination of BCG and IFN, Bazarbashi et al. (32) reported that 62% of the patients were recurrence-free after a median follow-up of 55.8 months. Eighteen percent of the patients developed grade 3 dysuria and 14% developed grade 3 frequency (32).

Mycobacterial Cell Wall Extracts

Intravesical BCG, currently the gold standard treatment for high-risk NMIBC, seems to stimulate an inflammatory response in target cells (33). Research on mycobacteria first started in 1970 with animal studies, and the first study regarding its successful intravesical use in humans was published by Morales et al. (34) in 1976. Although treatment with BCG obtained from live attenuated mycobacteria is undeniably effective, it also gives rise to local and systemic adverse effects (33). This has led to a search for more effective and less toxic agents (33). *Mycobacterium phlei* cell wall and mycobacterial cell wall-nucleic acid complex (MCNA) were tested in the treatment of NMIBC in 1996 and 1997, respectively (35,36). Morales et al. (37,38) first published initial results with the purportedly immunomodulatory and cytotoxic MCNA in 2001, and in a recent phase 3 trial of MCNA for BCG-resistant patients published in 2015, they reported complete response rates of 22% and 19% at 1 year and 2 years, respectively (36). However, MCNA failed to gain FDA approval in 2016 (39).

Targeted Therapies

Bladder cancer is one of the most immunogenic cancers, with high rates of somatic mutation (40). One of the unique features of the bladder is that it forms a defense against microorganisms without eliciting an immune response (41). This makes it rather difficult to generate an anti-tumor response against bladder tumors (41). Bladder tumor cells evade the immune system using immune checkpoints that block T-lymphocyte defense. Programmed death-1 (PD-1), programmed death ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated protein-4 are the most extensively studied checkpoints (42). Research has been based on the premise that immune checkpoint blockade would shrink the tumor cells. The search for less toxic second-line agents for metastatic bladder cancer patients who cannot be treated with cisplatin (MDP)-based chemotherapeutic agents resulted in the discovery of targeted agents, some of which have been approved by the FDA (43). Current research is focusing on targeted agents to be used in NMIBC when BCG fails (43). Phase 2 studies of anti-PD-1/PD-L1 seem promising for patients with intravesical BCG-refractory NMIBC (44,45). Intravesical use of targeted agents to reduce systemic side effects is an important and necessary area of research (46). VB4-845 is an immunomodulatory recombinant protein bound to *Pseudomonas* exotoxin that can be administered intravesically (9). This agent causes apoptosis of tumor cells, but a complete response rate of only 16% at 12 months was reported in a phase 2 trial (9).

Oncoviral Agents

The use of viral agents for tumor control is an area of intensive study in current medical practice. Inducing tumor cell lysis (oncolysis) via oncolytic viral agents can be achieved by direct stimulation of infected cells, by indirect stimulation of non-infected cells, or by stimulation of the immune system (47). In a phase 1 trial by Burke et al. (48) evaluating intravesical administration of CG0070 (adenoviral agents expressing granulocyte-macrophage colony-stimulating factor ([GM-CSF]) in 3 sessions over 28 days or in 6 weekly sessions, the response rate was 48.6% and the complete response rate was 61.5% at even the lowest doses. A single-arm, multi-center phase 3 trial evaluating the safety and efficacy of GC0070 in NMIBC patients who have previous BCG failure and refuse cystectomy is still in progress (47).

Photodynamic Treatment Approaches

Photodynamic therapy (PDT) is a method in which photosensitized agents are activated by specific wavelengths of light to cause apoptosis and necrosis of tumor cells (49). Dating back to the early 20th century, PDT has been used for tumor treatment in many fields (49). In 1976, Kelly and Snell (50) reported the first data on the use of PDT in bladder cancer. However, the degree of systemic toxicity necessitated the development of new agents. The first data on the use of 5-aminolevulinic acid (5-ALA) were reported by Kriegmair et al. (51) in 1996. Intravenous administration of 5-ALA in PDT resulted in a complete response rate of 31% at 1 year, and 19% of the patients experienced bladder spasms as an adverse effect (49). In a study by Lee et al. (52) including 34 patients, tumor-free survival rate was 90% at 12 months and 60% at 30 months. Berger et al. (53) reported a complete response rate of 40% at 1 year in patients treated with intravesical 5-ALA. When hexaminolevulinic acid was used for the same purpose, the complete response rate at 1 year was 12% (54). Although low response rates prevent the widespread use of PDT, it may become relevant as an alternative therapy in the future.

Combined Therapies

Because different chemotherapeutic agents have different mechanisms of action, combined therapies are utilized to create synergistic effects for cancer treatment (4). This known property of chemotherapeutics in cancer treatment has been investigated in salvage intravesical applications in patients with failed BCG (4).

In a study evaluating intravesical administration of an adriamycin and MMC combination, Fukui et al. (55) reported that 13 of 30 CIS patients were completely tumor-free at the end of 23 months follow-up, but the high rate of local toxicity (70%) compelled the researchers to seek new combinations.

In a retrospective study by Cockerill et al. (56) including 27 patients, 37% were recurrence-free at 22 months follow-up while recurrence was detected at a mean of 15 months in the other 63%, and 1 patient (3.7%) showed progression during treatment. In another retrospective multi-center study in which 47 patients with failed BCG received intravesical combined GC/MMC, Lightfoot et al. (57) reported a recurrence-free rate of 48% at 1 year and 38% at 2 years. The first known data on treatment with intravesical GC/DTX in patients with failed BCG were published by Steinberg et al. (58) who reported a

recurrence-free rate of 54% at 1 year and 34% at 2 years, and a complete response rate of 66%. Milbar et al. (59) retrospectively analyzed the data of 33 patients who received intravesical GC/DTX therapy and reported recurrence-free rates of 56% and 42% at 1 and 2 years, respectively. Only 2 (3%) patients could not tolerate the treatment (59).

Chen et al. (60) compared the success rates of BCG with those of an intravesical MMC, doxorubicin, and MDP protocol, and reported comparable recurrence rates at 5 years (37.9% vs 33.9%). With a 5.8% major adverse event profile, intravesical MDP seems superior to intravesical BCG, which had a 15% major adverse event profile (60). Despite these data, further research is needed on intravesical MDP therapy in patients resistant to intravesical BCG.

In a study of 54 patients with BCG failure, Steinberg et al. (61) added intravesical interleukin-2 and subcutaneous GM-CSF to intravesical BCG and IFN therapy, and reported success rates of 55% and 53% at 1 and 2 years, respectively. Treatment intolerance was observed in 6% of the patients (61).

Conclusion

Intravesical BCG has been used in high-risk NMIBC for nearly half a century (9). Nevertheless, radical cystectomy is still recommended in patients with resistance to or intolerance of intravesical BCG therapy. However, the FDA has also acknowledged the need for intravesical salvage therapy for patients who are ineligible for or refuse a complicated surgery like cystectomy, and research is being supported to accelerate the discovery of new agents for this patient group (3). All of the treatments described above appear to offer some degree of success, but most of the studies are focused on small and heterogeneous patient groups with short follow-up periods.

Consequently, therapies that are potentially useful for high-risk NMIBC patients with limited options should be reevaluated with appropriate endpoints.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Derleme / *Review*

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Mesane Kanserinde Organ Koruyucu Yaklaşım: Güncel Durum Değerlendirmesi

Organ-Preserving Approach in Bladder Cancer: Assessment of the Current Situation

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Öz

İntravezikal bacillus Calmette-Guérin (BCG) tedavisi yüksek riskli kasa invaze olmayan mesane kanserinde altın standart tedavi seçeneğidir. Bununla beraber BCG oldukça toksik bir ajandır. Tedaviye başladıktan sonra hastaların önemli bir kısmında BCG intoleransı izlenir. İster BCG başarısızlığı olsun, ister BCG intoleransı olsun radikal sistektomi bu aşamada önerilen tedavi yaklaşımı olmaktadır. Komorbiditeleri nedeniyle radikal sistektomiyi tolere edemeyecek ya da böylesi bir cerrahiyi kabul etmeyen hastalarda alternatif intravezikal kurtarma tedavilerine ihtiyaç vardır. Bu derlemede intravezikal BCG başarısızlığında radikal sistektomiye alternatif intravezikal güncel tedavi seçenekleri onkolojik sonuçlarıyla birlikte tartışılmıştır.

Anahtar Kelimeler: Mesane kanseri, bacillus Calmette-Guérin başarısızlığı, intravezikal kurtarma tedavisi

Abstract

Intravesical bacillus Calmette-Guerin (BCG) therapy is the gold standard treatment option in high-risk non-invasive bladder cancer. However, BCG is a very toxic agent. A significant proportion of patients have BCG intolerance after beginning intravesical treatment. Radical cystectomy is the recommended approach for patients with either BCG failure or BCG intolerance. Alternative intravesical salvage treatments are needed for patients who cannot tolerate radical cystectomy due to comorbidities or who refuse surgery.

In this review, current intravesical treatment alternatives to radical cystectomy in intravesical BCG failure are discussed with oncologic outcomes.

Keywords: Bladder cancer, bacillus Calmette-Guérin failure, intravesical salvage therapy

Giriş

Mesane kanseri erkek cinsiyette yedinci, her iki cinsiyet gözetildiğinde de on birinci en sık görülen kanser olma özelliğini taşımaktadır (1). Yalnızca 2016 yılı içinde Amerika Birleşik Devletleri'nde 76,960 yeni tanı almış olgu tanımlanmış ve 16,390 kansere özgü ölüm bildirilmiştir (2). Etkin bir endoskopik rezeksiyon ve gereğinde metastatik değerlendirme ile kanser evresi ve tedavi planlaması yapılabilmektedir. Olguların %70 kadarı ilk tanı anında kasa invaze olmayan yüzeyel kanser (KİOMK) şeklinde görülmekle beraber, bu olguların yaklaşık %20 kadarı karsinoma *in situ* (CIS) dahil yüksek dereceli Ta ve T1 tümörler oluşturmaktadır ki bu özel grup kanser progresyon ve nüks açısından yüksek risk taşımaktadır (3). Bu yüksek riskli KİOMK olgularında, intravezikal bacillus Calmette-Guerin (BCG) tedavisi temel tedavi yaklaşımını oluşturmaktadır (4). Kasa invaze mesane kanseri, metastatik değil ise radikal sistektomi en uzun sürvi beklentisini karşılayan altın standart tedavi seçeneği olarak bilinmektedir. Amaç tam tümörsüzlük olunca, %13'lük grade 3-4 komplikasyon görülme oranı ve %2,5-5,2'lik mortalite oranı kabul edilebilir görülmektedir (5).

KİOMK hastaları, intravezikal BCG ile başarılı bir şekilde tedavi edilebilse de 5 yıllık takiplerinde %80 nüks ve %40 progresyon oranları görülmektedir. İntravezikal BCG şeması 2000 yılında Güneybatı Onkoloji Grubu (SWOG) çalışmasında tanımlandığı şekilde; 6 haftalık indüksiyon tedavisi ardından yapılan endoskopik kontrolünde tümör izlenmez ise, 3 yıl boyunca idame şeklinde uygulanmaktadır (6). Ancak persistan veya nüks KİOMK varlığında hastaların önemli bir kısmı, alfa interferon (IFN) ile beraber veya değil; tekrar 6 haftalık indüksiyon tedavisinden yarar görebilmektedir (3). İntravezikal BCG tedavisi altında ilk sistoskopik kontrolünde yüksek dereceli KİOMK varlığında (7), ilk ve ikinci sistoskopik kontrolünde CIS varlığında (7), tedavi sırasında veya intravezikal BCG protokolü bitimi sonrası sistoskopik takiplerinde yüksek dereceli kanser varlığında (7) BCG direncinden söz edilir. Tedavinin devam etmesini imkansız kılan yan etki oluşması durumunda ise BCG intoleransından söz edilir (7,8). BCG direnci veya BCG intoleransı olan KİOMK hastaları radikal sistektomi adayıdırlar (9).

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Ancak özellikle ileri yaş hastalarda beraberinde çeşitli komorbid durumların bulunması ve genç hastaların böylesi bir cerrahi riski almak istememeleri radikal sistektomiye alternatif lokal tedavi arayışlarını artırmıştır (5).

Mitomisin C

Thiotepa, adriamisin ve mitomisin c (MMC) önceleri BCG duyarlı ancak BCG alamayan hastalar için tercih edilen ilk sıra ajanlardı (9). Bu özelliğini günümüzde ancak MMC korumaktadır (10). MMC kemoterapetik ajanlar içinde önemli bir yere sahiptir. DNA sentezini bozan alkalleyici bir ajandır (4). KİOMK tedavisinin perioperatif ayağında özellikle tümör ekimini bloke edici özelliği nedeni ile kulanılmaktadır (4). Ancak BCG başarısızlığında idame tedavisinin yüz güldürücü sonuçları bulunmamaktadır (10). Bu amaçla intravezikal ilaç uygulama tekniklerindeki gelişmeler ile olumlu sonuçlar alınmaya başlanmış görünmektedir. Kemohipertermi (K-HT) ve elektromotif ilaç uygulaması (EMDA) bu amaçla geliştirilmiş iki yöntemdir. K-HT uygulamasında özel geliştirilmiş üretral kateter ile mesane içine uygulanan radyofrekans dalgaları ile ısı artışı oluşturulmaktadır. Bu etki ile MMC için hücre geçirgenliği artırılmakta, tümör hücrelerinde oluşturulan stres ile apoptoz artırılmaktadır (11). Nativ ve ark. (12) BCG başarısız 111 hastada yaptıkları çalışmada bir yıl için %85, iki yıl için %56 rekürrensizlik oranı bildirmişlerdir. Avrupa'da 15 merkezden BCG başarısız 51 hastanın dahil edildiği çalışma sonunda, Witjes ve ark. (13) %92 başlangıç ve iki yıl sonunda ise %50 tam yanıt oranı bildirmişlerdir. K-HT, birçok otorite tarafından kabul görse de Amerikan Gıda ve İlaç Dairesi (FDA) halen değerlendirme aşamasındadır. EMDA tedavisinde, elektromanyetik bir alan oluşturularak MMC'ye karşı mesane yüzey epitel hücre geçirgenliğinin artırılması amaçlanmaktadır (14). EMDA, K-HT uygulaması gibi orta ve yüksek riskli KİOMK'de MMC etkinliğini artırmak için hedeflenmiş olup, intravezikal BCG direnci sonrası uygulamalarında yüz güldürücü sonuç alınamamıştır. Sockett ve ark. (15) bir çalışmalarında, EMDA ile MMC uygulanmış BCG başarısız 13 hastanın 15 aylık takiplerinde %31 nüks bildirmişlerdir.

Gemsitabin

Gemsitabin (GC), ribonükleotid redüktaz ve sistidin diaminazı inhibe ederek tümör hücrelerinde DNA sentezini bozan nükleotid antimetabolitidir (4). Addeo ve ark. (16) randomize kontrollü çalışmalarında; GC'nin MMC'den daha etkili, bunun yanında daha az toksik olduğunu görmüşlerdir. Skinner ve ark. (17) yaptıkları faz 2 çalışma sonucunda, intravezikal GC ile tedavide ilk yılın sonunda %28 rekürrensizlik oranı tanımlamışlardır. Prasanna ve ark. (18) yaptıkları çalışmada intravezikal GC'nin intravezikal BCG ile karşılaştırıldığında benzer hastalıksız sağkalım yanında daha düşük toksisiteye neden olduğunu bildirmişlerdir. Her ne kadar intravezikal BCG halen yüksek riskli KİOMK tedavisinin altın standart tedavisi olsa da sistektomiye uygun olmayan BCG dirençli olgular ile BCG toksisitesini tolere edemeyen hastalarda alternatif ilk sıra intravezikal tedavi olarak önerilebilir (18).

Valrubisin

Sentetik bir antrasiklin analoğu olan valrubisin; nükleik asit dizeleri içine nüfuz ederek, hücre siklusunu duraklatarak toksik etki oluşturmaktadır (19). Steinberg ve ark. (19) oluşturdukları valrubisin çalışma grubunun yürüttüğü BCG dirençli CIS'si olan 90 hastalık çalışmalarında, 18 aylık takip süresinde %21 tam kür ve %8 hastalıksızlık oranı bildirmişlerdir. Bu çalışma neticesinde intravezikal valrubisin tedavisi, BCG dirençli CIS olgularında FDA onayı almış tek kemoterapetik ajandır (20).

Taksanlar (Dokataksel ve Paklitaksel)

Taksan grubu ajanlar, mikrotübül fonksiyonlarını bozarak hücre bölünmesini M-fazında durdurarak etki ederler (21). Preklinik çalışmalarda taksan grubu kemoterapetiklerin mesane kanser hücrelerine oldukca etkili olduğu gösterilmiştir (22). Laudano ve ark. (22) intravezikal BCG yanıtsız 18 hastaya dokataksel (DTX) intravezikal uygulayarak yürüttüğü faz 1 çalışmada, ortalama 48 aylık takip süresince tam yanıt oranı %22, kısmi yanıt oranı %17 ve yanıtsızlık oranı %61 olarak bildirilmiştir. Yine Barlow ve ark. (23) intravezikal DTX kullandıkları BCG yanıtsız 54 hastalık çalışmaları sonucunda, bir ve üç yıllık nükssüzlük oranlarını sırasıyla %40 ve %25 olarak bildirmiştir.

Maksimum etkinlik için intravezikal ajanların 2 saat mesane içinde beklemesi gerekmektedir (24). Ancak mesane irritabilitesi veya düşük mesane kapasitesi gibi nedenler dolayısı ile çoğu zaman istenen bekleme süresine ulaşılamamaktadır (24). 1967 yılında paklitaksel (PTX) ilk tanımlandığından beri taksanların lipofilik özellikleri ve düşük hücre penetrasyonları nedeniyle etkinliklerini artırmak için birçok taşıyıcı madde üzerinde çalışılmıştır (4). McKiernan ve ark. (25) intravezikal nanoparçacıklı albümin (NPA) bağlanmış PTX kullanarak yürüttükleri faz 1 çalışmada, 6 haftada tam yanıt oranını %28 olarak bildirmiş ve 18 hastanın 10'unda sadece derece 1 toksisite bildirmiştir. Daha sonra yürüttükleri faz 2 çalışmada 1 yıl sonunda tam yanıt oranını %35,7 olarak bildirmiş, toksisite oranını ise %32,1 olarak bildirmişlerdir (26). Yakın zamanda Robins ve ark. (27) yürüttükleri çalışma sonucunda BCG başarısız hastalarda uyguladıkları intravezikal NPA bağlanmış PTX uygulanmış hastalarda 41 aylık takip sonunda %18 hastalıksızlık oranı bildirmişler, kanser spesifik sürvi oranını ise %9 olarak bildirmişlerdir.

İnterferon

IFN immünomodülatör, antiprolferatif ve antiviral özelliği olan bir sitokindir (28). Geçmiş çalışmalarda IFN monoterapisinin KİOMK tedavisinde yeri bulunmadığı gösterilmiştir (28). İlk olarak 1990 yılında Glashan'ın (29) yürüttüğü 87 olguluk prospektif randomize çalışmada, hastalar düşük (10 milyon Ü) ve yüksek (100 milyon Ü) intravezikal IFN monoterapi dozuna göre iki gruba ayrılmış ve 12 ay takip edilmişlerdir. Bir yılın sonunda yüksek doz kolunda %43, düşük doz kolunda %5 tam cevap bildirmişlerdir (29). En sık grip benzeri yan etkiler görülmüş olup, yüksek doz kolunda %17 ve düşük doz

kolunda %8 olarak bildirilmiştir (29). Ne var ki 1995 yılında, Hudson ve Ratliff (30) intravezikal IFN (100 milyon Ü) tedavisi uyguladıkları önceden BCG tedavisi yanıtı alınamamış 12 hastalık prospektif çalışmalarında, tam cevap oranını 24 ayın sonunda %8 olarak bildirmişlerdir. Joudi ve ark. (31) yürüttükleri çok merkezli randomize faz 2 çalışmalarında, 24 aylık takip sonunda intravezikal BCG ve IFN kombine tedavisinde kansersiz sürvi oranını %13 olarak bildirmişlerdir. Bazarbashi ve ark. (32) intravezikal BCG ve IFN kombine tedavisi verdikleri 50 hastalık prospektif çalışmaları sonunda, ortalama 55,8 aylık takip sonunda %62 nükssüzlük oranı bildirmişlerdir (32). Çalışmaya katılan hastaların %18'inde derece 3 dizüri ve %14'ünde derece 3 işemede sıklık bildirilmiştir (32).

Mikobakter Hücre Duvar Ekstreleri

İntravezikal BCG, yüksek riskli KİOMK'ler için günümüzün altın standart tedavisidir (33). BCG, hedef hücrelerde enflamatuvar yanıtı uyarıyor görünmektedir (33). Mikobakteriler ile ilgili çalışmalar ilk defa 1970 yılında hayvan çalışmaları olarak başlamış, 1976 yılında da insanlar üzerindeki intravezikal başarısı ile ilgili ilk çalışma Morales ve ark. (34) tarafından yayınlanmıştır. Canlı atenüe mikobakterilerden elde edilen BCG tedavisinin etkinliği tartışılmaz olmasına rağmen önemli lokal ve sistemik yan etkileri de beraberinde getirmektedir (33). Bu sebepledir ki daha etkin ve daha az toksik ajanların arayışı gündeme gelmiştir (33). 1996 yılında *Mycobacterium phlei* hücre duvarı, ardından 1997 yılında mikobakterial hücre duvarı nükleik asit kompleksi (MHNA) KİOMK tedavisinde çalışılmıştır (35,36). Kanser hücreleri için immünomodülatör ve sitotoksik olduğu düşünülen MHNA ile ilgili Morales ve ark. (37,38) tarafından 2001 yılında ilk sonuçları bildirilmiş ve 2015 yılında yayınladıkları son faz 3 çalışmasında BCG dirençli olgularda MHNA kullanımı ile bir yılın sonunda %22, iki yılın sonunda %19 tam yanıt bildirmişlerdir (36). Ne var ki MHNA, 2016 yılında FDA tarafından onay alamamıştır (39).

Hedefe Yönelik Tedaviler

Mesane kanseri, yüksek somatik mutasyon oranları ile en immünojenik kanserlerden biridir (40). Bağışıklık cevabı oluşturmadan mikroorganizmalara karşı savunma oluşturmak mesanenin ayrıcalıklı özelliklerinden biridir (41). Bu özelliğinden dolayı mesane tümörüne karşı anti-tümör yanıt oluşturmak oldukça zordur (41). Mesane tümör hücreleri, bağışıklık sistemini atlatmak için T-lenfosit savunmasını bloke eden immün kontrol noktalarını kullanmaktadır. Programmed death-1 (PD-1), programmed death ligand-1 (PD-L1) ve cytotoxic T-lymphocyte-associated protein-4 üzerinde en çok çalışılmış kontrol noktalarıdır (42). Bu kontrol noktalarının bloke edilmesi ile tümör hücrelerinin küçüleceği fikri üzerine çalışılmıştır. Metastatik mesane kanserinde sisplatin (MDP) bazlı kemoterapetik ajanların verilemeyeceği hasta grubuna yönelik ikinci sıra daha az toksik ajanların arayışı, bir kısmı FDA tarafından onay almış hedefe yönelik ajanların keşfine neden olmuştur (43). Günümüzde özellikle BCG başarısız KİOMK'de kullanılmak üzere hedefe yönelik ajanlar çalışılmaktadır (43). Anti-PD-1/PD-L1 ile yapılan faz 2 çalışmalar intravezikal BCG dirençli KİOMK hastaları için umut vaat edecek gibi görünmektedir (44,45). Sistemik yan etkileri azaltmak için hedefe yönelik ajanların intravezikal kullanımı, araştırılması gerekli önemli bir alandır (46). VB4-845, intravezikal uygulanabilen *Pseudomonas* ekzotoksinine bağlı bağışıklık düzenleyici rekombinant bir proteindir (9). Tümör hücrelerinde apoptoza neden olan bu ajan ile yapılmış faz 2 çalışmada, 12 ayın sonunda ancak %16 tam yanıt oranı bildirilmiştir (9).

Onkoviral Ajanlar

Tümör kontrolünde viral ajanların kullanımı günümüz tıp pratiğinde üzerinde ciddi olarak çalışılan bir konu olmuştur. Onkolitik viral ajanların kullanılarak tümör hücrelerinin lizize uğratılması (onkoliz) enfekte hücrelerin direkt ya da enfekte olmayan hücrelerin indirekt ya da bağışıklık sisteminin uyarılması ile gerçekleşmektedir (47). Burke ve ark. (48) yürüttükleri faz 1 çalışmada CG0070 [granülosit makrofaj koloni uyarıcı faktör (GM-CSF) eksprese eden adenoviral ajan] 28 günde bir 3 seans ya da haftalık 6 seans intravezikal uyguladıklarında %48,6 yanıt oranı ve en düşük dozlarda bile %61,5 tam yanıt oranı bildirmişlerdir. İntravezikal BCG tedavisinin başarısız olduğu ve sistektomiyi kabul etmemiş KİOMK hastalarında GC0070 güvenliği ve etkinliğini değerlendiren, tek kollu çok merkezli faz 3 çalışma halen devam etmektedir (47).

Fotodinamik Tedavi Yaklaşımları

Fotodinamik tedavi (FDT) belli bir dalga boyunda ışık ile aktive olan fotosensitize ajanların kullanılarak tümör hücrelerinin apoptozu ile nekrozunu sağlayan yöntemdir (49). FDT, 20. yüzyıl başlarına dayanan hikayesi ile birçok alanda tümöral tedavilerde kullanılmıştır (49). 1976 yılında Kelly ve Snell (50) tarafından FDT'nin mesane kanserindeki kullanımı ile ilgili ilk veriler paylaşılmıştır. Ancak sistemik toksisitenin fazla olması yeni ajanların geliştirilmesi ihtiyacını doğurmuştur. 5-aminolevolonik asit (5-ALA) kullanımı ile ilgili ilk verileri Kriegmair ve ark. (51) 1996 yılında bildirmişlerdir. FDT'de 5-ALA intravenöz uygulandığında ilk yıl %31 tam cevap oranı ve yan etki olarak %19 mesane kontraktürü bildirilmiştir (49). Lee ve ark. (52) 34 hastalık çalışmalarında 12. ayda %90 ve 30. ayda %60 tümörsüz sağkalım oranı bildirmişlerdir. Berger ve ark. (53), intravezikal 5-ALA uyguladıkları hastalarda ilk yıl %40 tam yanıt oranı bildirmişlerdir. Bu amaçla heksaminolevulinik asit kullanıldığında ilk yıl %12 tam yanıt bildirilmiştir (54). Yanıt oranlarının düşük olması FDT yaygın kullanımını engellemekle beraber ileride belki de alternatif tedavilerde tekrar gündeme gelecektir.

Kombine Tedaviler

Farklı kemoterapetik ajanların farklı etki mekanizmaları olduğundan dolayı kanser tedavisinde sinerjik etki oluşturmak için kombine tedavilerden yararlanılmaktadır (4). Kanser tedavisinde

kemoterapetiklerin bu bilinen özelliği, BCG başarısızlığında salvage intravezikal uygulamalarda araştırılmıştır (4).

Fukui ve ark. (55) yürüttükleri çalışmada, adriamisin ile MMC kombinasyonunu intravezikal olarak uyguladıkları 30 CIS hastasının ortalama 23 aylık takibinde 13 hastada tam tümörsüzlük bildirmişlerdir; ancak %70 gibi yüksek lokal toksisite oranı araştırmacıları yeni kombinasyon arayışına itmiştir.

Cockerill ve ark. (56) 27 hastayı değerlendirdikleri retrospektif çalışmalarında, 22 aylık takipte %37 hastada rekürrens izlenmezken, ortalama 15 ayda %63 hastada rekürrens görülmüş ve tedavi süresinde 1 (%3,7) hastada progresyon izlenmiştir. Lightfoot ve ark. (57), BCG başarısız intravezikal kombine GC/MMC verilmiş 47 hastayı retrospektif değerlendirdikleri çok merkezli çalışmalarında ilk yıl %48, ikinci yıl %38 rekürrensizlik oranı bildirmişlerdir. BCG başarısızlığında GC/DTX intravezikal tedavisi ile ilgili ilk bilinen veriler Steinberg ve ark. (58) tarafından yayınlanmıştır. Bu çalışmada ilk yıl %54, ikinci yıl %34 rekürrensizlik oranı ve %66 tam yanıt oranı bildirilmiştir (58). Milbar ve ark. (59) intravezikal GC/DTX tedavisi uygulanmış 33 hastanın verilerini retrospektif olarak incelemişlerdir; ilk yıl %56, sonraki yıl için %42 nükssüzlük oranı bildirmişlerdir. Sadece 2 (%3) hasta tedaviyi tolere edememiştir (59).

Chen ve ark. (60) intravezikal MMC, doksorubisin ve MDP protokolü ile BCG başarısını karşılaştırdıkları çalışmalarında benzer 5 yıllık rekürrens oranı bildirmişlerdir (%37,9'a karşı %33,9). İntravezikal MDP, %5,8'lik majör yan etki profili ile intravezikal BCG'nin %15'lik yan etki profilinden daha iyi görünmektedir (60). Bu verilere rağmen intravezikal MDP tedavisinin, intravezikal BCG direncinde çalışılmasına ihtiyaç vardır.

Steinberg ve ark. (61) BCG başarısız 54 hastada yürüttükleri çalışmada, intravezikal BCG ve IFN tedavisine intravezikal interlökin-2 ve subkutan GM-CSF eklenmesi ile %55, ikinci yıl %53 tedavi başarısı bildirmişlerdir. Tedaviyi tolere edemeyen hastaların oranını %6 olarak bildirmişlerdir (61).

Sonuç

İntravezikal BCG, neredeyse yarım yüzyıldır yüksek riskli KİOMK'de kullanılmaktadır (9). Bununla beraber intravezikal BCG tedavisine direnç veya intolerans varlığında radikal sistektomi halen önerilmektedir. Ancak sistektomi gibi komplike bir cerrahi için uygun olmayan ya da istemeyen hastalardaki intravezikal kurtarma tedavi ihtiyacı FDA tarafından da görülmüş olup, bu hasta grubunda hızlıca yeni ajanların bulunmasına yönelik çalışmalar desteklenmektedir (3). Yukarıdaki tedavilerin tümü özünde bir miktar başarı sağlıyor gibi görünmektedir; ancak çalışmaların çoğu küçük, heterojen ve kısa takip sürelerine sahip hasta gruplarından oluşmaktadır.

Son olarak, günümüzde fazla seçeneğe sahip olmayan yüksek riskli KİOMK hastaları için potansiyel olarak faydalı olabilecek tedaviler, uygun sona varım noktaları tanımlanarak yeniden gözden geçirilmelidir.

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Positron Emission Tomography in Renal Cell Carcinoma

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Abstract

Renal cell carcinoma is the most common solid kidney tumor. Conventional methods such as computed tomography and magnetic resonance imaging are usually chosen for diagnosis, staging, and evaluating recurrence and treatment response. However, the sensitivity of these methods is limited in each indication. For this reason, metabolic evaluation with positron emission tomography has an important value in most solid tumors. However, the role of 18-fluorine-fluorodeoxyglucose (18F-FDG), which is the most commonly used positron emission tomography (PET) radiopharmaceutical, is limited in the evaluation of primary kidney lesions due to urinary excretion. Therefore, new radiopharmaceuticals with no or limited urinary excretion have been developed. In this paper, the application of PET imaging with the widely used 18F-FDG and the newly developed fluorothymidine and gallium-68/18F prostate-specific membrane antigen in renal cell carcinoma are reviewed.

Keywords: Renal cell carcinoma, positron emission tomography, 18F-fluorodeoxyglucose, 18F-fluorothymidine, gallium-68 prostate-specific membrane antigen

Introduction

Renal cell carcinoma (RCC) is the most common solid kidney tumor. Contrast-enhanced computed tomography (CT) is the most frequently used imaging modality in the diagnosis, staging, and evaluation of recurrence and treatment response in patients with RCC. The overall success rate of CT for these indications is reported to be between 61% and 91% (1,2,3). However, as RCCs may appear isodense, hypodense, or hyperdense, it is difficult to distinguish benign and malignant renal masses by morphological methods (4). Magnetic resonance imaging (MRI) is recommended in cases where CT is contraindicated, such as patients who have contrast allergy or are pregnant. However, MRI is no more accurate than CT. This increases the importance of positron emission tomography (PET), which enables metabolic evaluation in addition to visualizing anatomic changes. In this review, we discuss currently available literature data regarding the use of PET applications with different radiopharmaceuticals in patients with RCC.

Applications of Positron Emission Tomography in Renal Cell Carcinoma

18-Fluorine-Fluorodeoxyglucose Positron Emission Tomography

PET is a metabolic imaging method that utilizes various positron-emitting radiopharmaceutical and can provide data on many different metabolic pathways. The most widely used radiopharmaceutical is a fluorodeoxyglucose molecule (FDG) labeled with 18-fluorine (18F). The modality is based on the principle of visualizing elevated glycolysis and glucose uptake in neoplastic tissues. Despite high success rates in many solid organ malignancies, the use of 18F-FDG for urinary system malignancies is limited due to excretion via the urinary tract. The first cases related to the use of 18F-FDG PET in RCC were described by Wahl et al. (5) in the early 1990s. The use of 18F-FDG PET in the detection of primary RCC is especially controversial (6,7,8,9,10). High and variable levels of background renal activity make it difficult to detect the primary focus. Forced diuresis with hydration may increase the sensitivity

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of 18F-FDG PET (11). However, many studies have shown that forced diuresis does not increase the sensitivity of 18F-FDG PET, and that background renal activity is actually increased in up to 60% of patients after diuretic injection due to physiological retention in the renal tubular epithelium (11,12,13,14,15,16). In addition to background physiological activity in the kidney, sensitivity is also affected by the size of the primary tumor and the rate of 18F-FDG uptake. It has been shown that tumors exhibiting uptake on 18F-FDG PET are larger in size and contain more glucose transporter-1 (GLUT-1) receptor compared to tumors without uptake (7,17,18). As a result, even when performed with forced diuresis, 18F-FDG PET is not an ideal imaging modality for diagnosing RCC. It is not possible to reach a conclusion about the place of 18F-FDG PET/CT in RCC diagnosis based on the limited information available in the literature (Table 1).

The introduction of hybrid PET/CT systems in routine practice has enabled more successful determination of tumor location. Sensitivity increases significantly in the detection of extrarenal lesions, although specificity does not change (19). Another advantage of the hybrid PET/CT system when monitoring for recurrence is the ability to differentially diagnose postoperative scar tissue, surgical clips, and displacement of the surrounding organs, which are difficult to distinguish in CT (20). Finally, 18F-FDG PET/CT allows whole-body assessment with a single imaging session, without the risk of contrast allergy or nephrotoxicity (21).

The quantitative evaluation of uptake using standard uptake value (SUV) has prognostic significance. Patients with higher SUV values at baseline are shown to have poorer prognosis and shorter survival. In addition, the presence of metastases may affect the mean SUV of the primary lesion. The mean SUV value of primary lesions of patients without distant organ metastasis was calculated as 2.6, compared to 5.0 for patients with distant metastases (22). Besides SUV values, metabolic parameters such as metabolic tumor volume and total lesion glycolysis calculated with PET imaging also have prognostic significance (23,24).

The sensitivity and specificity of 18F-FDG PET in the detection of extrarenal lesions have been reported as 79% and 90%, respectively (25). Loss of sensitivity due to urinary excretion of FDG is not observed with extrarenal lesions. However, 18F-FDG PET cannot detect small lesions as well as it does large lesions. The sensitivity of FDG PET increases from 76% to 93% when lesion size increases from 1 cm to 2 cm (26). Furthermore, high-grade tumors are located more accurately than low-grade tumors (Table 2) (19,21). 18F-FDG PET/CT has high sensitivity in detection of distant organ metastases and restaging RCC (Figures 1 and 2) (22). Another common indication for 18F-FDG PET/CT is evaluating response to tyrosine kinase inhibitor therapy. The Response Evaluation Criteria in Solid Tumors (RECIST) are frequently used when evaluating treatment response with anatomical methods such as CT and MRI. In this method, response is evaluated based on change in target lesion size. However, most antiangiogenic therapies used in recent years are cytostatic instead of cytotoxic, and usually cause tumor stabilization rather than tumor shrinkage. Another disadvantage of conventional methods is that they require a relatively long time for treatment response to be apparent radiologically. Many publications have reported that 18F-FDG PET/CT provides a more accurate assessment than the radiologic RECIST (22,27,28,29). 18F-FDG PET/CT is particularly superior for assessing treatment response in bone metastasis because the RECIST describe soft tissue lesions (28).

18-Fluorine-Fluorothymidine Positron Emission Tomography

18F-Fluorothymidine (FLT) is a thymidine analog that accumulates in the cell after phosphorylation by thymidine kinase but is not integrated into DNA structures (30). This radiopharmaceutical

Table 1. Diagnostic accuracy of 18-fluorine-fluorodeoxyglucose positron emission tomography/computed tomography for primary renal cell carcinoma lesions

Authors	TP	FP	TN	FN	Sensitivity	Specificity
Ramdave et al. (6)	15	0	1	1	94	100
Miyakita et al. (18)	6	0	13	0	32	–
Aide et al. (12)	14	1	16	4	47	80
Kang et al. (8)	9	0	6	2	60	100

TP: True positive, FP: False positive, TN: True negative, FN: False negative

Table 2. Diagnostic accuracy of 18-fluorine-fluorodeoxyglucose positron emission tomography/computed tomography for extrarenal lesions

Authors	TP	FP	TN	FN	Sensitivity	Specificity
Ramdave et al. (6)	2	0	0	15	100	100
Chang et al. (39)	9	1	1	4	90	80
Aide et al. (12)	10	3	0	40	100	93
Jadvar et al. (7)	15	1	6	3	71	75
Majhail et al. (26)	14	0	7	3	67	100

TP: True positive, FP: False positive, TN: True negative, FN: False negative

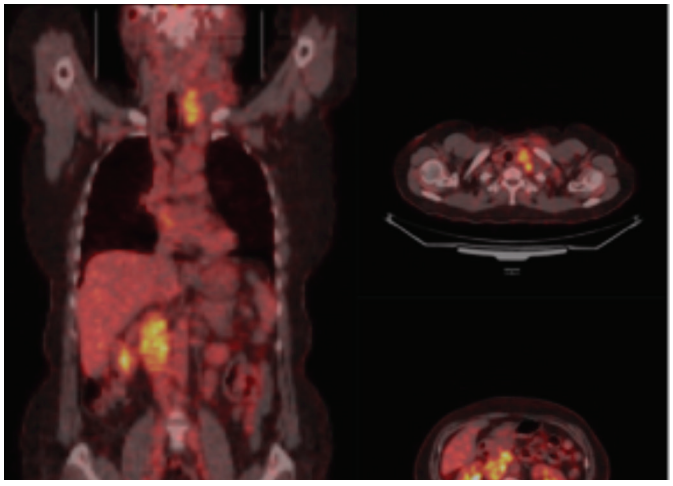

Figure 1. A 61-year-old female patient with history of renal cell carcinoma excision underwent 18-fluorine-fluorodeoxyglucose positron emission tomography/computed tomography for restaging of a soft tissue structure detected in the paraaortic area during follow-up. Pathologic uptake levels were noted in conglomerate lymph nodes filling the left supraclavicular and posterior cervical region (SUV_{max}: 8.4) and in the abdominal lymph nodes in the paraaortic and retrocrural area (SUV_{max}: 10.3)

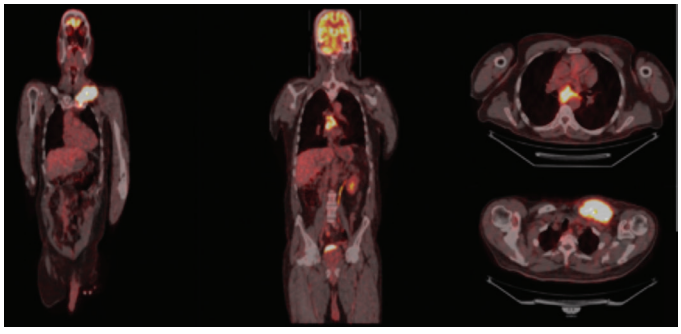

Figure 2. A 60-year-old male patient being under follow-up after right nephrectomy underwent 18-fluorine-fluorodeoxyglucose positron emission tomography/computed tomography due to detection of left supraclavicular and subcarinal lymph nodes on computed tomography. Intense pathologic 18-fluorine-fluorodeoxyglucose uptake was seen in the left supraclavicular lymph nodes (SUV_{max}: 22.0) and subcarinal lymph nodes (SUV_{max}: 16.3)

has the potential to enable PET evaluation of tumor proliferation (31,32). As a radiopharmaceutical that allows assessment of proliferation, its greatest advantage over 18F-FDG is the ability to more accurately distinguish inflammation and tumors. FLT uptake and higher initial FLT uptake are prognostic indicators in RCC (30). A correlation was shown between FLT uptake and Ki-67 index, a histopathologic proliferation marker (33). Although SUV values are lower than with 18F-FDG, metastatic lesions can be detected successfully because the physiological background activity is lower in regions such as the brain and mediastinum. However, it has a limited role in the assessment of liver metastases due to uptake associated with physiological activity in the liver. There are reports that FLT PET can be used successfully in the evaluation of treatment response in many tumors (34). Liuet al. (35) conducted FLT PET studies in 16 patients with RCC before sunitinib treatment, at the end of the first cycle of sunitinib treatment, and at the end of the washout period. Although they noted a marked decrease in proliferation during treatment, cell proliferation was markedly increased in the washout period. FLT PET allows evaluation of treatment response much earlier than FDG PET, even within the first week of therapy (36). Hybrid PET/MRI systems, which were recently introduced in clinical practice to assess treatment response of recurrence and solid organ metastases such as liver, are still used experimentally in many centers and have yielded encouraging results (37,38).

Gallium-68/18-Fluorine Prostate-Specific Membrane Antigen Positron Emission Tomography/Computed Tomography

Prostate-specific membrane antigen (PSMA) is an antigenic molecule present on the surface of prostate cancer cells. It is also expressed in RCC and many solid tumors with tumor neovascularization (39,40). PSMA is an exocrine expressed in the proximal tubule cells in normal kidney and to varying degrees in neovascular clear cell RCC (75%), chromophobe RCC (31%), oncocytoma (53%), and transitional cell carcinoma (21%) (40). PET imaging can be performed by binding PSMA to target molecules gallium (Ga)-68 or 18F. Ga-68 PSMA uptake in RCC was first reported as a case report (41). Histopathologic evidence indicates that while PSMA uptake does occur in areas of neovascularization, uptake in the proximal tubules occurs not in the adjacent vascular structures, but rather in the tubule cells (42). Moreover, it has been shown that PSMA expression is lost in RCCs arising from proximal tubule cells that express PSMA (40). In another case series, 18F PSMA uptake was assessed in 5 patients. In these five cases, 18F PSMA uptake was observed at varying levels with SUV values ranging from 1.6 to 19.3 in different metastatic lesions, and more metastatic foci were detected compared to conventional imaging methods (43). PSMA PET/CT seems to be particularly useful in patients with suspicious lesions detected by conventional imaging methods, such as when evaluating oligometastatic patients with subcentrimetric lesions or when identifying potentially resectable neighboring tumor foci in patients scheduled for cytoreductive nephrectomy (44). In addition to its high sensitivity, PSMA PET is also a functional imaging method that enables *in vivo* assessment of baseline neovascularization in metastatic lesions and may help predict treatment response prior to anti-vascular therapies such as tyrosine kinase inhibitors and bevacizumab. Another interesting finding is that sarcomatoid degeneration in RCCs is correlated with 18F-FDG uptake, not PSMA uptake, and histopathological samples show loss of PSMA expression and increased GLUT-1 receptor expression in sarcomatoid degeneration (45). The combined use of two PET studies may allow the non-invasive evaluation of sarcomatoid degeneration in different metastatic foci. Based on currently available data, PSMA PET seems likely to serve as a complementary method to enable detection of small metastatic foci undetectable by conventional methods and help evaluate response to treatments targeting neovascularization in future RCC patients.

However, most of the data in the literature are from case series and small patient groups. Therefore, the results of prospective studies involving larger numbers of patients are needed.

Conclusion

PET studies using different radiopharmaceuticals can be performed with varying sensitivity in the diagnosis, staging, and evaluation of recurrence and treatment response in patients with RCC. The ability to detect primary tumoral lesions by 18F-FDG PET is limited due to renal excretion. However, the success rate is high for metastatic foci. FLT PET, which demonstrates proliferation, and PSMA PET, which targets neovascularization, are also effective both in diagnosis and treatment response evaluation. In addition, high uptake at time of diagnosis is a prognostic indicator for all three pharmaceuticals.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: C.S., Y.Ü., Design: Y.Ü., Data Collection or Processing: C.S., Analysis or Interpretation: C.S., Y.Ü., Literature Search: C.S., Writing: C.S., Y.Ü.

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Derleme / *Review*

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Renal Hücreli Kanserde Pozitron Emisyon Tomografisi

Positron Emission Tomography in Renal Cell Carcinoma

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Öz

Renal hücreli kanser en sık görülen solid böbrek tümörüdür. Tanı, evreleme, nüks ve tedavi yanıtının değerlendirilmesinde bilgisayarlı tomografi ve manyetik rezonans görüntüleme gibi konvansiyonel yöntemler sıklıkla tercih edilmektedir. Ancak her bir endikasyonda bu yöntemlerin duyarlılıkları sınırlıdır. Bu nedenle pek çok solid tümörde başarı ile uygulanan pozitron emisyon tomografisi ile metabolik değerlendirme önem arz etmektedir. Ancak en yaygın kullanılan pozitron emisyon tomografisi (PET) radyofarmasötiği olan 18-flor-florodeoksiglikozun (18F-FDG) üriner ekskresyonu nedeni ile primer böbrek lezyonlarının değerlendirmesindeki yeri sınırlıdır. Bu nedenle üriner ekskresyon göstermeyen ya da üriner ekskresyonu sınırlı olan yeni radyofarmasötikler geliştirilmektedir. Bu makalede yaygın olarak uygulanan 18F-FDG ve yeni geliştirilen florotimidin ve galyum-68/flor-18 prostat spesifik membran antijen ile PET görüntülemenin renal hücreli kanserde uygulamaları derlenmiştir.

Anahtar Kelimeler: Renal hücreli kanser, pozitron emisyon tomografisi, 18F-florodeoksiglukoz, 18F-florotimidin, galyum-68 prostat spesifik membran antijen

Abstract

Renal cell carcinoma is the most common solid kidney tumor. Conventional methods such as computed tomography and magnetic resonance imaging are usually chosen for diagnosis, staging, and evaluating recurrence and treatment response. However, the sensitivity of these methods is limited in each indication. For this reason, metabolic evaluation with positron emission tomography has an important value in most solid tumors. However, the role of 18-fluorine-fluorodeoxyglucose (18F-FDG), which is the most commonly used positron emission tomography (PET) radiopharmaceutical, is limited in the evaluation of primary kidney lesions due to urinary excretion. Therefore, new radiopharmaceuticals with no or limited urinary excretion have been developed. In this paper, the application of PET imaging with the widely used 18F-FDG and the newly developed fluorothymidine and gallium-68/F prostate-specific membrane antigen in renal cell carcinoma are reviewed.

Keywords: Renal cell carcinoma, positron emission tomography, 18F-fluorodeoxyglucose, 18F-fluorothymidine, gallium-68 prostate-specific membrane antigen

Giriş

Renal hücreli kanser (RHK) en sık görülen solid böbrek tümörüdür. RHK'li hastalarda tanı, evreleme, nüks ve tedavi yanıtının değerlendirilmesinde en sık kullanılan görüntüleme yöntemi kontrastlı bilgisayarlı tomografidir (BT). BT'nin bu endikasyonlarda genel olarak başarısı %61 ile %91 arasında bildirilmiştir (1,2,3). Ancak RHK'ler isodens, hipodens ya da hiperdens görünebildiği için renal kitlelerin benign/malign ayrımının morfolojik yöntemler ile yapılması zordur (4). Manyetik rezonans görüntüleme (MRG) ise BT'nin kontrendike olduğu kontrast alerjisi ya da gebelik mevcudiyeti gibi durumlarda önerilmektedir. Ayrıca MRG de daha yüksek doğruluğa sahip değildir. Bu nedenle anatomik değişiklikler yanında metabolik değerlendirmeye olanak sağlayan pozitron emisyon tomografisi (PET) önem kazanmaktadır. Bu derlemede farklı radyofarmasötikler ile yapılan PET uygulamalarının RHK olgularında kullanımı ile ilgili literatürde mevcut bilgi sunulmuştur.

Renal Hücreli Kanserde Pozitron Emisyon Tomografisi Uygulamaları

18-Flor-Florodeoksiglikoz Pozitron Emisyon Tomografisi

PET pozitron yayan radyofarmasötiklerin kullanıldığı ve pek çok farklı metabolik yolağın gösterilebildiği metabolik bir görüntüleme yöntemidir. En yaygın kullanılan radyofarmasötik 18-flor (18F) ile florodeoksiglikoz (FDG) molekülüdür. Neoplazik dokularda artmış glikoliz ve artmış glikoz uptake'sinin görüntülenmesi prensibine dayanır. Pek çok solid organ malignitesinde yüksek başarısına rağmen 18F-FDG üriner yol ile ekskrete edildiğinden üriner sistem vile ilgili ilk olgular Wahl ve ark. (5) tarafından 1990'ların başında tanımlanmıştır. Özellikle primer RHK odağının saptanmasında 18F-FDG PET'nin kullanımı tartışmalıdır (6,7,8,9,10). Yüksek ve değişken böbrek zemin aktivitesi primer odağın saptanmasını zorlaştırmaktadır. Hidrasyon eşliğinde zorlu diürez 18F-FDG PET'nin duyarlılığını artırabilir (11). Ancak yapılan pek çok çalışmada zorlu diürezin 18F-FDG PET'nin

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duyarlılığını artırmadığı, hatta diüretik enjeksiyonu sonrasında %60'a kadar olguda renal tübül epitelinde fizyolojik tutulum nedeni ile böbrek zemin aktivitesinin daha da arttığı gösterilmiştir (11,12,13,14,15,16). Böbrekteki fizyolojik zemin aktivitesi dışında primer tümörün boyutu ve 18F-FDG tutulum oranı da duyarlılığı etkilemektedir. 18F-FDG PET'de tutulum izlenen tümörlerin tutulum göstermeyenlere göre daha büyük boyutlu olduğu ve daha yüksek oranda glikoz transport-1 (GLUT-1) reseptörü içerdiği gösterilmiştir (7,17,18). Sonuç olarak zorlu diürez eşliğinde yapılsa dahi 18F-FDG PET, RHK tanısında tercih edilmesi gereken bir görüntüleme yöntemi değildir. Literatürde mevcut sınırlı bilgi ile 18F-FDG PET/BT'nin RHK tanısındaki yeri hakkında sonuca varmak doğru olmayacaktır (Tablo 1).

Hibrid PET/BT sistemlerinin rutin uygulamaya girmesi ile tümöral lezyonların anatomik lokalizasyonu daha başarılı yapılmaktadır. Ekstrarenal lezyonların saptanmasında sensitivite değişmemekle birlikte duyarlılık belirgin olarak artmaktadır (19). Hibrid PET/BT sisteminin bir diğer avantajı; lokal nüksün değerlendirmesinde BT'de değerlendirmenin zor olduğu postoperatif skar dokusu, cerrahi klipsler, çevre organların operasyon lojuna yer değiştirmesi gibi durumların ayırıcı tanısının yapılabilmesidir (20). Son olarak 18F-FDG PET/BT kontrast alerjisi ya da nefrotoksisite riski olmadan tek görüntüleme ile tüm vücut değerlendirmeye olanak sağlar (21).

Aynı zamanda izlenen aktivite tutulumunun kantitatif olarak standart uptake değeri (SUV) ile değerlendirilmesi de prognostik öneme sahiptir. Başlangıçta daha yüksek SUV değerlerine sahip hastaların daha kötü prognozlu olduğu ve daha kısa sağkalıma sahip olduğu gösterilmiştir. Ayrıca metastaz varlığı primer lezyonun ortalama SUV değerlerini etkileyebilmektedir. Uzak organ metastazı saptanmayan hastaların primer lezyonlarının ortalama SUV değeri 2,6 olarak hesaplanırken, uzak metastaz saptanan hastalarda bu değer 5,0 olarak hesaplanmıştır (22). SUV değerlerinin yanında PET görüntüleme ile hesaplanan metabolik tümör volümü ve total lezyon glikolizisi gibi metabolik parametrelerin de prognostik önemi olduğu gösterilmiştir (23,24) Ekstrarenal lezyonların saptanmasında ise 18F-FDG PET'nin duyarlılığı ve özgüllüğü sırası ile %79 ve %90 olarak hesaplanmıştır (25). Ekstrarenal lezyonlarda üriner FDG ekskresyonu nedeni ile oluşan duyarlılık kaybı izlenmemektedir. Ancak 18F-FDG PET küçük boyutlu lezyonları büyük boyutlu lezyonlar kadar iyi saptayamamaktadır. Lezyon boyutu 1 cm'den 2 cm'ye çıktığında FDG PET'nin duyarlılığı %76'dan %93'e çıkmaktadır (26). Boyut yanında yüksek grade'li tümörleri düşük grade'li olanlara göre daha doğru lokalize etmektedir (Tablo 2) (19,21). 18F-FDG PET/BT uzak organ metastazlarının saptanmasında ve RHK'lerin yeniden evrelemesinde yüksek duyarlılığa sahiptir (Şekil 1, 2) (22). 18F-FDG PET/BT'nin en yaygın kullanıldığı bir diğer endikasyon ise tirozin kinaz inhibitör tedavisine yanıtın değerlendirilmesidir. Tedavi yanıtının değerlendirilmesinde kullanılan BT ve MRG gibi anatomik yöntemlerle tedaviye yanıt değerlendirmede sıklıkla the Response Evaluation Criteria in Solid Tumors (RECIST) kriterleri kullanılmaktadır. Bu yöntemde, yanıt değerlendirmesi hedef lezyonlardaki boyut değişimine göre yapılmaktadır. Ancak son dönemde kullanılan antianjiyojenik tedavilerin çoğunluğu sitotoksik değil, sitostatiktir ve çoğunlukla tümör küçülmesinden ziyade tümör stabilizasyonu sağlarlar. Ayrıca klasik yöntemlerde, tedavi yanıtının radyolojik olarak görülebilmesi için nispeten uzun süre gerekmesi bu yöntemlerin diğer dezavantajıdır. Pek çok yayında 18F-FDG PET/BT'nin radyolojik RECIST kriterlerine göre daha doğru değerlendirme yaptığı bildirilmiştir (22,27,28,29). Özellikle kemik metastazında tedavi yanıtının değerlendirilmesinde RECIST kriterleri yumuşak doku lezyonlarında tanımlanmış olduğu için 18F-FDG PET/BT daha başarılıdır (28).

18-Flor-Florotimidin Pozitron Emisyon Tomografisi

18F-florotimidin (FLT) timidin kinaz tarafından fosforile edildikten sonra hücre içinde biriken ancak DNA'nın yapısına katılmayan bir timidin analoğudur (30). Tümör proliferasyonunun PET ile değerlendirilmesine olanak sağlayan potansiyel bir radyofarmasötiktir (31,32). Proliferasyonun değerlendirilmesine izin veren bir radyofarmasötik olarak 18F-FDG'nin en büyük avantajı enflamasyon tümör ayrımını daha doğru yapabilmesidir. RHK'lerde de FLT tutulumu olduğu ve başlangıçta daha yüksek FLT tutulumunun prognostik değeri olduğu bilinmektedir (30). Histopatolojik olarak proliferasyonu gösteren Ki-67 indeksi ile FLT tutulumu arasında korelasyon olduğu gösterilmiştir (33). 18F-FDG'ye göre daha düşük SUV değerleri

Tablo 1. Primer renal hücreli kanser lezyonlarında 18-flor-florodeoksiglikoz pozitron emisyon tomografisi/bilgisayarlı tomografinin tanısal doğruluğu

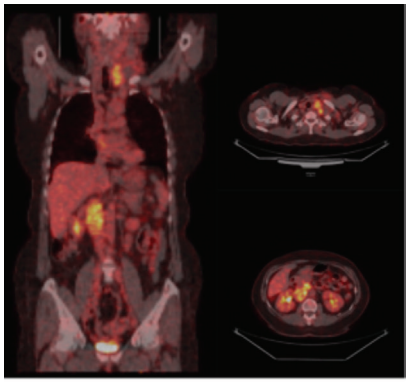
Yazarlar	GP	YP	GN	YN	Duyarlılık	Özgüllük
Ramdave ve ark. (6)	15	0	1	1	94	100
Miyakita ve ark. (18)	6	0	13	0	32	–
Aide ve ark. (12)	14	1	16	4	47	80
Kang ve ark. (8)	9	0	6	2	60	100

GP: Gerçek pozitif, YP: Yalancı pozitif, GN: Gerçek negatif, YN: Yanlış negatif

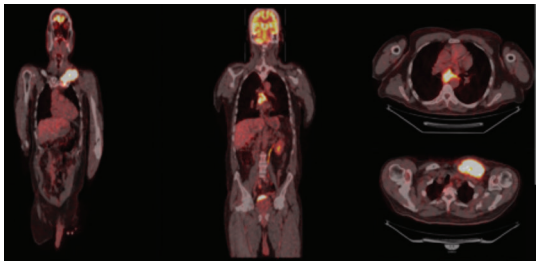
Tablo 2. Ekstrarenal lezyonların saptanmasında 18-flor-florodeoksiglikoz pozitron emisyon tomografisi/bilgisayarlı tomografinin tanısal doğruluğu

Yazarlar	GP	YP	GN	YN	Duyarlılık	Özgüllük
Ramdave ve ark. (6)	2	0	0	15	100	100
Chang ve ark. (39)	9	1	1	4	90	80
Aide ve ark. (12)	10	3	0	40	100	93
Jadvar ve ark. (7)	15	1	6	3	71	75
Majhail ve ark. (26)	14	0	7	3	67	100

GP: Gerçek pozitif, YP: Yalancı pozitif, GN: Gerçek negatif, YN: Yanlış negatif



Şekil 1. Opere renal hücreli kanser tanısı ile takipli 61 yaşında kadın hastanın takibinde paraaortik alanda saptanan yumuşak doku yapılanması nedeni ile yeniden evreleme amacı ile yapılan 18-flor-florodeoksiglikoz pozitron emisyon tomografisi/bilgisayarlı tomografide sol supraklaviküler ve arka servikal bölgeyi dolduran konglomere lenf nodlarında (SUV_{max}: 8,4), abdomende sağ paraaortik ve retrokrural alanda mevcut lenf nodlarında (SUV_{max}: 10,3) patolojik aktivite tutulumları izlendi



Şekil 2. Sağ nefrektomi sonrası takip edilen 60 yaşında erkek hasta; bilgisayarlı tomografide sol supraklaviküler ve subkarinal alanda lenf nodları saptanması nedeni ile yapılan 18-flor-florodeoksiglikoz pozitron emisyon tomografisi/bilgisayarlı tomografi sol supraklaviküler lenf nodlarında (SUV_{max}: 22,0) ve subkarinal lenf nodlarında (SUV_{max}: 16,3) yoğun patolojik 18F-FDG tutulumları izlendi

izlenmesine rağmen beyin ve mediasten gibi bölgelerde fizyolojik zemin aktivite daha düşük olduğu için metastatik lezyonlar başarı ile saptanabilmektedir. Ancak karaciğerdeki fizyolojik aktivite tutulumu nedeni ile karaciğer metastazlarının değerlendirilmesindeki yeri sınırlıdır. Günümüzde FLT PET'nin pek çok tümörde tedaviye yanıtın değerlendirilmesinde başarıyla kullanılabileceğine dair yayınlar mevcuttur (34). Liu ve ark. (35) sunitinib tedavisi alan metastatik RHK'li 16 hastada tedavi başlanmadan önce, ilk kür sonunda ve ara verildiği dönemde FLT PET çalışması yapmıştır. Sonuç olarak tedavi sırasında proliferasyonda belirgin azalma izlenirken bırakıldıktan sonraki dönemde hücre proliferasyonunun belirgin şekilde arttığını göstermiştir. FLT PET, FDG PET'den çok daha erken dönemde henüz tedavinin ilk haftasında tedavi yanıtının değerlendirilmesine olanak sağlamaktadır (36). Nefrektomi lojunda saptanan nüks lezyonların ve karaciğer gibi solid organ metastazlarının tedavi yanıtının değerlendirilmesinde son yıllarda klinik uygulamaya giren, ancak pek çok merkezde hala deneysel kullanımda olan hibrid PET/MRG sistemleri umut vadeden sonuçlar vermektedir (37,38).

Galyum-68/18-Flor Prostat Spesifik Membran Antijen Pozitron Emisyon Tomografisi/Bilgisayarlı Tomografi

Prostat spesifik membran antijen (PSMA) prostat kanserli hücrelerin yüzeyinde bulunan bir antijen molekülüdür. Ayrıca RHK'lerde ve tümör neovaskülarizasyonu izlenen pek çok solid tümörde de eksprese olduğu gösterilmiştir (39,40). PSMA normal böbrekte proksimal tübül hücrelerinde ve ayrıca neovaskülarizasyon izlenen şeffaf hücreli (%75), kromofob (%31), onkositoma (%53) ve transiyonel hücreli karsinomalarda (%21) da değişik oranlarda eksprese olmaktadır (40). PSMA'yı hedef alan moleküller galyum (Ga)-68 ya da 18F ile bağlanarak PET görüntüleme yapılabilmektedir. RHK'de Ga-68 PSMA tutulumu ilk kez olgu bildirimi şeklinde bildirilmiştir (41). Ayrıca PSMA tutulumunun histopatolojik olarak neovaskülarizasyon izlenen alanlarında tutulduğu ancak proksimal tübülde komşu vasküler yapıda değil, tübül hücrelerinde PSMA ekspresyonu olduğu gösterilmiştir (42). Dahası PSMA eksprese eden proksimal tübül hücrelerinden kaynaklanan RHK'lerde PSMA ekspresyonunun kaybolduğu da gösterilmiştir (40). Bir diğer olgu serisinde ise 18F PSMA tutulumu 5 olguda değerlendirilmiştir. Bu beş olguda farklı metastatik lezyonlarda 1,6 ile 19,3 arasında değişen SUV değerleri ile farklı düzeylerde 18F PSMA tutulumu izlenmiş ve konvansiyonel görüntüleme yöntemlerine göre daha fazla sayıda metastatik odak saptanmıştır (43). PSMA PET/BT özellikle konvansiyonel görüntüleme yöntemlerinde şüpheli lezyonları olan hastalarda subsantimetrik lezyonları dahi değerlendirerek gerçek oligometastatik hastalar ya da sitoredüktif nefrektomi planlanan hastalarda olası rezektabl komşu tümör odaklarının saptanması açısından yararlı gibi görünmektedir (44). Yüksek duyarlılığının ötesinde PSMA PET aynı zamanda tümör vaskülarizasyonunu hedefleyen tirozin kinaz inhibitörleri ve bevasuzimab gibi tedaviler öncesi metastatik lezyonların neovakülarizasyonunun *in vivo* olarak değerlendirilmesine ve tedavi yanıtının öngörülmesine yardımcı olabilecek bir fonksiyonel görüntülemedir. Bir diğer ilginç bulgu ise RHK'lerde izlenen sarkomoid dejenerasyonun PSMA tutulumu yerine 18F-FDG tutulumu ile körele olduğu ve histopatolojik örneklemde de sarkomoid dejenerasyonun PSMA ekspresyon kaybı ve GLUT-1 reseptör ekspresyonunda artış ile seyrettiğidir (45). İki PET çalışmasının kombine uygulanması farklı metastatik odaklardaki sarkomoid dejenerasyonun noninvaziv olarak değerlendirilmesine olanak sağlayabilir. Bugün mevcut bilgi ile PSMA PET gelecekte RHK'li hastaların evrelemesinde konvansiyonel yöntemlerde saptanamayan küçük metastatik odakların saptanması ve neovaskülarizasyonu hedefleyen tedavilere yanıtın değerlendirilmesi aşamalarında tamamlayıcı bir yöntem olarak yer alacak gibi görünmektedir. Buna karşın literatürde mevcut bilginin büyük kısmı olgu serileri ve küçük hasta gruplarından oluşmaktadır. Bu nedenle daha çok hastanın dahil edildiği prospektif çalışmaların sonuçlarını beklemek gerekmektedir.

Sonuç

Farklı radyofarmasötikler kullanılarak yapılan PET çalışmaları RHK'li hastalarda tanı, evreleme, nüks ve tedavi yanıtının değerlendirilmesinde farklı duyarlılıklar ile uygulanabilmektedir. 18F-FDG PET'nin renal ekskresyonu nedeni ile primer tümöral lezyonların saptanmasında başarısı sınırlıdır. Ancak metastatik odaklarda başarısı yüksektir. Ayrıca proliferasyonu gösteren FLT ve neovaskülarizasyonu hedef alan PSMA PET hem tanı hem tedavi yanıtının değerlendirilmesinde oldukça başarılıdır. Ayrıca her üç farmasötik için de tanı anında yüksek tutulum prognostik değere sahiptir.

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Case Report
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Oncocytic Adrenocortical Carcinoma: A Rare Case Report

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Abstract

Oncocytic neoplasms of the adrenal cortex are uncommon and generally benign and non-functioning. About 20% of adrenocortical oncocytic neoplasms show malignant components. A 39-year-old woman with an adrenocortical oncocytic carcinoma is reported in this article. The patient presented with mild right-sided pain. Computed tomography (CT) showed a 3 cm x 2 cm tumor in the right adrenal gland. The mass was atypical for adrenal adenoma and follow-up was recommended. Follow-up CT after 1 year showed tumor growth (5 cm) and the patient underwent laparoscopic surgery for pathologic verification. She was diagnosed as oncocytic adrenocortical carcinoma based on the pathologic diagnostic criteria. Due to their rarity, especially in cases of malignancy, there are no clear treatment and follow-up protocols. Curative surgical treatment should aim for complete excision of the tumor. As the literature about these tumors develops, more information about the nature of the disease will come to light.

Keywords: Oncocytic neoplasm, adrenal cortex, oncocytic adrenocortical carcinoma, laparoscopic adrenalectomy

Introduction

Oncocytic neoplasms can be seen in various organs, but they are usually detected in the thyroid, salivary glands, and kidneys. They contain oncocytic tumor cells that are recognized by their broad, eosinophilic and granular cytoplasm due to anomalous mitochondrial collection (1). Oncocytic neoplasms of the adrenal gland are uncommon and are generally benign and non-functioning. These tumors are more common in women and on the left adrenal gland. To date, 147 cases have been reported (2). Recent reports indicate that about 20% of the adrenocortical oncocytic neoplasms show malignant components and 10-20% produce hormones which may cause symptoms of Cushing's syndrome or virilism (3).

The most recent classification according to histopathological features is the Weiss criteria modified by Aubert. The Weiss criteria include high nuclear grade, more than 5 mitoses per 50 high-power fields, atypical mitosis, <25% clear cells, diffuse architecture, indeterminate, sinusoidal or capsular invasion. A malignant diagnosis is made in the presence of 3 or more of these criteria (4).

Bisceglia et al. (5) used a new method to classify oncocytic adrenocortical neoplasms. In this algorithm, more than 5 mitoses per 50 high-power fields, atypical mitotic figures, and venous invasion were identified as major criteria. The presence of necrosis, capsular invasion, and sinusoidal invasion were defined as minor criteria, with a diameter exceeding 10 cm and/or weight exceeding 200 grams. Tumors with one major criterion are considered malignant. Tumors with 1 to 4 minor criteria are considered to have indeterminate malignancy potential. Tumors that do not meet any of the criteria are defined as benign (5).

Case Presentation

Herein we present a 39-year-old woman with an adrenocortical oncocytic carcinoma. The patient underwent surgery for a 5 cm right-sided adrenal tumor. The patient provided informed consent for this article.

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In August 2016, a 39-year-old woman with complaints of mild right-sided pain was admitted to hospital. Computed tomography (CT) showed a 3 cm x 2 cm tumor in the right adrenal gland. The mass had atypical density for a usual adrenal adenoma and follow-up was recommended.

Physical examination revealed no specific findings of any urological or endocrine system disease. In laboratory tests, the patient's blood count values, serum electrolytes, and glucose levels were within normal ranges. Hormone tests were performed to determine if the tumor was active. No anomalies were detected in morning plasma cortisol and adrenocorticotropic hormone levels, thyroid hormones, or creatinine levels. There were no signs of hepatic invasion in radiological imaging or in serum levels such as aspartate amino transferase, alanine amino transferase, international normalized ratio, and other liver function tests. Her blood pressure was also normal. She had been operated for a benign breast cyst approximately ten years earlier.

She was under active surveillance for a year. In July 2017, magnetic resonance imaging (MRI) revealed a 4x4x3 cm right adrenal mass with an apparent diffusion coefficient value of $1.01x10^{-3}$ mm^2/s and signal loss of 10%. The mass showed heterogeneous contrast enhancement on MRI and was atypical for adrenal adenoma. Hormone tests to determine tumor activity were repeated and again showed no anomalies.

Another CT scan done before adrenalectomy (Figure 1) showed the same dimensions as the last MRI. The mass had no invasion to any vasculature or to the liver. Its borders were well defined and washout was measured as 61.5%, which previous reports have suggested may indicate a lipid-poor adenoma. There was no organ metastasis according to the last screenings. She underwent laparoscopic adrenalectomy.

The patient was diagnosed with oncocytic adrenocortical carcinoma according to the method used by Bisceglia et al. (5). The mass was 5 cm at its maximum diameter and weighed 46 grams with a slim capsule. The tumor consisted of polygonal oncocytes with granular, eosinophilic cytoplasm (Figure 2). The mitotic rate was 5 per 50 high-power fields. The tumor had atypical mitoses with no necrosis. No capsular, vascular, or sinusoidal invasion was detected.

The patient remains under postoperative follow-up. Three months after the operation, she underwent blood tests and cross-sectional imaging, as well as positron-emitting tomography (PET) scan which showed no evidence of residual mass or distant metastases. The patient continues to be closely monitored and performance assessment after discharge is highly encouraging.

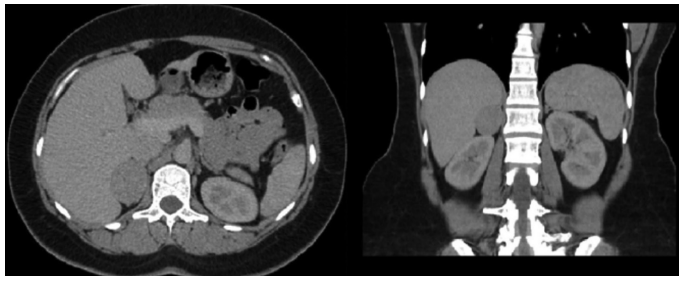

Figure 1. Contrast computed tomography image of the adrenocortical oncocytic carcinoma

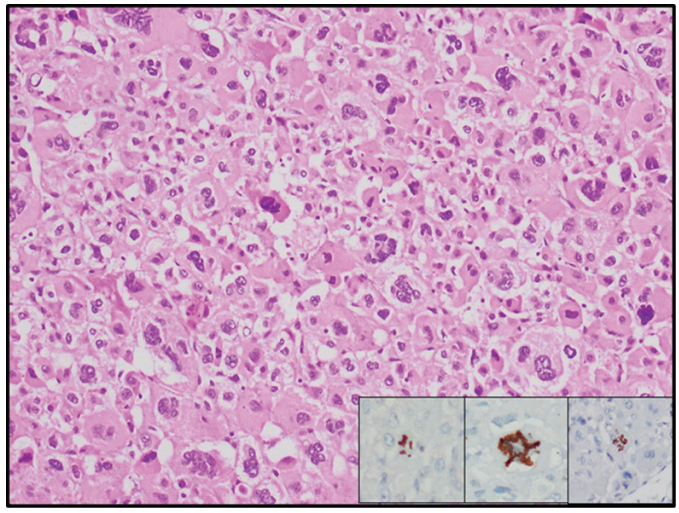

Figure 2. The tumor is composed of oncocytic cells with eosinophilic cytoplasm and nuclear pleomorphism; inset: distinctive atypical mitotic figures

Discussion

Oncocytic neoplasms of the adrenal cortex are uncommon, and are generally benign and non-functioning. According to latest reports, about 20% of adrenocortical oncocytic neoplasms show malignancy and 10-20% produce hormones (3).

In our case, the patient was diagnosed with oncocytic adrenocortical carcinoma according to the method described by Bisceglia et al. (5). There was a positive finding of atypical mitotic figures, which is a major component. There was no finding compatible with any other criteria, major or minor.

With current technology, these types of tumors cannot be definitively diagnosed by CT or MRI without obtaining the necessary histopathologic samples. If possible, laparoscopic adrenalectomy is still the only option. Since there are limited examples in the literature and there is a lack of experience, it is still not possible to make definite interpretations about pre- and postoperative approaches.

Regarding diagnosis and follow-up, apart from conventional cross-sectional imaging methods, PET appears to have an increasing prevalence. Although shown in a limited number of studies, it has been shown that 18-fluorine-fluorodeoxyglucose (18F-FDG) PET is effective for benign/malignant differentiation in radiographically and pathologically diagnosed oncocytic adrenal masses. It is also a valuable test in terms of distant metastasis and recurrence. It should be remembered that these tumors can show increased 18F-FDG uptake, which would bring a new perspective to the subject (6).

A follow-up period of at least 5 years after surgery is recommended. However, oncocytic adrenocortical carcinoma can invade nearby tissues or metastasize to distant organs. The 5-year survival rate is 50-60% after standard surgical excision, but if the patient is not a surgical candidate, radiotherapy or chemotherapy are palliative or curative options (2).

Oncocytic neoplasms of the adrenal cortex are uncommon and generally non-functioning and benign. However, a small proportion of them exhibit malignant features. Due to their rarity, especially in malignant cases, there is no definitive treatment method. Curative surgical treatment should aim for complete excision of the tumor. In selected cases, radiotherapy or chemotherapy with cytotoxic drugs could be a palliative or curative option.

As the literature concerning these rare tumors develops, the complexity of diagnosis, treatment, and follow-up will be reduced and more accurate information about the nature of the disease will come to light.

Ethics

Informed Consent: Informed written consent was obtained from the patient for the writing of the case presentation containing pathological diagnosis and follow-up information.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report
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Wunderlich Syndrome, Tuberous Sclerosis-Related Giant Renal Angiomyolipoma Rupture: Case Report

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Abstract

Angiomyolipoma (AML) is a mesenchymal tumor of the kidney that is composed of morphologically abnormal smooth muscle cells, blood vessels, and adipose-like foci. Renal AML is usually clinically asymptomatic and detected incidentally during imaging. Rarely, renal AML can cause life-threatening spontaneous massive retroperitoneal hemorrhage, known as Wunderlich syndrome. A 39-year-old man with tuberous sclerosis was admitted to the emergency room with left flank pain, hematuria, and nausea. On physical examination, there was a hard sensitive mass extending from the upper left half of the abdomen to the midline. Left renal AML and extensive retroperitoneal hematoma measuring about 360x220x195 mm were detected on abdominal computed tomography. The patient exhibited signs of hypovolemic shock and emergency total nephrectomy was performed. He was discharged from the intensive care unit on postoperative day 1 and from the hospital on day 5.

Keywords: Tuberous sclerosis, angiomyolipoma, Wunderlich syndrome

Introduction

Renal angiomyolipoma (AML) is a mesenchymal tumor of the kidney that is composed of morphologically abnormal blood vessels, smooth muscle cells, and adipose-like foci (1). Renal AML is usually clinically asymptomatic and may be detected incidentally during imaging. AMLs may become symptomatic as they increase in size. Rarely, renal AML can cause spontaneous massive hemorrhage in the renal subcapsular and/or perirenal area, which is a potentially life-threatening condition also known as Wunderlich syndrome (2).

Here we present a rare case of Tuberous sclerosis syndrome with hypovolemic shock (Wunderlich syndrome) after left renal AML rupture.

Case Presentation

A 39-year-old male patient was evaluated in the emergency department for left flank pain, hematuria, and nausea. From his medical history it was learned that he had tuberous sclerosis and was under regular follow-up due to bilateral renal AMLs. The patient also had mental retardation and was receiving antiepileptic therapy due to epilepsy. He had no history of anticoagulant use. On physical examination, a painful hard mass extending from the upper left region of the abdomen to the umbilical region was palpated. Numerous nodular skin lesions (adenoma sebaceum) were apparent between the nasal wings and the cheek. His arterial blood pressure was 70/40 mmHg, pulse was tachycardic (125 beats/min), and body temperature was 36.2 °C. In complete blood count, hemoglobin level was

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6.1 g/dL and hematocrit was 17.7%; serum biochemistry and coagulation tests were normal. Emergency full abdomen computed tomography (CT) with radiopaque contrast was performed. The CT scan revealed solid masses consistent with renal AML measuring 230x164x109 mm on the right and 360x220x195 mm on the left, and a large hematoma in the left retroperitoneal space (Figure 1). The patient underwent emergency laparotomy. An area of rupture extending to the collecting system of the anterior upper pole and extensive perirenal hematoma were detected. Left radical nephrectomy was performed. Two units of fresh frozen plasma and four units of erythrocyte suspension were transfused perioperatively. Postoperatively, the patient was intubated and admitted to the intensive care unit. He was extubated and transferred to an inpatient unit on postoperative day 1 and discharged on postoperative day 5.

On macroscopic examination, the tumor appeared to be an encapsulated mass measuring 34x21x9 cm in size and weighing approximately 3100 g Cross-sectional appearance was solid and yellow-gray in color with hemorrhages in some areas (Figure 2). Pathological examination of sections stained with hematoxylin and eosin revealed tumor tissue separated from the normal renal parenchyma by a smooth border and composed of vascular structures, myoid spindle cells, and mature fat tissue with no cellular atypia or mitosis. Immunohistochemical staining was positive for smooth muscle actin, vimentin, and HMB-45, and negative for CD68 and CD117. CD31 staining was observed in the vascular endothelial cells. The Ki-67 index was 0-1% in tumor cells, and the findings were considered consistent with renal AML.

The data used in this report was obtained with the consent of the patient's relatives.

Discussion

Tuberous sclerosis was described in 1862 by Von Recklinghausen after detecting sclerotic foci and cardiac tumors in autopsies (3). The term tuberous sclerosis complex (TSC) is now preferred due to the widespread systemic involvement of the disease. TSC is a rare genetic disease that manifests with epilepsy, mental retardation, and facial angioma (Vogt's triad) (4).

TSC can involve the brain, kidneys, heart, skin, eyes, bones, and lungs. Neurologic involvement is the most common, followed by renal involvement, which is present in 60-75% of cases (5). AMLs occur in 70-80% of tuberous sclerosis patients with renal involvement, renal cysts in 20%, and renal cancer is also seen in rare cases (6). There are two different types of renal AML: the first type occurs concomitantly with different diseases such as tuberous sclerosis, von Hippel Lindau, and von Recklinghausen neurofibromatosis, while the second type is isolated. The first type (20%) of renal AML is generally bilateral, multiple, and symptomatic and affects both sexes equally. The second, isolated type (80%) are single asymptomatic lesions with a female/male ratio of 4:1 and usually occur in women 50-60 years of age. Renal AMLs may be detected in 40-80% of patients with tuberous sclerosis (1).

AMLs are usually asymptomatic and often detected incidentally by radiological imaging (2). As the AML increases in size,

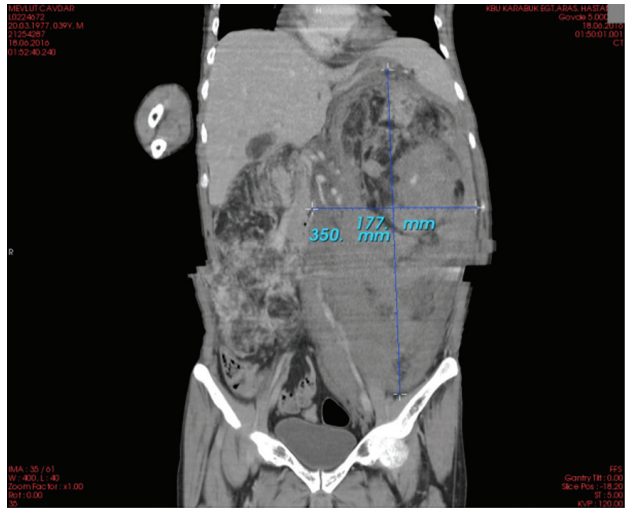

Figure 1. Computed tomography image of ruptured angiomyolipoma

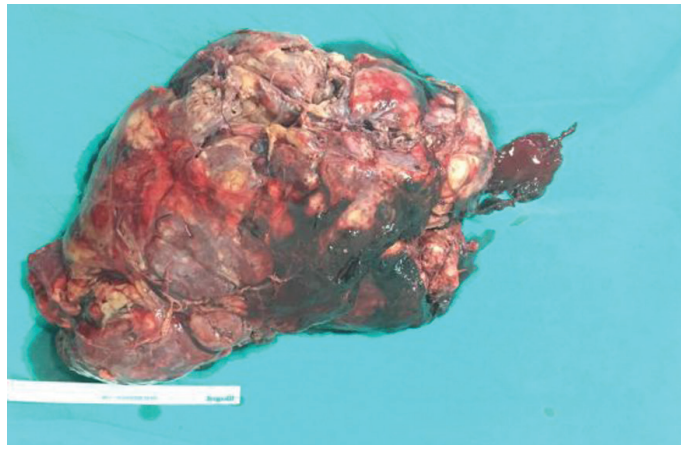

Figure 2. Macroscopic view of nephrectomy specimen

patients may present to the clinic with flank pain, palpable abdominal mass, or hematuria. One of the most dangerous clinical manifestations is spontaneous hemorrhage into the subcapsular and/or perirenal area, characterized by the classic triad of acute abdominal pain, palpable abdominal mass, and hypovolemic shock. This condition is called Wunderlich syndrome (2). A correlation has been observed between tumor size and hemorrhage risk. Oesterling et al. (7) reported that 82% of patients with AMLs over 4 cm in size were symptomatic, 9% of whom were in hemorrhagic shock at the time of diagnosis, whereas the symptomatic rate among patients with tumors smaller than 4 cm was 23%. Çalışkan et al. (8) determined that the main factors affecting the growth and symptomatic development of AMLs were tumor size, the presence of multiple tumors, and having tuberous sclerosis. In another study, Steiner et al. (9) also determined that patients with tuberous sclerosis require surgical intervention more often because they often have bilateral masses, they are younger, and their tumors are larger. Therefore, they emphasized the high risk of requiring surgery or developing symptoms in the presence of AML larger than 4 cm or TSC (9).

To the best of our knowledge, the largest unilateral AML to date, reported by Taneja and Singh (10) was 39x29x9 cm in size and weighed 7500 g Kalsi et al. (11) reported a case of TSC-associated bilateral renal AML with 30x21x13 cm and 30x18x10 cm tumors and a total tumor burden of 7843 g. Mistry et al. (12) reported a total tumor burden of 8305 cc in a patient with bilateral AMLs 29x27.5x15.5 cm and 30x19x13 cm in size, the highest tumor burden reported in this literature. In our case, we detected as a mass weighing approximately 3100 g and measuring 34x21x9 cm in size.

Monitoring is the first choice for asymptomatic AMLs smaller than 4 cm. Guidelines recommend imaging for renal morbidity every 1-3 years in patients with tuberous sclerosis (13). Treatment options should be evaluated based on tumor size, presence of TSC, and number of tumors. Selective arterial embolization, partial nephrectomy, and total nephrectomy are other treatment alternatives (14). Selective arterial embolization may be recommended for selected patients with solitary masses or hemorrhagic AML. In patients with tuberous sclerosis, pharmacologic approaches are currently recommended as first-line treatment options for AMLs larger than 3 cm and especially those exhibiting growth. There have been reports of significant response in tumor size with the mammalian target of rapamycin inhibitors (15).

A ruptured AML causing retroperitoneal hemorrhage can lead to life-threatening hypovolemic shock. Large renal AMLs should be monitored closely and treated electively. Partial or total nephrectomy may be life-saving in patients who develop Wunderlich syndrome.

Ethics

Informed Consent: It was taken.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

Conflict of Interest: No conflict of interest was declared by the authors.

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Wunderlich Sendromu, Tüberoskleroz ile İlişkili Dev Renal Anjiyomiyolipom Rüptürü: Olgu Sunumu

Wunderlich Syndrome, Tuberous Sclerosis-Related Giant Renal Angiomyolipoma Rupture: Case Report

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Öz

Anjiyomiyolipom (AML), morfolojik olarak anormal kan damarları, düz kas hücreleri ve yağ dokusu benzeri odaklardan oluşan böbreğin mezenkimal bir tümörüdür. Renal AML klinik olarak çoğunlukla asemptomatiktir ve insidental olarak görüntüleme yöntemleri sırasında saptanabilir. Renal AML nadiren "Wunderlich sendromu" olarak bilinir ve hayatı tehdit edebilen, retroperitoneal spontan masif kanamalara sebep olabilir. Tüberoskleroz hastalığı bulunan 39 yaşındaki erkek hasta; sol yan ağrısı, hematüri ve bulantı ile acil servise başvurdu. Fizik muayenede karın sol üst yarısından orta hatta uzanan sert hassas kitle mevcuttu. Çekilen abdominal bilgisayarlı tomografide 360x220x195 mm boyutlarında sol renal AML ve yaygın retroperitoneal hematom saptandı. Hipovolemik şok tablosunda olan hastaya acil radikal nefrektomi yapıldı. Hasta postoperatif 1. gün yoğun bakım ünitesinden, 5. gün hastaneden taburcu edildi.

Anahtar Kelimeler: Tüberoskleroz, anjiyomiyolipom, Wunderlich sendromu

Abstract

Angiomyolipoma (AML) is a mesenchymal tumor of the kidney that is composed of morphologically abnormal smooth muscle cells, blood vessels, and adipose-like foci. Renal AML is usually clinically asymptomatic and detected incidentally during imaging. Rarely, renal AML can cause life-threatening spontaneous massive retroperitoneal hemorrhage, known as Wunderlich syndrome. A 39-year-old man with tuberous sclerosis was admitted to the emergency room with left flank pain, hematuria, and nausea. On physical examination, there was a hard sensitive mass extending from the upper left half of the abdomen to the midline. Left renal AML and extensive retroperitoneal hematoma measuring about 360x220x195 mm were detected on abdominal computed tomography. The patient exhibited signs of hypovolemic shock and emergency total nephrectomy was performed. He was discharged from the intensive care unit on postoperative day 1 and from the hospital on day 5.

Keywords: Tuberous sclerosis, angiomyolipoma, Wunderlich syndrome

Giriş

Anjiyomiyolipom (AML), morfolojik olarak anormal kan damarları, düz kas hücreleri ve yağ dokusu benzeri odaklardan oluşan böbreğin mezenkimal bir tümörüdür (1). Renal AML klinik olarak çoğunlukla asemptomatiktir ve insidental olarak görüntüleme yöntemleri sırasında da saptanabilir. AML boyutunun artması ile semptomatik bir hale gelebilir. Renal AML nadiren, Wunderlich sendromu olarak da bilinen ve hayatı tehdit edebilen, renal subkapsüler ve/veya perirenal alan içine olan spontan masif kanamalara sebep olabilir (2).

Sol renal AML rüptürü sonrası hipovolemik şok gelişen (Wunderlich sendromu) Tüberoskleroz sendromu bulunan nadir bir olgu sunuyoruz.

Olgu Sunumu

Sol yan ağrısı, hematüri ve bulantı nedeniyle 39 yaşında erkek hasta acil serviste değerlendirildi. Tıbbi geçmişi araştırıldığında, tüberoskleroz hastası olduğu ve bilateral renal AML'ler nedeniyle düzenli takipte olduğu öğrenildi. Hastada ayrıca mental retardasyon olduğu ve hastanın epilepsi nedeniyle antiepilektik tedavi aldığı saptandı. Hastanın tıbbi geçmişinde antikoagülan ilaç kullanımı mevcut değildi. Yapılan fizik muayenesinde, karın sol üst bölgesinden başlayıp, umblical bölgeye kadar uzanan ağrılı sert kitle palpe edildi. Yüzde burun kanatları ile yanak arasında çok sayıda nodüler tarzda deri lezyonları (adenoma sebaseum) izlendi. Tansiyon arteriyel: 70/40 mm/Hg, nabız taşikardik: 125 atım/dk, vücut sıcaklığı: 36,2 °C olarak

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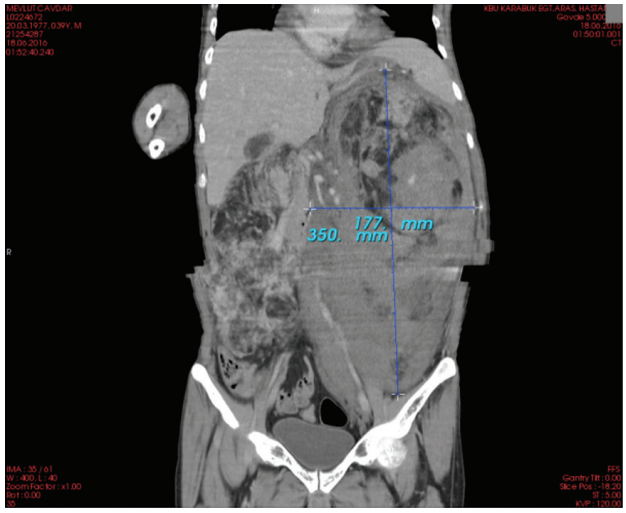
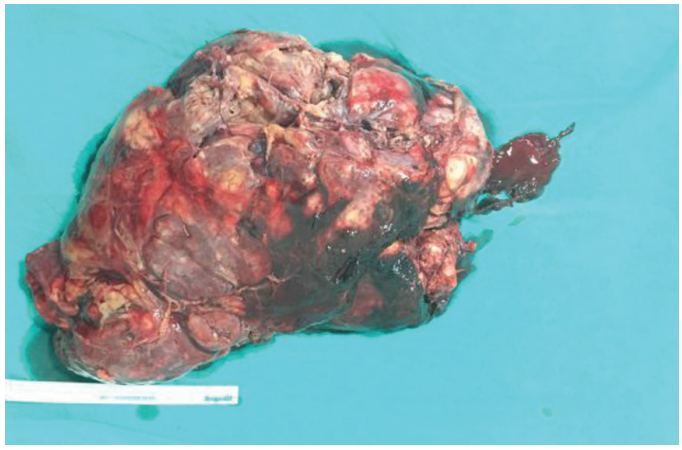


Resim 1. Rüptüre anjiyomiyolipom bilgisayarlı tomografi görüntüsü



Resim 2. Nefrektomi spesmeni makroskopik görünüm

saptandı. Yapılan tam kan sayımında, hemoglobin: 6,1 g/dL, hematokrit: %17,7, serum biyokimyası, koagülasyon testleri normal olarak bulundu. Hastaya acil opaklı tüm abdomen bilgisayarlı tomografi çekildi. Tomografide; sağda 230x164x109 mm, solda ise 360x220x195 mm boyutlarında renal AML ile uyumlu solid kitleler ve sol retroperitoneal alanda geniş hematom izlendi (Resim 1). Hastaya acil laparatomi yapıldı. Böbrek üst pol anteriorda toplayıcı sisteme uzanan rüptüre alan ve yaygın perirenal hematom saptandı. Hastaya sol radikal nefrektomi yapıldı. Peroperatif 2 ünite taze donmuş plazma ve 4 ünite eritrosit süspansiyonu transfüze edildi. Hasta postoperatif entübe olarak yoğun bakım ünitesine alındı. Postoperatif 1. günde ekstübe olan hasta servise alınarak, postoperatif 5. günde taburcu edildi.

Spesmenin makroskopik incelemesinde; yaklaşık 3100 g ağırlığında, 34x21x9 cm boyutlarında kapsüllü görünümde kitle halinde izlenen, kesit yüzeyi geniş alanda solid, sarı-gri renkli, bazı alanlarda hemorajik görünümde tümör izlendi (Resim 2). Hematoksilen eozin ile boyanan kesitlerin patolojik incelemesinde, normal böbrek parankiminden düzgün bir sınırla ayrılmış vasküler yapılar, miyoid iğsi hücreler ve matür yağ dokusundan oluşmuş hücresel atipi ve mitoz izlenmeyen tümöral doku izlendi. İmmünohistokimyasal boyamada; düz kas aktin (+), vimentin (+), HMB-45 (+), CD68 (-), CD117 (-) izlendi. CD31 vasküler endotelyal hücrelerde pozitif gözlendi. Ki-67 indeksinin tümör hücrelerinde %0-1 olduğu gözlendi ve bulgular renal AML ile uyumlu bulundu.

Hastaya ait bilgiler, olgu sunumunda kullanılmak üzere yakınlarının onayı ile alındı.

Tartışma

Tüberoskleroz hastalığı, 1862 yılında Von Recklinghausen'in yaptığı otopsilerde beyinde sklerotik odaklar ve kardiyak tümörlerin saptanması sonucu tariflenmiştir (3). Hastalığın yaygın sistemik tutulum göstermesi nedeniyle artık tüberosklerozis kompleksi (TSK) terimi tercih edilmektedir. TSK epilepsi, mental retardasyon ve yüzde anjiyoma (Vogt triadı) ile seyreden nadir bir genetik hastalıktır (4).

TSK beyin, böbrek, kalp, deri, göz, kemik ve akciğer tutulumu ile seyredebilir. En yaygın nörolojik tutulum izlenmekte olup ikinci sıklıkla renal tutulum görülür. %60-75 insidansında renal tutulum mevcuttur (5). Böbrek tutulumu olan tüberosklerozlu hastalarda %70-80 oranında AML, %20 böbrek kisti ve ender olarak da böbrek kanseri görülebilir (6). İki farklı tipi olan böbrek AML'nin; birinci tipi tüberoskleroz, von Hippel Lindau, von Recklinghausen nörofibromatozis hastalığı gibi farklı hastalıklarla beraber gözlenirken; ikinci tip ise izole izlenir. Birinci tip (%20) renal AML genellikle bilateral, multipl, semptomatik ve her iki cinsiyette benzer oranda izlenirken; ikinci tip olan izole grupta (%80) ise tek ve asemptomatik lezyonların kadın/erkek oranı 4:1'dir; genellikle 50-60 yaş aralığındaki kadınlarda yaygındır. Tüberosklerozlu hastalarda %40-80 oranında böbrek AML'si saptanabilir (1).

AML genellikle asemptomatiktir ve sıklıkla radyolojik görüntüleme yöntemleri ile insidental olarak saptanır (2). AML boyutunun artması ile birlikte yan ağrısı, karında ele gelen kitle veya hematüri şikayeti ile hasta kliniğe başvurabilir. En tehlikeli klinik tablolardan biri, akut karın ağrısı, batında ele gelen kitle ve hipovolemik şok klasik triadı ile karakterize subkapsüler ve/veya perirenal alan içine olan spontan kanamalardır. Bu durum Wunderlich sendromu olarak tanımlanır (2). Tümör boyutu ile kanama riski arasında korelasyon saptanmıştır. Oesterling ve ark. (7) çalışmalarında, 4 cm ve üzeri AML olan hastaların %82'sinin semptomatik olduğunu ve bu hastaların %9'unun tanı anında hemorajik şok tablosunda saptandığını; buna karşın 4 cm'nin altında tümörlü hastaların semptomatik olma oranını ise %23 olarak yayınlamışlardır. Çalışkan ve ark. (8) AML'lerin büyümesini ve semptomatik hale gelmesini etkileyen ana faktörleri; tümörün büyüklüğü, multipl tümör varlığı, tüberoskleroz mevcudiyeti olarak belirtmişlerdir. Başka bir çalışmada Steiner ve ark. (9) da tüberosklerozlu hastalarda kitlelerin sıklıkla bilateral olması, daha genç yaşta ve daha büyük boyutlu olması sebebiyle daha fazla sıklıkta cerrahi girişim gerektirdiğini belirtmişlerdir. Bundan dolayı, cerrahi gereksinim ve semptom gelişimi açısından 4 cm'den büyük AML veya TSK varlığının yüksek risk taşıdığı üzerinde durmuşlardır (9).

Bildiğimiz kadarıyla; literatürde bugüne kadar en büyük tek taraflı AML olgusu 39x29x9 cm büyüklüğü ve 7500 g tümör

yüküyle Taneja ve Singh (10) tarafından bildirilmiştir. Kalsi ve ark. (11), 30x21x13 cm ve 30x18x10 cm büyüklüğünde ve toplam tümör yükü 7843 g olan TSK zemininde gelişen bilateral renal AML olgusu bildirmişlerdir. Mistry ve ark. (12) 29x27,5x15,5 cm ve 30x19x13 cm büyüklüğünde bilateral AML toplam tümör yükünü 8305 cc olarak yayınlamışlardır; bu literatürde bildirilmiş en büyük tümör yüküdür. Bizim olgumuz ise yaklaşık 3100 g ağırlığında ve 34x21x9 cm boyutlarında bir kitle olarak saptandı. 4 cm'nin altında semptomatik olmayan olgularda izlem ilk tercih edilecek yöntemdir. Kılavuzlarda tüberosklerozlu olgularda 1-3 yılda bir renal morbidite yönünden görüntüleme yapılması önerilmektedir (13). Tümör büyüklüğü, TSK varlığı, multipl tümör varlığına göre tedavi seçenekleri değerlendirilmelidir. Selektif arteriyel embolizasyon, parsiyel nefrektomi, total nefrektomi diğer tedavi alternatifleridir (14). Özellikle soliter böbrekte kitle veya kanamalı AML olgularında selektif arteriyel embolizasyon uygun hastalara önerilebilir. Tüberosklerozlu olgularda, 3 cm'den büyük ve özellikle büyüme eğiliminde olan AML'ler için farmakolojik yaklaşımlar artık ilk basamak tedavi seçeneği olarak önerilmektedir. Rapamisin protein kompleksinin memeli hedefi inhibitörleri ile tümör boyutunda anlamlı yanıt alındığını bildiren yayınlar mevcuttur (15).

Rüptüre olarak retroperitoneal kanamaya sebep olan AML, hipovolemik şoka neden olarak hayatı tehdit edebilir. Büyük renal AML'ler yakın izlenmeli ve elektif koşullarda tedavi edilmelidir. Wunderlich sendromu gelişmesi durumunda, parsiyel veya total nefrektomi hayat kurtarıcı olabilir.

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