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

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The Bulletin publishes basic and clinical research original articles, reviews, editorials, case reports, surgery videos on urooncology (video-urooncology) and letters to the editor relevant to urooncology (prostate cancer, urothelial cancers, testis and kidney cancer, benign prostatic hyperplasia, and any aspect of urologic oncology). The Bulletin of Urooncology is indexed by several well-known international databases including Emerging Sources Citation Index (ESCI), TUBITAK/ULAKBIM Turkish Medical Database, Directory of Open Access Journals (DOAJ), EBSCO, CINAHL Complete Database, Gale/Cengage Learning, ProQuest, Index Copernicus, British Library. All submitted manuscripts are committed to rigorous peer review.

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4) References,

5) Figure legends,

6)Short Quiz for review articles.

Tables and figures should be uploaded separately.

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

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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/);

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

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These are manuscripts which are prepared on current subjects by experts who have extensive experience and knowledge of a certain subject and who have achieved a high number of publications and citations. Reviews are usually submitted directly or by invitation of the editorial board. Submitted reviews within the scope of the journal will be taken into consideration by the editors. The content of the manuscript should include the latest achievements in an area and information and comments that would lead to future studies in that area. Number of authors should be limited to 3.

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-Conclusions

-References (Number of references should not exceed 100).

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D. Literature Review

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

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

G. Surgery videos on urooncology (video-urooncology)

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

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3) Summary: Summary should point out critical steps in the surgery up to 150 worlds. This part was published as an abstract to summarize the significance of the video and surgical techniques.

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B. Title Page

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-Running title

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-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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First page (Title- abstract – keywords), introduction,....., references, figure legends (described in detail for each article type)

4) Table(s)

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2) Title Page

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5) Video

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Is Anterior Exenteration Necessary in Women Undergoing Radical Cystectomy?

Taha Numan Yıkılmaz MD[1], Yalçın Kızılkan MD[2], Erdem Öztürk MD[3], Melih Balcı MD[2], Altuğ Tuncel MD[2], Cüneyt Özdeş MD[2], Halil Başar MD[3]

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Abstract

Objective: Radical cystectomy is the gold standard for the treatment of muscle-invasive bladder cancer. Anterior exenteration with cystectomy is standard practice in female patients. In this study, we aimed to evaluate the necessity of anterior exenteration in female patients who underwent cystectomy for invasive bladder cancer.

Materials and Methods: Thirty-one women who underwent open radical cystectomy for bladder cancer between January 2010 and July 2018 were included in the study. The demographic characteristics, pathology results and genital organ involvement of these cases were retrospectively analyzed.

Results: The mean age of the patients was 63 (range, 33-80) years. Eleven of the cases underwent anterior exenteration with cystectomy, while only two (6%) of these cases had gynecologic organ involvement of uroepithelial origin. One patient who had positive smear sampling prior to cystectomy also had genital organ involvement in the final pathology.

Conclusion: In the light of our findings, anterior exenteration during radical cystectomy is beneficial in patients with no expectation of advanced sexual function or fertility to protect them from gynecological cancers that may develop simultaneously or later. However, in young patients and patients without suspicion of invasion in preoperative evaluation, organ sparing approaches are considered appropriate.

Keywords: Cystectomy, exenteration, bladder cancer, female, smear

Introduction

Bladder cancer is the most common urinary tract malignancy in women and is the ninth most common cancer among women in the United States (1). The risk of occurrence in men is 3-4 times higher, but women have been reported to have local advanced stage disease more frequently at the time of diagnosis (1-4). Surrounding organ involvement is frequently seen in advanced stage tumors (3,4). In women, gynecologic organ involvement is reported to be very low (2.6%) (5). Therefore, in the last decade organ sparing approaches have come up.

The main treatment principle in invasive bladder cancer is eradication of the tumor, improving the quality of life and keeping morbidity low. In anterior exenteration, uterus, fallopian tubes, ovaries and 1/3 anterior wall of vagina are excised besides bladder. With this surgery, the duration of the operation is prolonged, morbidity increases, the number of organ loss increases and postoperative sexual activity is lost. Therefore, we retrospectively evaluated the necessity of anterior exenteration in female patients who underwent cystectomy for invasive bladder cancer.

Materials and Methods

Thirty-one female patients who underwent open radical cystectomy and extended pelvic lymph node dissection for bladder cancer between January 2010 and July 2018 were eligible for the study. Demographic characteristics, follow-up times, final pathology results, genital organ involvement and operative time were recorded. Cases with and without simultaneous anterior exenteration along with radical cystectomy were divided into two groups and the variables between groups were compared. Transurethral resection (TUR) was performed with the diagnosis of primary bladder tumor before radical cystectomy in all cases and re-TUR was performed within 2-6 weeks in cases with no muscle sampling could be performed at the first resection. Cystectomy was decided because of the presence of resistant carcinoma *in situ*, high-grade tumor, and non-responsiveness

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to intravesical treatment in non-muscle invasive bladder tumors. Routine laboratory tests (blood biochemistry and complete blood count) and thoracoabdominopelvic computed tomography were performed in all patients for staging before surgery. Alkaline phosphatase was evaluated for possible bone metastases and cases with metastasis were not taken into surgery. Tumor-focused sections and dissected lymph nodes were stained with hematoxylin-eosin and examined under light microscope by uropathologists. The 2002 Tumor, nodes, metastases classification was used for clinical staging (6). In the pathological examination, the grading system adopted by the World Health Organization in 2004 was used (7). Ileal conduit was preferred as urinary diversion in all cases.

Statistical Analysis

Demographic and pathological data were recorded separately in cases with and without exenteration. The results were compared between the groups. Statistical analysis was performed using chi-square test through SPSS Windows 21.0 package program. $p<0.05$ was accepted as the minimum limit of significance.

Results

The mean age of the 31 female patients included in the study was 63±5 years (33-80 years), with a mean follow-up of 19±6 months (3-41 months) (Table 1). According to the age, sociocultural level, preoperative radiological and pathological examinations, patient preference and surgeon preference, some patients underwent simultaneous anterior exenteration with radical cystectomy, while others did not. Eleven patients underwent anterior exenteration and gynecologic organ involvement was observed only in three patients (10%), and two of these patients had bladder cancer related involvement. Tumor tissue in the rectum, vaginal cuff, cervix, endometrium, ovary and tuba was observed in one patient. The patient also had metastatic involvement in the lymph node. The case was considered as stage p4b and additional treatment was required in the postoperative period. Only one ovarian tumor was diagnosed in one of the other two cases. In the detailed pathological examination of the patient's sections, it was accepted that the tumor was not uroepithelial in origin, the vaginal cuff was reported as benign and the cystectomy pathology was T1G3 and the case was considered to be the second primary. The last case had cervical intraepithelial neoplasia (CIN-2) pathology in smear sampling before cystectomy. Among the patients who underwent exenteration, four patients had benign gynecologic diseases including ovarian cysts in two patients and endometrial polyps in two patients, and none of the pathologies were surgical indications alone.

In two cases with gynecologic organ involvement associated with bladder cancer, the common feature was the diagnosis of high-grade muscle-invasive bladder tumors and lymph node positivity was found in both cases.

Of the 13 patients who underwent smear sampling prior to cystectomy, only one had CIN and gynecologic organ involvement was observed in the final pathology. Although smear was negative in six of 13 cases, exenteration was performed and pathology was negative. In four cases, cystectomy and exenteration were performed without smear sampling before cystectomy, and gynecologic organ involvement was observed in two of these cases.

None of the 20 patients who did not undergo simultaneous anterior exenteration with cystectomy developed invasive bladder cancer-related gynecologic organ involvement. In six of these cases, smears were taken before cystectomy and the samples were negative. There was no significant difference between the patients who underwent exenteration and who did not in terms of preoperative and postoperative complications ($p=0.2$). There was a significant decrease in the operative time in patients who did not undergo exenteration (280 min. and 345 min., $p<0.05$) (Table 2).

Table 1. Demographic and pathological characteristics of women who underwent radical cystectomy

Parameters (n=31)	
Mean age (years)	63
Mean follow-up period, months	19
Pathological stage	
T0	2
T1	6
T2	13
T3	9
T4	1
Lymph node positivity	4
Ureter surgical border involvement	2
Urethral involvement	-
Genital organ involvement	3
Mean operative time, minutes	303

Table 2. Characteristics of cases with and without anterior vaginal exenteration

	Patients with exenteration (n=11)	Patients without exenteration (n=20)	P
Mean age (years)	68	59	0.08
Mean follow-up period, months	10	23	0.1
Pathological stage			
T0	-	2	-
T1	2	4	0.1
T2	7	6	0.2
T3	3	6	0.2
T4	1	-	-
Lymph node positivity	2	2	0.1
Ureter surgical border involvement	1	1	0.1
Urethral involvement	-	-	-
Genital organ involvement	3	-	-
Mean operative time, minutes	345	280	0.05*
The number of cases with complications	6	9	0.2

Ileal conduit method was preferred as urinary diversion in all cases. No urethral surgical margin involvement was observed in any of the cases, whereas ureteral lower end involvement was observed in two cases. Lymph node involvement was positive in four cases. Demographic and pathological evaluation of all cases is summarized in Table 1.

Discussion

In the treatment of muscle-invasive bladder cancer in women, radical cystectomy and bilateral pelvic lymph node dissection as well as anterior exenteration, which is surgical removal of uterus, upper 1/3 of vagina, tuba and ovaries, is accepted as the standard approach (8,9). While radical cystoprostatectomy is the gold standard treatment approach in men as 25% of prostate cancers are associated with invasive bladder cancer, anterior exenteration is still the standard practice despite the low rates of accompanying gynecological cancer in women. In studies conducted on this subject, the involvement is found to be in the range of 2.6% to 5% (5). In the study conducted by Chang et al. (9), this rate was determined as 7.5% and the authors concluded that anterior exenteration should be performed only in suspicious cases after screening gynecological organs radiologically and pathologically before surgery. In a limited number of studies on this subject, it has been reported that genital organ involvement should be investigated with radiological evaluation, smear samples and random vaginal biopsies in patients with planned gynecological organ sparing surgery before cystectomy, and anterior exenteration procedure should be performed in suspected cases (5,8,10). In a study conducted in our country, genital organ involvement was observed in three (18.7%) of 16 female cystectomy cases and anterior exenteration was added to radical cystectomy by detecting gynecologic organ involvement in two of these cases. However, in one case, vaginal cancer was found to be secondary primary, although there was a negative finding in terms of genital organ involvement in preoperative scans (8). In our study, two of the 11 patients who underwent exenteration had genital organ involvement and one had simultaneous ovarian tumor. While genital organs were radiologically examined preoperatively in all cases, vaginal smear sampling was performed additionally to 13 of them and exenteration was performed in one case diagnosed with CIN-2. In this case, vaginal cuff involvement was observed pathologically. In the other patient with organ involvement, perivesical region and genital organ involvement were detected radiologically. Peripheral organ involvement was observed in the final pathology and it was reported as stage 4b. In one case, anterior exenteration was performed according to the preference of the surgeon without any suspicious condition in the preoperative scans and ovarian carcinoma was detected in this case. In cases where exenteration was not performed, no uroepithelial related genital organ tumor was detected during follow-up. When the literature is reviewed, it is reported that genital organ involvement is common in lymph node positivity, high-grade bladder tumor, bladder posterior wall involvement and bladder neck tumors and genital organ sparing should be avoided in these cases (5,8). A similar presentation was observed in our results. There was no gynecologic malignancy in the follow-up period of the patients who did not have preoperative gynecologic involvement and who did not undergo anterior exenteration.

Performing anterior exenteration may lead to prolongation of operation, increased surgical morbidity and postoperative sexual dysfunction (11). Similar techniques have been developed in women, such as the prostate-sparing radical cystectomy technique in men, to protect sexual dysfunction (12,13). Kolodziej et al. (13) reported a 27-year-old case who experienced pregnancy after genital organ-sparing radical cystectomy, and therefore emphasized the importance of protecting genital organs, especially in young patients considering sexual activity. Procedures such as early hormonal manipulations and oocyte freezing can be performed after surgery to prevent acute early menopause and fertility loss in patients. In our study, postoperative sexual dysfunction status could not be evaluated. However, it was found that the patients who underwent exenteration were older, and in the comparison, it was found that the operative time was significantly longer in the patients who underwent exenteration, and similarities were observed in surgical complications.

Conclusion

In conclusion, although the main principle of invasive bladder cancer surgery is eradication of tumor tissue, it is a condition that the sexual functions of the patients and therefore their quality of life should be maintained. Simultaneous anterior exenteration during radical cystectomy is beneficial in cases where there is no expectation of advanced sexual function or fertility to prevent gynecological cancers that may develop simultaneously or later. In cases where genital organ conservative radical cystectomy is decided, preoperative radiological evaluation and smear or vaginal random biopsy sampling should be performed.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

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

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Original Article

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Clinical and Histopathological Features of Genitourinary Sarcomas: Our Experiences and Case Series at a Single Center

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Abstract

Objective: The incidence of genitourinary sarcomas is very low, so the published reports in the literature are very limited. We aimed to present our experiences of eight cases originating from various genitourinary organs treated in our clinic.

Materials and Methods: We retrospectively reviewed the data and postoperative follow-up findings of eight cases aged 3-72 years who were diagnosed as genitourinary sarcoma and treated between January 2013 and February 2017.

Results: All eight cases were male and the mean age at diagnosis was 47.87 (range = 3-72) years. The most common site was paratesticular area (five cases, 62.5%) followed by kidney (two cases, 25%) and prostate (one case, 12.5%). Histological types of tumors were rhabdomyosarcoma (RMS) (two cases, 25%), liposarcoma (LPS) (two cases, 25%), leiomyosarcoma (LMS) (two cases, 25%), synovial sarcoma (one case, 12.5%) and malignant fibrous histiostoma (MFH) (one case, 12.5%). At a median follow-up of 23.5 (range = 4-62) months, the recurrence-free and progression-free survival rate was 50%, while the overall survival rate was 50%. Among the five paratesticular sarcomas, the worst prognosis was seen in LMS (local recurrence at the 4th, overall survival was 28 months) and MFH (local recurrence at the 8th, overall survival was 33 months). Among all sarcoma cases, LMS and synovial sarcoma were the histologic types with the worst prognosis. The histological types with the best prognosis were LPS and RMS with no recurrence or progression during follow-up. In all cases with a median tumor size of 52.5 mm (range = 11-210), LPS was found to have a better prognosis, although the largest tumor size was in renal LPS. According to FNCLCC classifications, local recurrence-free survival was significantly higher in grade II sarcomas than in grade III (p=0.042).

Conclusion: Histopathological features and oncologic outcomes of genitourinary sarcomas differ. The prognosis of paratesticular sarcomas is better than other genitourinary organ sarcomas. LPS has higher cure rates after treatment in histological subtypes. The prognosis of histopathologically poorly differentiated subtypes and high-grade tumors is poor. If adjuvant treatments are not added, they may be fatal with local recurrence or distant metastasis in a short time.

Keywords: FNCLCC grading system, overall survival, genitourinary sarcomas, paratesticular sarcomas

Introduction

Genitourinary sarcomas (GUS) originate from embryonic mesenchymal cells and are very rare tumors with poor prognosis. Sarcomas constitute approximately 1% of all malignancies (1). While less than 5% of all sarcomas originate from the genitourinary system, GUS accounts for 1-2% of all malignant genitourinary tumors (1). In the literature, studies with a large patient population are very few due to the rarity of GUS (2,3). Therefore, there is not much information about its natural course and prognosis. To our knowledge, the two largest series of patients belong to Sichuan University West China Hospital (188 patients) and Memorial Sloan-Kettering Cancer Center (131 patients) (3,4).

Tumor stage, grade, size and localization are important in predicting resectability and survival (2,3). While complete surgical resection is known to increase survival rates, adjuvant treatment protocols have not yet been standardized and their

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contribution to survival varies in different studies (3). Since our knowledge about GUS is limited, in this study, we aimed to evaluate the prognostic factors that may have an impact on oncologic outcomes by examining the clinicopathological features of GUS patients diagnosed in our clinic.

Materials and Methods

We retrospectively reviewed the clinical and pathological data and the postoperative follow-up findings of eight cases aged 3-72 years who were diagnosed as genitourinary tract soft tissue sarcoma between January 2013 and February 2017 in our clinic. Demographic data of the patients, presenting complaint, primary organ, tumor side, localization, metastasis at the time of diagnosis, pathological tissue diagnosis, pathological tumor size, applied surgical treatments, surgical resection status (complete/incomplete), surgical margin positivity, adjuvant therapies during postoperative follow-up, postoperative follow-up period, local recurrence, progression and survival were recorded.

In the pathological examination of GUS, all cases were graded according to the classification determined by ''FNCLCC'' (The French Fédération Nationale des Centers de Lutte Contre le Cancer) and the pathological grade of each patient was recorded. In this system, three parameters as tumor differentiation, mitotic activity and tumor necrosis degree, are scored separately and according to the total score, patients are classified as grade I, II, III (low, medium, high grade) in terms of sarcoma grade (5,6).

Statistical Analysis

Kaplan-Meier method was used for survival analysis and differences between patient groups were evaluated by log rank test. This study was not suitable for the multivariate model because of the small sample size. Analyses were performed using IBM SPSS Statistics 21 (IBM, Armonk, NY USA) software. $p<0.05$ was considered statistically significant.

Results

All eight patients included in the study were male and the mean age at diagnosis was 47.87 (range = 3-72) years. The most common site was paratesticular area (five cases, 62.5%) followed by kidney (two cases, 25%) and prostate (one case, 12.5%). The most common presenting complaint was palpable mass, which was present in all five paratesticular sarcomas (four in the scrotum and one in the inguinal region). Histological types of tumors were rhabdomyosarcoma (RMS) (two cases, 25%), liposarcoma (LPS) (two cases, 25%), leiomyosarcoma (LMS) (two cases, 25%), synovial sarcoma (SS) (one case, 12.5%) and malignant fibrous histiostoma (MFH) (one case, 12.5%). Seven patients (87.5%) underwent surgical excision, while one of these patients (14.2%) had positive surgical margins.

During the median follow-up of 23.5 (range = 4-62) months, none of the eight patients received neoadjuvant therapy. Adjuvant chemotherapy (CT) was planned in five patients, adjuvant radiotherapy (RT) in one patient, palliative RT + CT in one patient and one patient was followed-up. Local recurrence developed in two patients (25%) after a mean of 6 months (range = 4-8 months). In two cases, progression was observed in a very short period of 4 months (range = 3-5 months) after the diagnosis and cancer-related death occurred at 5th month. The only metastatic patient at the time of diagnosis was prostate LMS, and metastasis was observed in paraaortic area, paravertebral area, lung, spleen and liver.

Among the five paratesticular sarcomas, the worst prognosis was seen in LMS, which had local recurrence in the early postoperative period the 4th month, although radical orchiectomy followed by adjuvant RT was performed due to surgical margin positivity. After being out of follow-up, it was learned that the overall survival of this patient was 28 months. In another case of MFH with a poor prognosis, local recurrence was observed the 8th month and the patient was out of follow-up. In this patient, the overall survival was 33 months.

Among the eight GUS, the histological types with the worst prognosis were LMS and SS. One of our two LMS cases had prostate origin and surgical resection could not be performed in this patient who was metastatic at the time of diagnosis due to poor general condition. Despite palliative RT + CT treatment, the patient died at the 5th month. The other patient with LMS had paratesticular origin. The case of SS had of renal origin and progressed rapidly within two months and died at the 5th month despite debulking surgery + adjuvant CT.

The histologic types with the best prognosis were LPS (one paratesticular and one renal origin) and RMS (two paratesticular origin) with no recurrence or progression during follow-up. The median tumor size was 52.5 mm (range = 11-210) in all eight cases. Although the largest tumor size belongs to renal LPS, we observed that LPS has a better prognosis among histological subtypes. Table 1 presents the characteristics of the cases.

During a median follow-up of 23.5 (range = 4-62) months, the recurrence-free and progression-free survival rate was 50% and the overall survival rate was 50%. Oncologic results were evaluated in terms of tumor histopathologic subtype, FNCLCC grading system, primary organ from which the tumor developed and tumor size >5 cm. According to FNCLCC classification, local recurrence-free survival was significantly higher in grade II sarcomas than in grade III ($p=0.042$, Figure 1) in Kaplan-Meier analysis. Other parameters did not significantly affect local recurrence-free survival, metastasis-free survival and cancer-specific survival (Figures 2,3,4).

Discussion

Since the series reported in the literature on GUS include a relatively small number of patients, there is still limited consensus on optimal treatment regimens and follow-up protocols (7,8). In the relatively large number of patients reported in the literature, LPS was the most common type of all soft tissue sarcomas. LMS (29%) was the most common histological type among all GUS, followed by LPS (26%) and RMS (18%) (3,9). In the most recent and large-scale study by Wang et al. (4), the incidence was 41% for LMS, 20.2% for LPS and 19.1% for RMS. In our small case series study, we found equal numbers (two cases, 25%) of all three types. In the literature, survival rates in bladder and paratesticular sarcomas have been reported to be higher than in sarcomas originating from prostate and

Table 1. Demographic, clinical, pathological data and oncologic outcomes of patients

1	19	Male	Right scrotal swelling	Paratesticular	Spindle cell variant RMS Grade 2	55x45x45	Right inguinal orchiectomy + 7 cycles of CT due to left paraaortic 10x8 mm diameter lymph node (vincristine, actinomycin D, cyclophosphamide)	62	No relapse, Survivor
2	59	Male	Right scrotal swelling	Paratesticular	LPS Grade 2	45x40x27	Right inguinal orchiectomy + active surveillance	48	No relapse, Survivor
3	72	Male	Swelling in the left inguinal region	Paratesticular	LMS Grade 3	50x40x30	Left inguinal orchiectomy + inguinal mass excision + adjuvant RT due to surgical margin positivity	4	Local recurrence at the 4th month The patient was out of followed up. It was learned that he dead at the 28th month.
4	3	Male	Right scrotal swelling	Paratesticular	Embryonal RMS Grade 2	11x10x5	Right inguinal orchiectomy + 12 cycles of CT (vincristine)	39	No relapse, Survivor
5	60	Male	Left scrotal swelling	Paratesticular	Malignant fibrous histiocytoma Grade 3	50x49x45	Left inguinal orchiectomy + 4 cycles of CT (ifosfamide, mesna, a driamycin)	8	Local recurrence at the 8th month The patient was out of followed up. It was learned that he dead at the 33th month.
6	47	Male	Left flank and abdominal pain	Renal	Synovial sarcoma Grade 3	90x70x60	Left radical nephrectomy, Splenectomy + retroperitoneal metastasectomy for metastasis 2 months later + single dose CT (doxorubicin)	5	Multiple metastases in the lung, spleen, paraaortic and paravertebral areas at the 2th month. Metastasis in the liver at the 4th month. Dead at the 5th month
7	57	Male	Bilateral lower extremity edema	Renal, Mass that makes pressure to vena cava	LPS Grade 2	210x200x90	Right radical nephrectomy + right adrenalectomy + 4 cycles of adjuvant CT (ifosfamide, mesna, adriamycin)	44	No relapse, Survivor
8	66	Male	Weakness, constipation, perineal pain	Prostate	LMS Grade 3 (Outcome of TRUS-prostate biopsy)	55x35x30	At the time of diagnosis, PSA=12, invasion of anal canal and pelvic floor muscles, metastasis in lung Palliative RT to the prostatic area + 2 cycles of CT (doxorubicin, cyclophosphamide, cisplatin)	5	PSA progression at the 3th month Dead at the 5th month

RMS: Rhabdomyosarcoma, LPS: Liposarkoma, LMS: Leiomyosarcoma, TRUS: Transrectal ultrasonography, CT: Chemotherapy, RT: Radiotherapy, PSA: Prostate specific antigen

kidney (3,4). This condition was attributed to the diagnosis in early stages due to scrotal swelling in paratesticular sarcoma and early presentation of patients with hematuria in bladder sarcoma (2). Similarly, recurrence-free and progression-free survival rates were higher in paratesticular cases than in renal and prostate cases (60% vs 33.3%) in our study.

Retroperitoneal soft tissue sarcomas constitute 10-20% of all sarcomas. Eighty percent of patients present with intra-abdominal mass symptoms, and the second most common symptom is pain. Since these masses do not show any symptoms until they reach a large size, they are diagnosed in the late period (10). The most common histological type is LPS, which also has better biological course and prognosis (11). However, tumor prognosis may vary depending on tumor grade, size and stage (12). In our study, a patient with renal LPS presented to the advanced clinical stage with bilateral lower extremity edema because of a mass compressing the vena cava at the time of diagnosis. The mass was resected completely by radical nephrectomy + adrenalectomy and histopathological grade was grade II according to FNCLCC. Following four cycles of adjuvant CT, no recurrence or progression was observed in the 44-month follow-up.

Prostate sarcomas are extremely rare and data about treatment modalities and survival rates is based on case reports and expert opinions. Surgical resection is the mainstay of treatment in these cases, usually by cystoprostatectomy or total pelvic

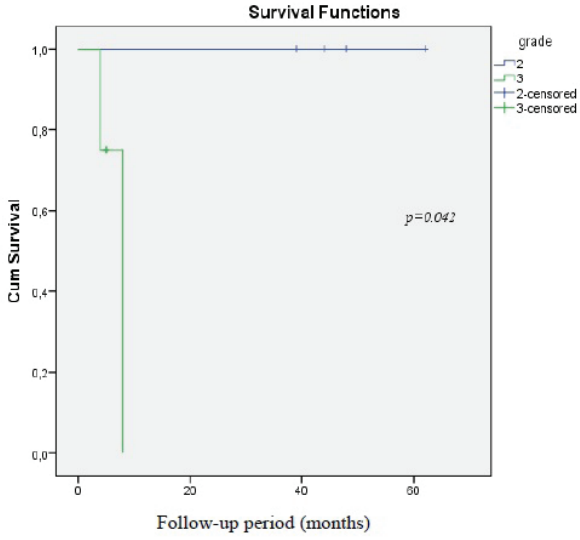

Figure 1. Kaplan-Meier survival curves of all cases according to histopathologic grade

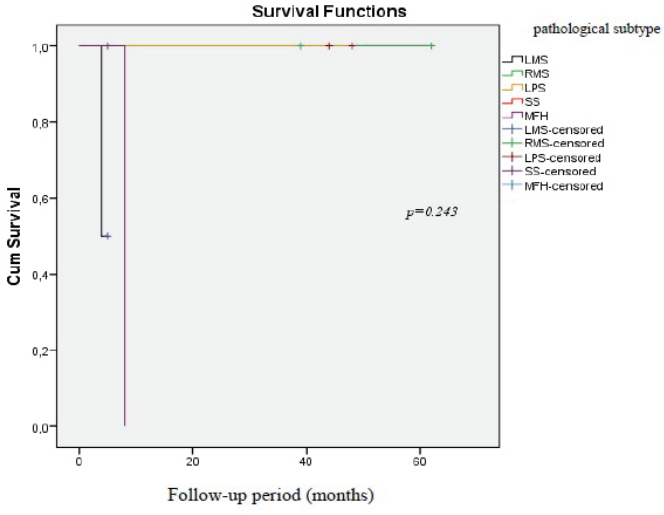

Figure 2. Kaplan-Meier survival curves of all cases according to pathological subtype

LMS: Leiomyosarcoma, RMS: Rhabdomyosarcoma, LPS: Liposarcoma, SS: Synovial sarcoma

exenteration. In a series of 21 patients, 1, 3 and 5-year survival rates were reported as 81%, 43% and 38%, respectively (13). LMS is the most common primary sarcoma of the prostate in adults and constitutes 38-52% of primary prostate sarcomas. It has a highly aggressive clinical course (14). Due to its rarity, definitive treatment protocols have not been established yet. Numerous publications have reported widespread metastasis to the lung and liver in approximately one-third of patients at the time of diagnosis or shortly after diagnosis. In addition to surgical resection, multimodal treatment combinations such as neoadjuvant or adjuvant CT and RT are recommended (8,14). In our case, FNCLCC grade III LMS was diagnosed in the biopsy performed due to high PSA level, and invasion of the anal canal and pelvic floor muscles and lung metastasis were present at

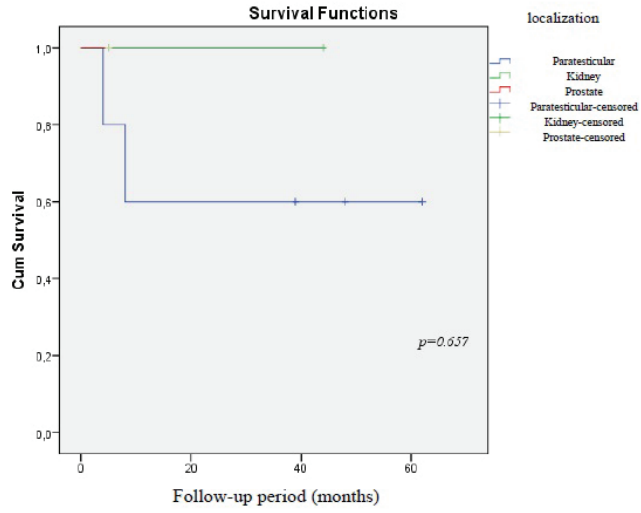

Figure 3. Kaplan-Meier survival curves of all cases according to tumor localization

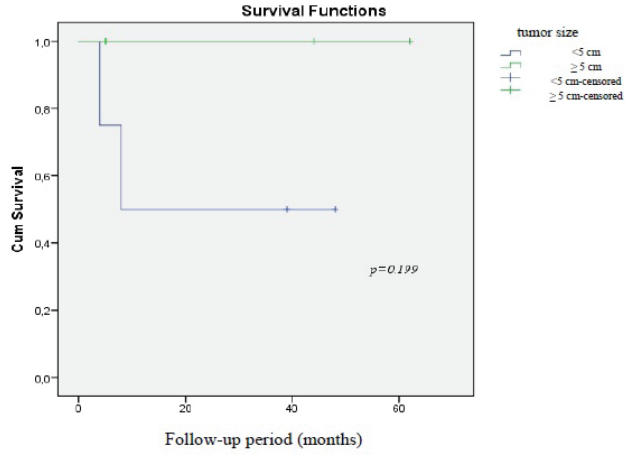

Figure 4. Kaplan-Meier survival curves of all cases according to tumor size

the time of diagnosis. In the patient whose general health status could not tolerate surgery, RT + CT was applied to the prostatic area for palliative purposes. The patient died at 3th month following a rapid PSA progression.

The most common complaint in paratesticular sarcomas is a painless scrotal mass that develops from the mesenchymal elements of the spermatic cord, epididymis and testicular sheath. RMS is the most common soft tissue sarcoma in childhood and is the most common primary paratesticular malignant neoplasm between seven and 36 years of age (mean age 10 years) (15). It accounts for 80% of paratesticular tumors under the age of 21 and and accounts for 24% in adults (16). In our study, we observed the histopathological subtype of two paratesticular RMS cases as ''embryonal'' with a better prognosis and ''spindle cell variant'', which is considered a subtype of it. The degree of sarcoma in both cases was II according to FNCLCC. In both cases, adjuvant CT was performed following radical orchiectomy. The mean follow-up was 50.5 months (range = 39-62 months).

In contrast to paratesticular RMS, there are fewer reported cases of paratesticular LMS and LPS (17,18). Fisher et al. (17) showed that recurrence and metastasis could be prevented in low-grade paratesticular LMS cases by radical orchiectomy. In our case, although radical orchiectomy + inguinal mass excision was performed for complete excision, adjuvant RT was performed because surgical margin positivity was observed. In our case, which was higher grade according to FNCLCC, local recurrence could not be prevented at the 4th month despite multimodal treatment. Paratesticular LPS is mostly well differentiated and it has been reported that the expected survival is longer (13,18). Our patient with grade II paratesticular LPS was followed up without radical adjuvant therapy after radical orchiectomy. No recurrence or progression was observed in the 48-month follow-up.

Since the role of retroperitoneal lymph node dissection (RPLND) in paratesticular sarcomas has not been well defined, controversial views are still available on the additional therapeutic benefit (13,19,20). Therefore, in our patient with grade II, spindle cell variant RMS with 10x8 mm diameter lymph node in the left paraaortic area at the time of diagnosis, only CT was applied instead of RPLND as adjuvant. No recurrence or progression was observed in this patient at 62 months follow-up.

MFH is very rare in the urinary system and usually progresses rapidly. Mondainia et al. (2) reported the incidence of MFH in their case series as 4.5% in all GUS and 11.1% in paratesticular sarcomas (2). Size, depth and histopathological features of the tumor are important factors for the development of metastasis. Despite multimodal treatment, 3-year survival is approximately 40% (21). In our study, local recurrence occurred at 8th month in grade III paratesticular MFH despite adjuvant CT after radical orchiectomy. Although we do not know the overall survival status of the patient who is out of follow-up, it is highly likely to show progression in a short time.

SS constitute 1-3% of all malignant renal masses and 5-10% of adult soft tissue sarcomas (22). Primary renal SS is much rarer, and approximately 60 cases have been reported in the literature to date (22). Primary renal SS often clinically mimics renal cell carcinoma. Histopathologically, it is difficult to differentiate from Wilms tumor, sarcomatoid kidney cell carcinoma, hemangiopericytoma and undifferentiated carcinoma (23,24). Although the rate of metastasis at the time of diagnosis has been reported to be low in the literature (23,24), the prognosis of renal SS is quite poor, regardless of the type of treatment administered (13). Although the primary treatment approach is surgical, the role of neoadjuvant or adjuvant CT in these cases is not clear (24). The clinical course of our case was consistent with this data and our patient developed metastasis in 2 months following nephrectomy and died at the 5th month despite metastasectomy and adjuvant CT.

Disease-specific survival rate in GUS is worse than in other soft tissue sarcomas (25). This poor prognostic feature of GUS can be explained by presentation at metastatic stage, high-grade tumor, larger tumor size and primary anatomical region of involvement. In addition, heterogeneity between different subgroups of GUS may lead to a significant difference in prognosis among patients (13). According to the multivariate analysis by Dotan et al. (3), increased tumor size, incomplete surgical resection, positive surgical margin and presence of metastasis at the time of diagnosis lead to a significant decrease in disease-specific survival. In addition, tumor size was reported to be predictive of recurrence-free survival, and age, tumor grade and tumor histology as independent predictive factor of metastasis-free survival. Wang et al. (4) detected renal sarcomas, female gender, presence of metastasis at diagnosis and positive surgical margin status as poor prognostic factors affecting recurrence-free survival. They reported the presence of incomplete surgical resection and positive surgical margins as poor prognostic factors affecting metastasis-free survival. In a multicenter study with the largest series (53 patients) in our country, male gender, advanced age (≥50 years), metastatic stage at diagnosis, incomplete resection, FNCLCC grade III cases and renal sarcomas were reported as poor prognostic factors (26).

Cho et al. (13) reported 1, 3 and 5-year disease-specific survival rates as 88.9%, 76.2% and 67.7%, respectively, whereas Mondainia et al. (2) reported these rates as 85.9%, 62.0% and 48.8%, respectively. Dotan et al (3). reported 5-year local recurrence rate as 32%, metastasis-free survival rate as 60%, and disease-specific survival rate as 56%. In the largest-scale publication in the literature, Wang et al. (4) found a 5-year local recurrence-free survival rate of 34.6%, metastasis-free survival rate of 34.9%, and overall survival rate of 47.7%. In our median follow-up of 23.5 (range = 4-62) months, we found that the recurrence-free and progression-free survival rates were 50% and the overall survival rate was 50%. Although our follow-up duration and number of patients were more limited compared to these studies, we observed similar rates.

In our study, local recurrence-free survival was significantly higher in grade II sarcomas compared to grade III according to FNCLCC classification. Cho et al. (13), in their series, reported that tumor grade had a poor prognostic value on disease-specific survival (27). Mondainia et al. (2) reported 5-year survival rates as 100% for FNCLCC grade ≤II and 27.4% for FNCLCC grade >II. In the same study, disease-free survival rates were 100% for tumor size ≤5 cm and 11.2% for tumors >5 cm. In several publications using the American Joint Committee on Cancer Classification for pathologic tumor grading, 5-year disease-specific survival rates for low-grade and high-grade tumors were 99% and 87%, respectively, for tumors <5 cm. The same rates were 64% and 48%, respectively, for tumor size ≥5 cm (3, 28). In our study, during median 23.5 (4-62) months follow-up, we found the disease-specific rates to be 100% and 50% in grade II and III patients, respectively. When we evaluated the effect of tumor size, localization and histopathologic subtype on survival, we could not observe a statistically significant difference. However, we cannot ignore the fact that our short-term follow-up period and the small number of patients limit our ability to perform a better analysis. In some publications, it has been stated that grade III cases may benefit from adjuvant CT (29,30). Wang et al. (4) reported the absence of adjuvant CT as an independent predictor of poor survival. In our study, four patients in grade III in our study had recurrence and progression despite adjuvant CT and/or RT.

Study Limitations

The retrospective design of our study, the limited number of patients, therefore the lack of randomization, the short follow-up period, and the follow-up results belonging to a single center are the main limiting factors.

Conclusion

GUSs are a rare group of tumors. Complete surgical resection plays a major role in improving survival in these patients. Survival rates may increase in localized resectable masses with the contribution of adjuvant therapy. The prognosis is poor especially in patients with metastatic disease, prostate sarcomas, MFH and SS. According to our findings, FNCLCC grade is the most important prognostic factor determining recurrence in all adult GUS cases. Therefore, combined multimodal treatments provide a very limited therapeutic effect, especially in grade III sarcomas. Further prospective, randomized, controlled, multicentre, large-population studies with longer follow-up periods are needed to identify prognostic factors that affect survival. To identify specific neoadjuvant or adjuvant therapies according to the tumor subtype are also required.

Ethics

Ethics Committee Approval: Approval was waived due to retrospective nature of the study.

Informed Consent: Each patient was informed prior to the surgery that their oncological follow-up information such as recurrence, metastasis development, survival analysis may be used without mentioning the patient names and identity information. The information of the patients who did not consent were not used.

Peer-review: Internally peer-reviewed.

Author Contributions

Surgical and Medical Practice: E.O.G., Concept: E.O.G., Design: İ.S., Data Collection or Processing: İ.S., Analysis or Interpretation: İ.S., E.O.G., Literature Search: İ.S., Writting: İ.S.

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Analysis of Prognostic Factors Affecting Cancer-specific Survival in Renal Tumors Larger than Ten Centimeters

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Abstract

Objective: The aim of this study was to evaluate the relationship between prognostic factors and cancer-specific survival (CSS) in renal tumors larger than ten centimeters.

Materials and Methods: We evaluated the data of 126 patients who underwent open radical nephrectomy due to a renal mass larger than 10 cm between January 2010 and June 2016. Kaplan-Meier analysis or Cox regression was used to analyze the relationship between CSS and variables. Pairwise group comparisons were also evaluated with the Log-Rank test. A p-value <0.05 was considered statistically significant.

Results: Mean follow-up was 68.5 months and mean survival was 39.2 months. The relationships between tumor histopathology, stage and CSS were significant. Tumor size negatively affected CSS, but the relationship was not significant. Tumor stage (T2b, T3b), tumor thrombus, lymph node metastasis and adjuvant therapy were the most effective independent factors affecting CSS according to Cox regression analysis results.

Conclusion: Although tumor size is an important prognostic factor for T2b and lower stage kidney tumors, this effect is less in larger tumors and other clinicopathological features should be considered further to predict prognosis.

Keywords: Renal cell carcinoma, prognosis, survival analysis, cancer-specific survival, nephrectomy

Introduction

Renal cell cancer (RCC) accounts for 2-3% of all cancers (1). According to World Health Organisation Report 2014, RCC was the 9th and 14th most frequent malign tumor in men and women in 2012, respectively, and the 16th most common cause of cancer-related death worldwide with 143,000 deaths (2). The number of RCCs has increased due to the widespread use of ultrasonography and computed tomography (CT), and these tumors are frequently small and low grade. Although most of these tumors consist of small masses, the number of large masses is quite high.

Factors affecting prognosis in renal tumors can be classified as anatomical, histological, clinical and molecular. Tumor size is an important prognostic factor for RCCs in Tumar, nodes, metostases classification. Some cut-off values for tumor size determine the T stage, such that, 4 cm and 10 cm are threshold values for T1a and T1b tumors and T2a and T2b tumors, respectively. Some authors argue that these thresholds do not have prognostic values (3) or that the use of other tumor size thresholds is better (4). Tumor size can also be considered as a threshold value for the proposed cancer treatment as 4 cm and 3 cm are widely accepted threshold values for partial nephrectomy and ablative therapies (5). However, in the modern era, these thresholds are not strictly restrictive for experienced surgeons thanks to the development of technological equipment such as robotic surgery.

On the grounds that the prognosis of RCC is variable, many researchers are trying to find prognostic factors that affect RCC survival. As with many cancers, tumor progression and grade are considered to be the most important prognostic factors in RCC. However, it is still unclear which factor and how much it affects the prognosis. In this study, we analyzed the prognostic factors that affect cancer-specific survival (CSS) in kidney tumors larger than 10 cm and tried to identify the most effective factors.

Materials and Methods

Patient Selection, Data Collection and Follow-up of the patients

one hundred and twenty-six patients who underwent radical

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nephrectomy due to ≥10 cm renal mass and whose pathology report was consistent with RCC between January 2010 and June 2016 were included in the study. Data was obtained from patient files. In localized disease, University of California, Los Angeles (UCLA) integrated staging system (UISS), which was developed by UCLA and combined TNM stage (I to IV), Eastern Cooperative Oncology Group (ECOG) performance status (PS) and Fuhrman degree, were used (6). The Memorial Sloan Kettering Cancer Center (MSKCC) prognostic system, which combines Karnofsky performance status, the interval between diagnosis and treatment, lactate dehydrogenase, corrected calcium, and hemoglobin, was used to determine the risk of recurrence of metastatic disease (7). Tumor pathology, stage, renal vein invasion, perinephric fat invasion, tumor thrombus, lymph node, adrenal and distant organ metastasis status, and ECOG PS Grade of the patient were recorded. Tumor size was calculated from histopathological evaluations because it was more consistent. In order for the histopathological types to be statistically significant, a minimum of seven subjects were required. Therefore, histopathological types less than seven (n=13) were excluded from the study. Tumor staging and nuclear grading were performed according to 2017 TNM classification and Fuhrman's nuclear grading system, respectively (8). Tumor staging and follow-up of patients were performed with enhanced thoracoabdominal CT or magnetic resonance imaging. Patients were subjected to regular controls and CSS rates were calculated. Patients identified as exitus by the hospital system and their exitus dates were also recorded. The present study was conducted in compliance with the Declaration of Helsinki and written informed consent was obtained from the patients. Because of the study was designed as a retrospective study, ethics committee approval was not obtained.

Statistical Analysis

Kaplan-Meier analysis or Cox regression was used to analyze the relationship between CSS and clinicopathological variables including gender, tumor size, side, location, pathological type, T stage, renal vein invasion, perinephric fat invasion, tumor thrombus, lymph node metastasis, adrenal metastasis, distant organ metastasis, and adjuvant treatment. Pairwise comparisons were evaluated using the Log-Rank test after Kaplan-Meier analysis. Forward stepwise (according to the method of likelihood ratio) multiple logistic regression analysis was used for RCC risk factor analysis. All statistical analyzes were performed using IBM SPSS version 23.0. A p-value <0.05 was considered statistically significant.

Results

A total of 445 patients underwent radical nephrectomy with the diagnosis of renal parenchymal tumors during the study period. The tumor of 307 patients was smaller than 10 cm. Ewing sarcoma (n=1), spindle cell sarcoma (n=1), liposarcoma (n=1), mixed epithelium stromal tumor (n=1), mucinous tubular and spindle cell sarcomas (n=2), neuroectodermal tumors (n=1), neuroendocrine tumors (n=1), pleomorphic sarcomas (n=1), squamous cell carcinomas (n=1) and urothelial carcinomas (n=2) were not included in the study because

Table 1. Demographic data of patients and characteristics of tumors

Variables	n[1]
Age (year)	59.10 (22-85)
Gender (female/male)	38 (30.2)/88 (69.8)
Tumor side (right/left)	57 (45.2)/69 (54.8)
Tumor location in the kidney (upper/middle/lower)	43 (34.1)/32 (25.4)/51 (40.5)
Tumor size (mm)	128.05 (100-220)
Histopathological subtypes	
Clear cell	84 (66.7)
Chromophobe cell carcinoma	18 (14.3)
Papillary tumor	24 (19.0)
Total	126 (100)
Fuhrman grade	
Grade 2	16 (22.2)
Grade 3	37 (51.4)
Grade 4	19 (26.4)
Tumor stages	
T2b	40 (31.7)
T3a	45 (35.7)
T3b	10 (8.0)
T4	31 (24.6)
Total	126 (100)
UCLA integrated staging system risk groups	
Low	28 (28.6)
Intermediate	53 (54.0)
High	17 (17.4)
MSKCC prognostic system	
Low	10 (35.7)
Intermediate	15 (53.6)
High	3 (10.7)
Renal vein invasion	
Positive	32 (25.4)
Negative	94 (74.6)
Perihilar fat invasion	
Positive	66 (52.4)
Negative	60 (47.6)
Tumor thrombus	
Positive	12 (9.5)
Negative	114 (90.5)
Metastatic lymph node	
Positive	15 (11.9)
Negative	111 (88.1)
Surrenal metastasis	
Positive	11 (8.7)
Negative	115 (91.3)
Distant organ metastasis	
Positive	28 (22.2)
Negative	98 (77.8)
Cancer-specific survival (month)	39.2 (1-168)

[1]Values are given as numbers and percent or mean and minimum-maximum
UCLA: University of California, Los Angeles, MSKCC: Memorial Sloan Kettering Cancer Center

the number of cases was insufficient to draw any statistical conclusions. The remaining 126 patients were included in the study. According to the ECOG performance status, 42 patients had grade 0, 40 had grade 1, 36 had grade 2, and eight had grade 3 performance status. There were no patients in the 4th grade. The majority of patients had good performance status. Therefore, the survival effect of ECOG status was insignificant. The mean age of the patients was 59.1 years. Most of the patients were male (88/126). The mean tumor size was 128.05 mm. The most common histopathological type and Fuhrman grade was clear cell grade 3 (29.4%). Tumors most commonly presented with T3a stage (35.7%), followed by T2b, T4 and T3b (31.7%, 24.6% and 8.0%, respectively). Renal vein invasion was detected in 32 patients (25.4%). Sixty-six patients (52.4%) had perinephric fat invasion. Twelve patients (9.5%) had tumor thrombus and 11 patients (8.7%) had adrenal metastasis. Twenty-eight patients (22.2%) had distant organ metastases. The mean disease-specific survival was 39.2 (range, 1-168) months. The majority of patients with localized disease was in the UCLA integrated staging system intermediate risk group and the majority of the metastatic patients were in the intermediate group according to the MSKCC prognostic system (54.0% and 53.6%, respectively). Patient and tumor characteristics are summarized in Table 1. A total of 87 patients received adjuvant treatment. The multidisciplinary urooncology council determined which treatment should be administered to which patient. Thirty eight of 66 patients with perinephric fat invasion received immunotherapy, seven of 12 patients with tumor thrombosis received targeted therapy, eight of 11 patients with adrenal metastasis received immunotherapy and one of them received targeted therapy, and 20 of 28 patients with distant organ metastasis received immunotherapy and four received targeted therapy. A total of nine patients received adjuvant temsirolimus treatment. Indications and distribution of adjuvant therapy are shown in Table 2.

Although not statistically significant, age negatively affected survival (p=0.091). Fifty-two (59.1%) men and 22 (57.9%) women died during the follow-up period. Twenty-two patients died due to myocardial infarction, 21 patients due to multiple organ failure as a result of generalized impairment, 19 patients due to acute respiratory distress syndrome and 12 patients due to cerebrovascular disease. The one-year CSS rate was 62.5% and 5-year CSS rate was 41.4% in men. In women, these rates were 75% and 45.9%, respectively. Mean CSS was 65.7 months for men and 61.3 months for women (p=0.753). Mean CSS was 60.6 months for right-sided tumors and 67.1 months for left-sided tumors (p=0.900). Mean CSS was 68.9 months for lower pole tumors, 52.6 months for middle pole tumors and 42.2 months for upper pole tumors (p=0.124). Renal vein invasion, perinephric fat invasion, tumor thrombus, lymph node metastasis, adrenal metastasis and distant organ metastasis negatively affected mean CSS (p<0.001, p<0.001, p<0.001, p<0.001, p=0.013, and p<0.001, respectively). Tumor size negatively affected CSS although the relationship was not statistically significant (p=0.058, OR: 1.007, 95.0% CI: 1.000-1.014). When survival rates were evaluated according to tumor histopathology, the 1-year CSS rate was 91.7%, 77.4%, 44.4%, 75%, and 83.3%, for clear cell grade 2, clear cell grade 3, clear cell grade 4, chromophobe, and papillary, respectively. Pairwise comparisons of tumor stages were shown in Table 3. Presence of renal vein invasion significantly affected survival (p<0.001). Perinephric fat tissue invasion was also a negative prognostic factor (p<0.001). Tumor thrombosis negatively affected survival (p<0.001) and lymph node metastasis was also a prognostic factor negatively affecting CSS (p<0.001). Estimated CSS in terms of renal vein invasion, perinephric fat tissue, tumor thrombus status and lymph node metastasis status is shown in Figures 1-4.

Table 2. Types and indications of adjuvant therapies

Type of adjuvant therapy	Total number	Indication of adjuvant therapy			
		Perinephric fat invasion	Tumor thrombosis	Adrenal metastasis	Distant organ metastasis
Immunotherapy Interferon alpha Interleukin-2	66 19 47	38 12 26	-	8 2 6	20 5 15
Targeted therapy Sunitinib Cabozantinib Pazopanib	12 5 3 4	-	7 2 2 3	1 1 - -	4 2 1 1
Temsirolimus	9	-	3	2	4

Table 3. Pairwise comparisons of tumor ''T'' stages

	Pathology	T2b		T3a		T3b		T4	
		Chi-square	Sig.	Chi-square	Sig.	Chi-square	Sig.	Chi-square	Sig.
Log Rank (Mantel-Cox)	T2b	-	-	*41.015*	***<0.001***	*8.982*	***0.003***	*45.617*	***<0.001***
	T3a	*41.015*	***<0.001***	-	-	*0.783*	*0.376*	*0.620*	*0.431*
	T3b	*8.982*	***0.003***	0.783	0.376	-	-	*1.700*	*0.192*
	T4	*45.617*	***<0.001***	*0.620*	*0.431*	*1.700*	*0.192*	-	-

Statistically significant values are given in bold and italics, Sig: Signetur

Five and 10-year estimated CSS rates according to the variables are shown in Table 4. The result of the reduced model of Cox regression analysis is given in Table 5, and it revealed that stage T2b, stage T3a, stage T3b, tumor thrombus, lymph node metastasis and adjuvant therapy were the most effective factors for CSS (HR=6.644, 2.358, 8.164, 3.149, 5.143, 6.188, and 2.014, respectively).

Discussion

RCC constitutes approximately 85% of primary renal cancers. As with all cancers, predicting prognosis in RCC is important for treatment management. In RCC patients, TNM stage, tumor nuclear grade and RCC subtype provide important prognostic information. Prognostic factors in renal cancers can be classified as anatomical, histological, clinical and molecular. Accurate staging is very important in order to decide the treatment of these tumors and to predict prognosis and response to treatment. Pathological staging determines the anatomic spread of the tumor and its relationship with the surrounding tissues. Tumor size in the TNM system used for the staging of renal tumors is one of the most important prognostic factors. Tumor size is not only a prognostic marker; it is also a determining factor for the type (partial/radical) and method of operation (open/laparoscopic). In the literature, the prognostic factors for T1 (≤7 cm) and T2 (≤10 cm) tumors are well established and there are many studies in this regard. However, there is uncertainty about the prognosis and surgical methods of renal masses larger than 10 cm. For this reason, in the present study, we performed a survival analysis by evaluating prognostic factors in renal tumors larger than 10 cm that underwent surgical treatment in our clinic and we aimed

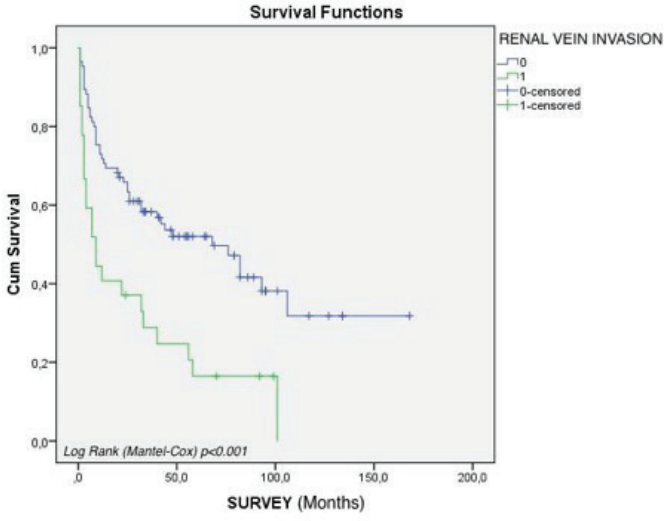

Figure 1. Kaplan-Meier survival curve of cancer-specific survival with and without renal vein invasion

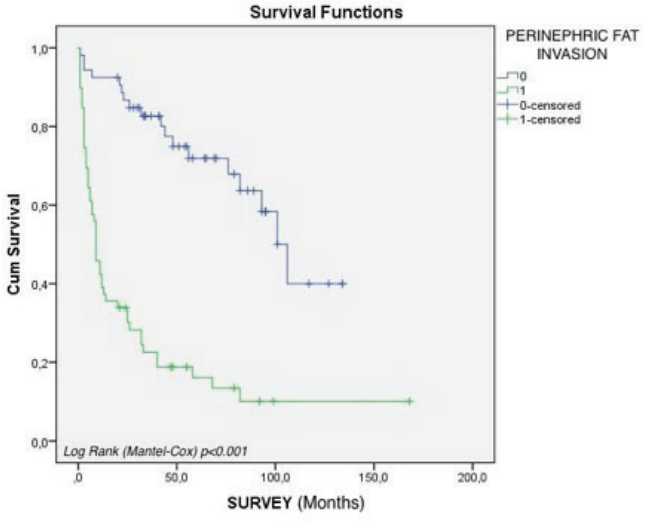

Figure 2. Kaplan-Meier survival curve of cancer-specific survival with and without perinephric fat tissue invasion

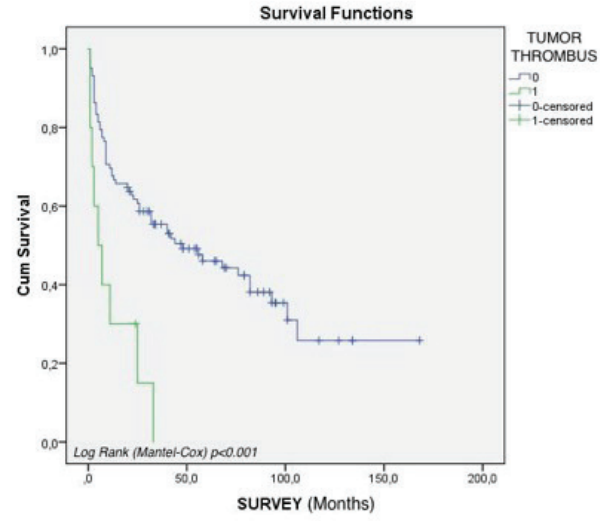

Figure 3. Kaplan-Meier survival curve of cancer-specific survival with and without tumor thrombus

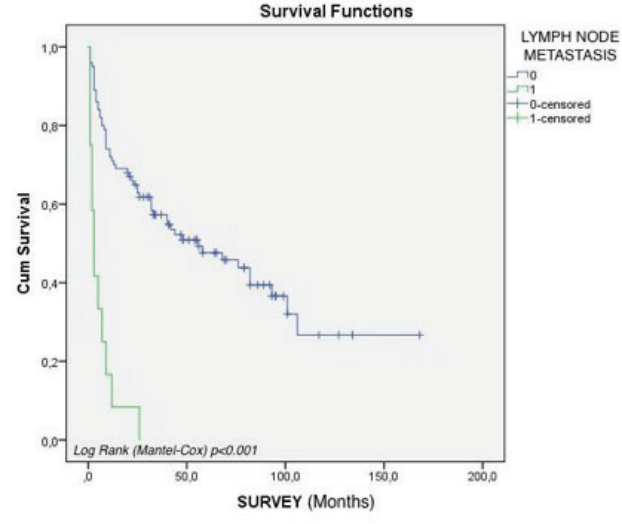

Figure 4. Kaplan-Meier survival curve of cancer-specific survival with and without lymph node metastasis

Table 4. 5-year and 10-year cancer-specific survival rates according to tumor and patient characteristics

Variables	Time[1]	Cumulative proportion surviving at the time		Number of Cumulative events	Number of Remaining events
		Est.	SE		
Gender					
Male	a	0.414	0.058	45	19
Female	b	0.239	0.090	48	3
Tumor side					
Right	a	0.432	0.077	26	12
	b	0.314	0.081	29	8
Left	a	0.438	0.069	31	16
	b	0.219	0.089	35	3
Tumor location					
Lower	a	0.505	0.087	17	14
	b	0.280	0.101	21	4
Middle	a	0.357	0.110	13	6
	b	0.143	0.090	16	2
Upper	a	0.329	0.101	17	5
	b	-	-	-	-
Pathology					
Clear cell grade 2	a	0.625	0.155	4	5
	b	0.313	0.174	6	1
Clear cell grade 3	a	0.367	0.093	18	8
	b	0.000	0.000	22	0
Clear cell grade 4	a	0.292	0.120	12	2
	b	-	-	-	-
Chromophobe	a	1.000	1.000	0	7
	b	0.750	0.217	1	1
Papillary tumor	a	0.729	0.135	3	5
	b	0.729	0.135	3	2
Stage					
T2b	a	0.936	0.044	2	20
	b	0.520	0.172	7	3
T3a	a	0.267	0.226	3	0
	b	0.080	0.065	33	1
T3b	a	0.160	0.065	32	4
	b	-	-	-	-
T4	a	0.132	0.069	22	3
	b	0.066	0.058	23	0
Fuhrman grade					
Grade 2	a	0.683	0.290	1	9
	b	0.322	0.317	3	3
Grade 3	a	0.481	0.599	7	14
	b	0.209	0.614	10	6
Grade 4	a	0.102	0.201	16	3
	b	-	-	-	-
Renal vein invasion					
Negative	a	0.520	0.057	39	32
	b	0.318	0.081	45	4
Positive	a	0.165	0.074	22	4
	b	0.000	0.000	23	0
Perinephric fat invasion					
Negative	a	0.719	0.068	13	22
	b	0.400	0.125	18	3
Positive	a	0.161	0.051	48	6
	b	0.101	0.047	50	1
Tumor thrombus					
Negative	a	0.460	0.053	52	28
	b	0.258	0.072	59	4
Positive	a	0.000	0.000	9	0
Lymph node metastasis					
Negative	a	0.476	0.054	49	28
	b	0.267	0.075	56	4
Positive	a	0.000	0.000	12	0
Adrenal metastases					
Negative	a	0.459	0.053	52	27
	b	0.238	0.077	59	4
Positive	a	0.100	0.095	9	1
	b	-	-	-	-
Distant organ metastasis					
Negative	a	0.667	0.098	9	10
	b	0.000	0.000	14	0
Positive	a	0.000	0.000	26	0
UCLA integrated staging system (UISS) risk group					
Low	a	0.732	0.291	2	18
	b	0.489	0.217	4	12
Intermediate	a	0.602	0.117	8	21
	b	0.311	0.086	13	10
High	a	0.218	0.014	22	0

MSKCC prognostic system					
Low	a	0.418	0.372	8	2
Intermediate	a	0.000	0.000	15	0
High	a	0.000	0.000	3	0
Adjuvant theraphy					
Negative Positive	a	0.748	0.039	22	8
	b	0.411	0.102	7	2
Immunotheraphy	a	0.000	0.000	66	0
Targeted theraphy	a	0.000	0.000	21	0

[1]Time is given in months. "a" indicates the 60-months period and "b" indicates the 120-months period. 120 months survival (b) was not given for the variables with a survival rate of 0 at 60 months.
Est: Estimated, SE: Standard error, UCLA: University of California, Los Angeles, UISS: UCLA integrated staging system, MSKCC: Memorial Sloan Kettering Cancer Center

Table 5. Results of multivariate Cox proportional-hazards regression analysis of factors correlated with cancer-specific survival

			95% CI for Exp (B)	
Variables	**Sig.[1]**	**Exp (B)**	**Lower**	**Upper**
Tumor size	***0.001***	1.014	1.005	1.022
Stage T2b	***0.018***	6.644	1.392	31.698
Stage T3a	0.421	2.358	0.292	19.070
Stage T3b	***0.009***	8.164	1.704	39.127
Tumor thrombus	-	-	-	-
Negative (12)	-	-	-	-
Positive (114)	***0.012***	3.149	1.291	7.681
Lymph node metastasis	-	-	-	-
Negative (111)	-	-	-	-
Positive (15)	***<0.001***	5.143	2.426	10.902
Adjuvant therapy	-	-	-	-
Immunotherapy	***0.024***	6.188	5.724	6.481
Targeted therapy	***0.039***	2.014	1.884	2.414

[1]Chi-square test. Statistically significant values are given in bold and italics.

to evaluate the prognostic factors for these masses. In our study, we used the current TNM classification system for staging purpose (8). Prognostic systems and nomograms may predict survival better than TNM classification or Fuhrman's grading system alone in localized and metastatic diseases in patients with RCC. We used the UISS developed by UCLA for localized disease. In metastatic disease, classification systems such as the MSKCC prognostic system and Hang's model are available. We used MSKCC prognostic system to assess recurrence risk in metastatic patients.

Tumor size has been addressed in many studies. In a study of 360 patients, Kunkle et al. (9) showed that every 1 cm increase in all tumor sizes increased the incidence of metastatic disease by 22%. In another study, it was shown that the life expectancy was dependent on tumor size and the survival rate was 84% in <5 cm tumors and 0% in >10 cm tumors (10). Similarly, although the relationship was not significant, tumor size and survival were inversely proportional in our study (p=0.058). The Fuhrman grade is the most widely accepted grading system in RCC grading and is an independent prognostic factor (11). Fuhrman grade was also an important factor affecting CSS in our cohort.

T stage is one of the important prognostic factors for RCC. Amin et al. (12) defined T stage as an independent predictor of aggressive clinical phenotype, defined as local recurrence, metastasis development and death from disease in chromophobe RCC. It is a well-established data that T1 stage causes higher CSS than T2-4. Bianchi et al. (4) reported a 5-year CSS rate of 80.7-86.2% for the 4,963 T2-stage RCC cases undergoing surgical treatment. Kopp et al. (13) also reported a 5-year CSS rate of 82.5-86.7% in 202 T2-stage RCC treated at multiple centers. In our results, the 5-year survival rate for stage T2 was 93%. The reason that this result is more optimistic may be due to the fact that the patients in the above studies are collected from different centers and that the patient groups were not homogeneously distributed. Laird et al. (14) found a 5-year survival rate of 64.4-67.3% for 252 stage T3 RCC cases from the British medical center. In two other studies, the 5-year CSS rate for T3 stage RCC was reported to be 46-51.1% (15,16). In our cohort, the 5-year CSS rate for stage T3a was 26% and 16% for T3b. Probably; the reason why these rates were lower than other studies are that we often have to operate these patients with cardiovascular surgeons. However, sometimes we have difficulties to organize together and the surgical procedure may be delayed.

Many drugs have shown clinical benefit in metastatic RCC. Recently, the efficacy of the immune-checkpoint inhibitors has been shown, as well as immunotherapy and targeted therapy. A recurrence rate of 35% despite surgical resection underlines the importance of these treatments (17). Prior to the use of tyrosine kinase inhibitors (TKIs), INF-α and IL-2 were the standard treatment of metastatic RCC. In the analysis of six prospective studies, Motzer et al. (18) showed a 13-month overall survival advantage in patients treated with INF-α. Identification of the von Hippel-Lindau gene has shed light on the understanding of RCC pathogenesis. However, targeting of angiogenesis and Mammalian terget of Rapamycin (mTOR) pathway has provided benefit in clinical outcomes. These agents include vascular endothelial growth factor receptor TKIs (sunitinib, pazopanib, axitinib, sorafenib) and mTOR inhibitors (temsirolimus and everolimus) (19,20). In our study, 87 patients received adjuvant therapy and adjuvant therapy was an important factor affecting CSS. This result also supports the efficacy of adjuvant therapy in tumors larger than 10 cm.

A large multicenter study analyzed 291 chromophobe-cell RCCs and suggested that gender was an independent predictor of CSS, and reported that female patients had a significantly lower risk of dying from the disease (21). In our study, on the contrary, the mean CSS rate was higher in males (65.7 vs 61.3), but the difference was not significant (p=0.753).

The relationship between tumor histopathology and survival has been examined in many studies and conflicting results have emerged. There are single-center studies reporting that the survival of chromophobe RCC is better than that of conventional RCC (22,23). However, in large, multicenter series, tumor histology has not been identified as an independent prognostic factor (24,25). Our results revealed that the histological type was an important prognostic factor and affected survival significantly.

In a single-center survival analysis of 1326 patients from China, the tumor thrombus [renal vein or inferior vena cava (IVC)] was a prognostic factor, but the level of IVC involvement was not associated with prognosis (26). Previously, controversial results have been reported about the relationship between IVC thrombus level and tumor prognosis. In our study, we did not stratify the level of thrombus, but tumor thrombus was an important prognostic factor for survival and one of the most important factors affecting CSS in multivariate analysis.

Siddiqui et al. (27) evaluated the prognostic value of perinephric fat invasion and concluded that it was a negative prognostic factor in all tumor sizes and that it was unnecessary to utilize the tumor size for grouping the T3a stage. On the other hand, Yoo et al. (28) found that >7 cm pT3a tumors had a worse prognosis than ≤7 cm pT3a tumors and concluded that tumor size should be included for more accurate staging for patients with perinephric fat tissue invasion. Murphy et al. (29) compared stage T2 and T3a patients according to clinicopathological features and pointed out that tumor size was a more significant prognostic factor than perinephric fat invasion. Gofrit et al. (30) also advocated that perinephric fat invasion was an insignificant prognostic factor, and in the new TNM staging system that they proposed, they excluded perinephric fat invasion and included tumor size and venous involvement. Our results, similar to the last two studies, confirmed that perinephric fat invasion was an important prognostic factor for survival alone, but not an independent factor in Cox regression analysis.

Tumor size is very important in the T staging of renal tumors and provides important information about prognosis, treatment method and survival. There are many studies mentioned above in which T1 and T2 stage renal tumors were stratified and the relationship between tumor size and other important prognostic factors was analyzed. In this study, we focused on T2b-stage tumors and evaluated the relationship between prognostic factors and survival. In the light of our study, perhaps further stages between T2b and T3 may be identified in the future with prospective, randomized, large patient group studies.

Our study is unique since it was the first study to evaluate prognostic factors in kidney tumors over 10 cm in diameter. The evaluation of pathologic specimens by an experienced, single genitourinary pathologist is a significant advantage of our study. Our study also had some limitations. Although the patient data were carefully reviewed from the files, the retrospective nature of the study and relatively small patient group were the main drawbacks. A total of 87 patients out of 126 received adjuvant treatment and this was a confounding variable that might affect the result. Another important limitation was the absence of a comparison group and that might have generated a selection bias.

Conclusion

Tumor size is an important factor affecting the treatment modalities, technique and prognosis in T1 and T2 stage tumors. However, our results showed that this effect was minimal and other clinicopathological features were important in T2b and higher stage tumors. Adjuvant therapy was also found to be a significant factor affecting CSS. Prospective studies are needed for a higher level of evidence.

Ethics

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

Informed Consent: Written informed consent was taken from all patients in order to be able to use their data in scientific studies without revealing their private information.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.K., A.Ş., E.A., S.K., S.Ş., B.S., Ç.Ç., İ.C., Concept: F.K., A.Ş., Design: F.K., A.Ş., Data Collection or Processing: F.K., A.Ş., E.A., S.K., S.Ş., B.S., Analysis or Interpretation: F.K., A.Ş., E.A., S.K., S.Ş., B.S., Ç.Ç., İ.C., Literature Search: F.K., Writing: F.K.

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Tamsulosin Can Improve Lower Urinary Tract Symptoms in Patients Under Active Surveillance Due to Low Risk Prostate Cancer: Prospective Controlled Study

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Abstract

Objective: We aimed to evaluate the efficacy of tamsulosin in the treatment of lower urinary tract symptoms (LUTS) in patients under active surveillance (AS) for low-risk prostate cancer (Pca).

Materials and Methods: Patients who underwent prostate biopsy between 2010 and 2014 were evaluated prospectively. Inclusion criteria for AS were PSA level below 10 ng/mL, a tumor in a maximum of two cores, a tumor core percentage below 50%, a clinical stage ≤ T2a and a Gleason score ≤6. Patients under AS with LUTS were included in the study group and patients with benign pathology results with LUTS were included in the control group. International prostate symptom score (IPSS) and uroflowmetry test were used to evaluate LUTS. The maximum flow rate (Q_{max}) was recorded. All patients received tamsulosin 0.4 mg once daily in a modified-release formulation (Flomax MR®, Astellas, Japan). Transurethral resection prostatectomy (TUR-P) was performed when surgical treatment was necessary for obstruction despite tamsulosin treatment.

Results: The study included a total of 91 patients, 41 patients in the AS group and 50 patients in the control group. Patients were assessed after six months. There was a 30% reduction in IPSS in the AS group and 24.5% in the control group (p=0.591). Q_{max} increased by 20.4% in the AS group and by 20% in the control group (p=0.985). The need for TUR-P was similar between the two groups (14.6% vs 20%, p=0.503) during three-year follow-up.

Conclusion: Tamsulosin can be used safely and with high efficacy for LUTS in patients under AS for low-risk Pca. The improvement in IPSS and Q_{max}, and the need for surgical treatment were similar to the control group.

Keywords: Prostate cancer, active surveillance, lower urinary tract symptoms, tamsulosin

Introduction

Prostate cancer (Pca) is the most common non-skin cancer among men (1). Currently, prostate-specific antigen (PSA) and multiparametric magnetic resonance imaging (mpMRI) are commonly used, and approximately 90% potential cure can be ensured in patients newly diagnosed with localized Pca (2). Treatments that may be applied in this stage are radical prostatectomy (RP) and radiotherapy (RT) (3). Apart from these, low-risk patients should not undergo curative treatment and there is the option of active surveillance (AS), which is defined as delay until certain progression criteria apply (3). AS is based on periodically repeated PSA tests, digital rectal examination (DRE) and control biopsy, and the main aim is to postpone or even avoid definitive treatment without disease progression (4).

Lower urinary tract symptoms (LUTS) associated with benign prostate enlargement observed in adult males involve complaints that disrupt the quality of life (QoL). These complaints are storage

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(frequent urination, night-time urination and sudden urgency), voiding (difficulty beginning urination, pain and discomfort during urination) and post-voiding symptoms (dripping after urination) (5). LUTS are defined by two different symptom frequencies of at least "sometimes" and at least "often" for all LUTS, except incontinence with at least "a few times" per month and at least "a few times" per week. Therefore, the overall prevalence of LUTS is approximately 72% and moderate-severe LUTS is 48% in men older than 40 years (6).

Although palliative (medication, lifestyle advice etc.) treatment improves LUTS, curative treatments (RP, RT and brachytherapy) worsen LUTS in patients with localized Pca (7). Tamsulosin is an effective and reliable drug used for all age groups in men with LUTS (8). It has been shown to reduce international prostate symptom score (IPSS) and residual urine, and increase maximum urinary flow rate (Q_{max}) in advanced stage Pca patients with LUTS (9).

We aimed to evaluate the efficacy and safety of tamsulosin treatment for LUTS in patients under AS patients for low-risk Pca.

Materials and Methods

Patients who underwent prostate biopsy at our clinic between June 2010 and November 2014 were investigated prospectively. Prostate biopsy was performed due to elevated PSA (>2.5 g/mL) and/or abnormality in DRE. Those with prostate biopsy results indicating Pca appropriate for AS were offered the AS option. Inclusion criteria for AS were PSA level below 10 ng/mL, tumor in a maximum of two cores, tumor core percentage below 50%, clinical stage ≤ T2a and Gleason score (GS) ≤6. AS was not offered to patients below the age of 50 and above the age of 75. Patients appropriate for AS regarding biopsy results, DRE findings and PSA level criteria were informed about AS along with definitive treatments. Re-biopsy was performed within a maximum of 3 months in patients who accepted AS. Patients with re-biopsy results appropriate for AS were included. Among these patients, people with LUTS were included in the study. PSA levels of the patients were evaluated and DRE was performed at six-month intervals. Control biopsy was performed one year later and every three years thereafter. All biopsies were performed under the guidance of transrectal ultrasound (TRUS). The first biopsy had 12 cores, while re-biopsies and annual check-up biopsies had 20 cores. The definitive treatment criteria were determined as GS upgrade on prostate biopsy, tumor core percentages above 50% or more than two tumor cores. Patients requiring definitive treatment (RP or RT) during AS were excluded from the final analysis (Figure 1).

Patients with benign biopsy results but without LUTS, patients with a surgical decision before biopsy (recurrent retention, macroscopic hematuria etc.), patients on LUTS drug before biopsy, patients on drugs other than alpha blockers (such as tadalafil for erectile dysfunction), and patients who did not participate (like not accepting long-term follow-up or living in other cities) or patients who were inappropriate due to paramedical reasons (insufficient intellectual level, living in rural areas, etc.) were not included in the study. All remaining patients were included in the study as the control group (Figure 1).

Prostate volumes were measured transrectally during biopsy and no additional imaging (such as mpMRI) was performed. Patients in both groups initially completed the IPSS form, QoL score, and underwent uroflowmetry test to record Qmax. Patients with no symptoms other than nocturia in the IPSS form were not included in the study, as this was not accepted as prostate-associated LUTS. Patients without LUTS or with mild LUTS (1-7 points in IPSS) were not included in the study. All patients received tamsulosin 0.4 mg once daily in a modified-release formulation (Flomax MR®, Boehringer Ingelheim, Germany). None of the patients received 5-alpha reductase inhibitors, anticholinergic drugs or phosphodiesterase-5 inhibitors, as these drugs may improve LUTS and cause confusion to the results of the study. Patients were called for LUTS examination at the 6th and 12th month of the first year and annually after one year. During each control, vital signs (blood pressure, pulse) were measured, side effects related to any drug were questioned, IPSS form was filled and uroflowmetry test with Qmax was recorded. During the controls, patients continued to use the drug and had used the drug on the day of the control. On check-up, TUR-P was performed if the following parameters were observed despite medical treatment: IPSS score above 20 (mainly obstructive symptoms), Q_{max} value not increasing above 10 mL/s, recurrent macroscopic hematuria, recurrent urinary tract infection, development of dilatation in the upper urinary tract, recurrent urinary retention, overflow incontinence, bladder diverticulum or stone formation. Due to possibility of subsequent definitive treatment requirement, open prostatectomy was avoided as it makes RP technically difficult. No TUR-P procedure was performed without the patient being included in the study for at least one year. IPSS and uroflowmetry values were not included in the final analysis after TUR-P operations (Ref no: 0671-5636).

Statistical Analysis

The minimum number of patients required was calculated by assuming that a mean difference of 10% between the two groups was significant with 80% accuracy and 5% error. The minimum number of patients in each group was calculated as 40. Due to the possibility of need for definitive treatment or loss during follow-up, the patient number in each group was determined as 55. Age, PSA values, prostate volumes, IPSS score, Qmax value and surgical treatment requirements were compared between the two groups. Student's t-test was used to compare the numerical data between the two groups, and Wilcoxon analysis was used to compare the variation in data over time within the groups. Pearson chi-square test was used for non-numerical data. A p value less than 0.05 was accepted as significant.

Results

A total of 410 prostate biopsy results were assessed, 170 (41.4%) were malignant and 240 (58.6%) were benign. After exclusion of other patients, AS group included a total of 55 patients. However, during follow-up, nine patients received definitive treatment (seven patients due to pathological upgrade and two due to patient anxiety) and five patients died, so 41 patients were included in the final analysis. The control group

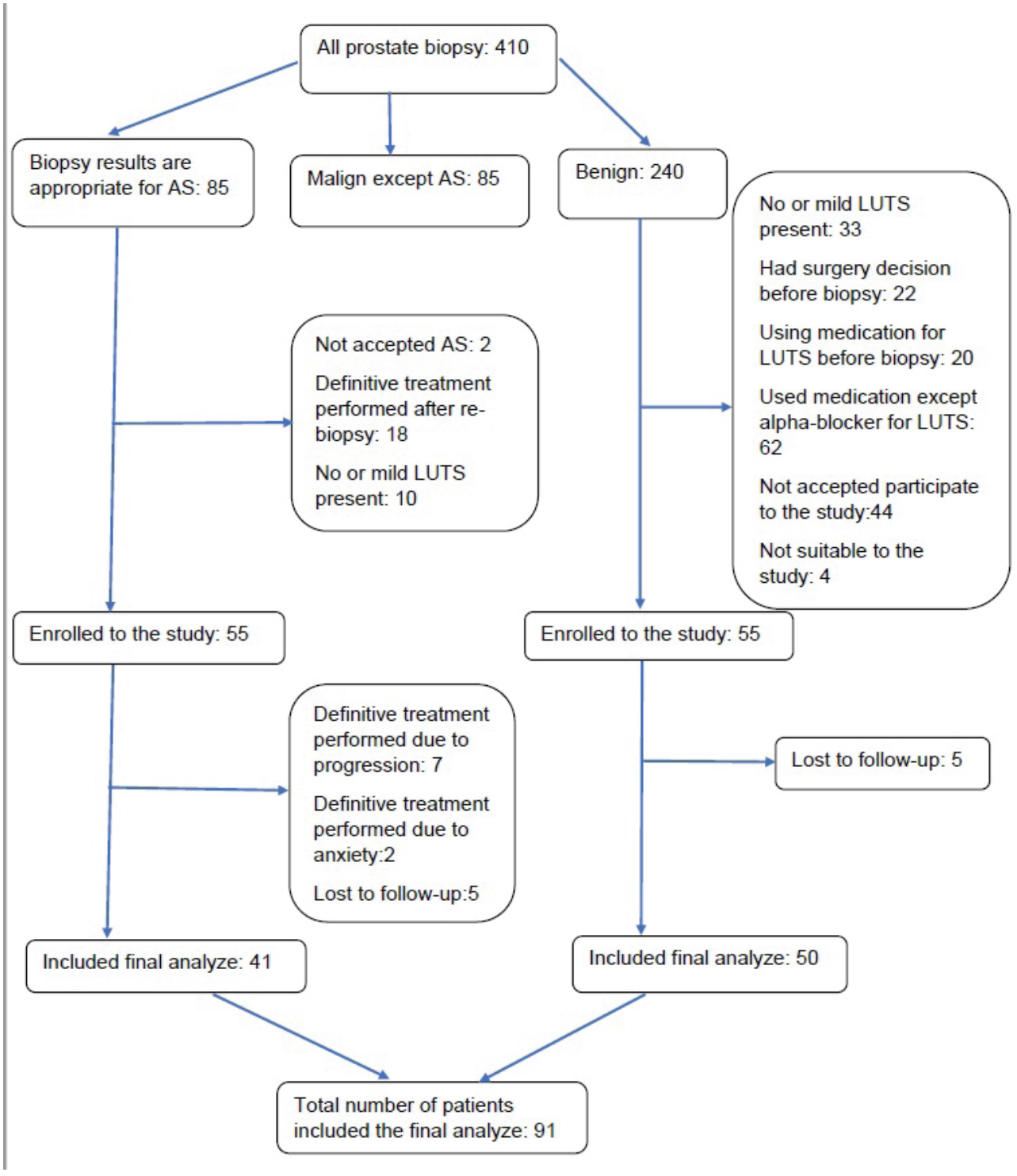

Figure 1. Figure shows inclusion and exclusion criteria and numbers (AS: Active surveillance, LUTS: Lower urinary tract symptoms)

included 55 patients. During follow-up, five patients died and the analysis included 50 patients. The mean follow-up was 5.3 (range = 3-7) years. In the control group, the number of patients who had increased PSA level and who underwent second biopsy was eight. No Pca was identified in any of these patients. The study results included a total of 91 patients; 41 in the AS group and 50 in the control group (Figure 1). The mean age of the patients was 61.4 years (range = 50-72). The mean PSA value was 4.74 (range = 2.7-9). Ten patients reported side effects related to the drug. These included dizziness and ejaculatory dysfunction. Patients were informed about side effects and told what to do; therefore, no patient discontinued the drug due to

side effects. A total of 16 patients required TUR-P due to LUTS. All TUR-P pathologies were reported as benign.

When the two groups were compared, the mean age and prostate volumes were similar. Although the mean PSA value was significantly higher in the AS group, it was moderate. In the first application, mean IPSS and Q_{max} values were similar in both groups. After 6 months of tamsulosin treatment, the change in IPSS, QoL score and Q_{max} scores were similar in both groups. Surgical requirements developed in six patients in the AS group and 10 patients in the control group, and the rates were statistically similar. Drug-related side effects were reported in four patients in the AS group and six patients in the control group, and the rates were similar (Table 1).

The change in mean IPSS score is shown in Figure 1. There was a 30% reduction in IPSS scores in the AS group and 24.5% reduction in the control group compared to first administration after tamsulosin use. Then, the mean IPSS score increased slightly in both groups during the year and formed a plateau (Figure 2).

The mean Q_{max} change is shown in Figure 2. After tamsulosin administration, there was a 20.4% increase in the AS group and 20% increase in the control group compared to the first administration. Later during the year, there was a slightly decreasing plateau in parallel in both groups (Figure 3).

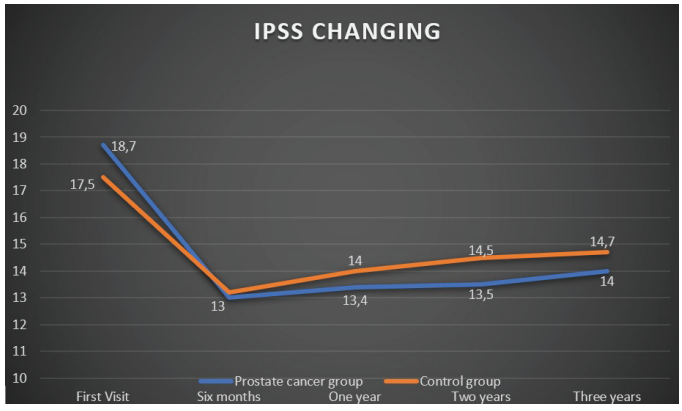

Figure 2. IPSS change of two groups over time (IPSS: International Prostate Symptom Score)

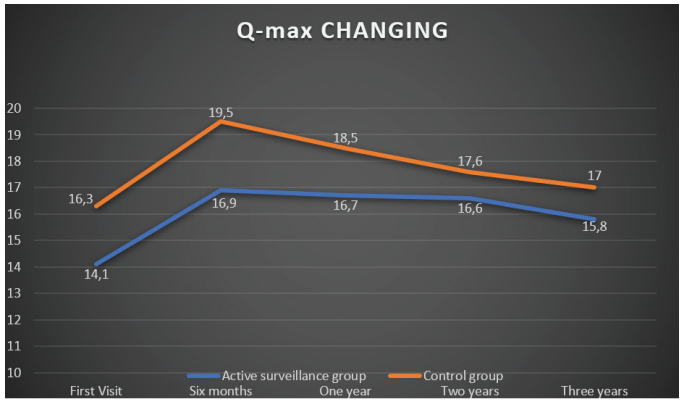

Figure 3: Maximum urinary flow rate (Q_{max}) change of two groups over time

Discussion

AS for low-risk Pca was first proposed by Klotz et al. (10). When long-term results from different clinics and high numbers of patients have been published, there is high cancer-specific survival (above 90%) and comorbidities caused by treatment are avoided as patients are not administered any medication (11,12,13). A study in Canada showed that more than three quarters of patients abiding by AS criteria chose AS (14). When RP is compared with AS for patients with local stage Pca, RP was found to be beneficial in patients with PSA above 10 ng/mL or with high-risk Pca, however, the 10-year survival rates for low-risk patients appear to be similar (15). During AS, the progression-related definitive treatment requirements are 10-35% (16,17). In our study, seven patients (14%) had definitive treatment due to progression (three patients had RP, four patients had RT). Apart from progression, patients may insist on definitive treatment due to anxiety leading to definitive treatment for 10% of patients (18). In our study, two patients (4%) had RP performed due to patient insistence in spite of no progression.

LUTS are a cluster of symptoms that is commonly seen, uncomfortable and disrupts QoL (19). LUTS has a wide range of treatment from lifestyle changes to open surgery and whatever the applied treatment, QoL increases due to improvements in symptoms (20). LUTS displays a dynamic situation over time; it worsens in some patients, remains the same in others and improves in some (21). However, the rate of patients with improvement in symptoms without treatment is very low (22). As a result, though surgical treatment is not performed in every patient, at least, lifestyle changes and/or drug treatment is recommended.

Tamsulosin binds to alpha-1 receptors showing antagonistic

Table 1. Comparison of the two groups according to characteristics and primary outcomes.

	Active Surveillance Group	Control Group	p
Number of patients	41	50	
Mean age (year) ± SD	61.5±5.4	61.3±6.7	0.981
Mean PSA (ng/mL) ± SD	5.2±1.8	4.3±1.3	0.009*
Mean prostate volume (cc) ± SD	41±12	47±17	0.41
Mean IPSS at first visit ± SD	18.7±6.9	18.5±7.4	0.806
Mean IPSS change after six months (percent of first IPSS)	30.5±17.7	24.5±19.6	0.591
Mean QoL score change ± SD	1.75±0.4	1.63±0.35	0.42
Mean Qmax (mL/sn) at first visit ± SD	14±4.3	15.1±5	0.152
Mean Qmax change after six months (percent of first Q_{max})	20.4±26.9	20±22.5	0.985
Need for surgery (%)	14.6%	20%	0.503
Adverse reaction (%)	4 (9.75)	6 (12)	0.733

SD: Standard deviation, PSA: Prostate specific antigen, IPSS: International Prostate Symptom Score, QoL: Quality of life, Qmax: Maximum urination flow rates
* indicates a statistically significant p value <0.05.

properties and causes relaxation of smooth muscles; thus, LUTS improve through expansion of the prostatic urethra and bladder neck (23). Regarding Combat study, there was a 30% reduction in IPSS score after three months in the tamsulosin-only group; however, the IPSS score increased slightly in the following months, and at the end of four years, the change in IPSS decreased to 23% (23). In our study, IPSS score reduced by 30% in AS patients after six months of tamsulosin treatment; however, IPSS increased slightly in the following months, and at the end of three years, there was a reduction of 25% compared to the initial IPSS score. In the Combat study, patients receiving tamsulosin alone had a 10% increase in Q_{max} values in the first month with a slight decrease over the months and a 7% increase by the end of four years (23). In our study, mean Q_{max} value in AS patients increased by 20.4% at the end of the six months; however, there was a decline in the following months, and at the end of three years, there was a 12% increase compared to first application. After six months, there is no further improvement in IPSS and Q_{max}, so this can give us a hint to decide the time of surgery. The IPSS reduction and Q_{max} increase rates obtained in our study were parallel to the change over the years in the Combat study; however, our study obtained better improvements. However, it should not be forgotten that the efficacy of tamsulosin decreases as the patient age increases (8). In our study the mean age of patients was 61.4 years, while it was 66.2 years in the Combat study (23). As a result, the better improvement in IPSS and Q_{max} values in our study compared to the Combat study may possibly be due to the lower mean patient age in our study. The addition of tamsulosin to androgen deprivation therapy (ADT) in patients with advanced stage Pca improved LUTS (9,24). The addition of tamsulosin to ADT in advanced stage Pca patients ensured a 50% improvement in IPSS and a 40% increase in Q_{max} (25). However, tamsulosin alone is not responsible for this objective amelioration in LUTS, because patients not receiving tamsulosin but just ADT obtained the same results but over a longer period (25). ADT is probably responsible for excessive improvement in IPSS and Q_{max} values.

Patients with LUTS require surgery due to benign prostate hyperplasia-related obstruction at a rate of 10-24% over 3 years (24,26). Surgery was required in 14.6% of AS patients and 20% of the control group. The rate of surgical requirement in our study was in parallel with the literature. RP results performed after TUR-P are similar to the results of patients in whom TUR-P is not performed (27). PSA elevation that causes anxiety in AS patients and unnecessary definitive treatment demands can be controlled by TUR-P; therefore, anxiety caused by urinary symptoms and PSA elevation improves (28). The benefits of AS and control group patients with performed TUR-P were similar.

The long-term use of 5-alpha reductase inhibitors reduces surgical requirements due to benign prostate hyperplasia by 50% (26). Administration of dutasteride to AS patients does not cause progression (29). In fact, it may even delay progression slightly (30). However, dutasteride increases the apparent diffusion coefficient of the tumor region in AS patients in mpMRI and causes uncertainty about the tumor area (31). As a result, AS patients should be careful about the use of dutasteride before mpMRI is performed or if mpMRI is going to be used during follow-up. All these studies were published after we initiated our study. As a result, there was insufficient data at the beginning of the study and the use of 5-alpha reductase inhibitors was avoided to prevent difficulties in PSA follow-up.

In our study, the number of patients seems to be a limitation and there may be a need for more patients for higher accuracy and stronger power values. Residual urine amounts after urination can only be accurately measured by using a catheter, and we believe that inserting a catheter after each uroflowmetry is excessively invasive. As a result, though residual urine after urination measurements are used in our clinic, we did not include this data in the study. We did not find any studies on the use of tamsulosin or another alpha-blocker for the treatment of LUTS in AS patients in PubMed and Cochrane databases as of December 2017. As a result, no direct comparisons were made. Therefore, we used studies that included advanced Pca patients. Detecting tumor volume may be important in AS patients via mpMRI, but it was not in routine use eight years ago; this might be another limitation of the study.

Conclusion

Tamsulosin can be used safely and with high efficacy in the treatment of LUTS in low-risk Pca patients under AS. The improvement in IPSS and Q_{max} obtained by tamsulosin treatment and the need for surgical treatment were similar between AS and control patients.

Ethics

Ethics Committee Approval: Ankara Training and Research Hospital Local Ethic Committee (Ref no: 0671-5636).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.T., A.D., K.H. Concept: G.B., O.T. Design: G.B., M.F.K., A.Y., Data Collection or Processing: M.F.K., A.M.Y. Analysis or Interpretation: G.B., O.T., K.H., A.D., Literature Search: A.Y., M.F.K Writing: G.B., A.D.

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

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Original Article

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Is Prostate Cancer Related to Low Vitamin D Level?

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Abstract

Objective: Prostate cancer (PC) is the most common malignancy among men worldwide. There are several epidemiological studies linking the risk and outcome of vitamin D with PC. In this study, we aimed to compare vitamin D levels in patients with PC and benign prostatic hyperplasia (BPH).

Materials and Methods: Patients with PC and BPH admitted to our urology outpatient clinic between 2017 and 2019 were included in this case-control study. Serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were measured to assess vitamin D status.

Results: The study was conducted with a total of 256 patients aged between 47 and 86 years between 2018-2019. The mean age of 128 patients with PC was 67.70±7.74 years, and the mean age of 128 patients with BPH was 67.03±7.89 years. There was a statistically significant difference between patients with PC and BPH in terms of 25-hydroxyvitamin D levels. When the patients diagnosed with PC were examined according to their subgroups, the mean 25-hydroxyvitamin D levels of 64 patients with ISUP Grade I tumors were significantly higher than the remaining 64 patients with ISUP Grade II, III and IV tumors.

Conclusion: According to our results, vitamin D levels were found to be significantly lower in patients with PC than in patients with BPH, and a significant decrease was found in vitamin D levels as the Gleason score increased. Since PC has a high prevalence and heterogeneous geographical distribution, randomized controlled trials are needed in order to demonstrate the relationship between vitamin D and cancer.

Keywords: Vitamin D, prostate cancer, benign prostatic hyperplasia

Introduction

Prostate cancer (PC) is the most common malignancy among men worldwide (1). In addition, the incidence of PC increased significantly in most Asian populations (2). New molecularly targeted therapies for PC patients have improved over the last 10 years (3,4). There are a limited number of modifiable risk factors identified for PC, and further studies are needed to identify some modifiable risk factors associated with PC. There are numerous epidemiological studies linking the risk and outcome of vitamin D with PC (5,6,7,8). Vitamin D is a steroid prohormone that dissolves in fat and is produced in skin by contact with sunlight. With various metabolic changes in the body, it becomes a hormone known as calcitriol, which plays an important role in calcium and phosphate metabolism. In addition to having an important role in many mechanisms in the body, Vitamin D deficiency can cause many adverse conditions.

In addition to its association with major public health problems such as obesity, diabetes, and hypertension, recent studies focus on the relationship between vitamin D and cancer with increasing prevalence and types. In addition, studies have been conducted on the anti-cancer effects of vitamin D as well as the effects that suppress cancer cell growth (9). In this study, we aimed to investigate whether there is a statistically significant difference between vitamin D levels in patients with PC and patients with benign prostatic hyperplasia (BPH).

Materials and Methods

This case-control study was initiated with the approval of Fatih Sultan Mehmet Training and Research Hospital Ethics Committee (Number: FSMEAH-KAEK 2017/6, date: 12.01.2017) and each patient included in the study signed informed consent form. Patients diagnosed with PC and BPH who admitted to our urology outpatient clinic between 2017 and 2019 were included in the study. The cases were newly diagnosed, followed-up and histopathologically proven PCs. Patients with metastatic PC, recent severe weight loss, and who underwent hormonal therapy or finasteride treatment were excluded. The control group consisted of patients with lower urinary

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tract symptoms who had no pathology on digital rectal examination (DRE) and had a PSA level <2.0 ng/mL. Serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were measured to assess vitamin D status. Vitamin D concentration was evaluated by ultra-performance liquid chromatography/ tandem spectrometry analysis.

Statistical Analysis

IBM SPSS Statistics 25 program was used for statistical analysis. When evaluating the study data, the normality of the parameters was evaluated with Shapiro-Wilk test. The descriptive statistical methods included mean and standard deviation, and Student-t test was used for the comparison of parameters with normal distribution. Significance was evaluated at $p<0.05$.

Results

The study was conducted with a total of 256 patients aged between 47 and 86 years between 2018-2019. The mean age of 128 patients with PC was 67.70±7.74 years, and the mean age of 128 patients with BPH was 67.03±7.89 years (Table 1). There was no statistically significant difference between patients with PC and BPH in terms of age ($p>0.05$).

Although the mean 1,25-dihydroxyvitamin D level in patients with PC was lower than those with BPH, no statistically significant difference was found ($p>0.05$). There was a statistically significant difference between both groups in terms of 25-hydroxyvitamin D levels ($p=0.000$). When the patients diagnosed with PC were examined according to their subgroups, the mean 1,25-hydroxyvitamin D levels of 64 patients with ISUP Grade I tumors were higher than the remaining 64 patients with ISUP Grade II, III and IV tumors, however, no statistically significant difference was found ($p>0.05$). When the patients diagnosed with PC were examined according to their subgroups, the mean 25-hydroxyvitamin D levels of 64 patients with ISUP Grade I tumors were significantly higher than the remaining 64 patients with ISUP Grade II, III and IV tumors ($p<0.01$) (Table 2).

Discussion

Although vitamin D has preventive roles in many cancers, its role in the development of PC is still unclear. In the human body, vitamin D is synthesized mainly in the skin after exposure to sunlight and also vitamin D can be taken from some foods (10,11). 25-hydroxyvitamin D, which is the most widely used biological form of circulating vitamin D, is the hydroxylated form of vitamin D and is widely used in clinical practice (12). It is then converted to the biologically active 1,25-hydroxyvitamin D (calcitriol) by 1-alpha-hydroxylase enzyme in the kidney and other tissues, including the prostate (13). The biomarker of vitamin D in humans is mainly 25-hydroxyvitamin D and partly 1,25-hydroxyvitamin D, and studies have been based on these indicators regarding vitamin D serum levels (14). Vitamin D serum level less than 20 ng/mL (50 nmol/L) is defined as inadequacy (15).

In epidemiological studies on vitamin D levels of cancer patients, it is stated that these levels are less than normal values (16). Vitamin D has been shown to cause dysfunction or inhibition of cell proliferation of PC cells, cell invasion, angiogenesis and altered gene expression, including c-Myc and telomerase expression, or induction of cell differentiation and apoptosis (17,18,19,20). *In vitro* cell culture and *in vivo* animal studies have shown that active vitamin D increases cell differentiation, inhibits cancer cell proliferation, and exhibits anti-inflammatory, pro-apoptotic and anti-angiogenic properties. In laboratory studies, it has been shown that active vitamin D inhibits the growth of cancer cells by binding to vitamin D receptor (VDR) and regulating various genes responsible for cell proliferation (21,22,23). Active vitamin D stimulates the expression of cell cycle inhibitors p21 and p27, and the expression of the cell adhesion molecule E-cadherin. It inhibits the transcriptional activity of α-catenin. Active vitamin D in keratinocytes has been shown to increase repair of DNA damage caused by UVR, reduce apoptosis, and increase p53 (16). Some studies (18,24,25,26) support the idea that high serum Vitamin D levels have protective effects. Other studies have shown different results (27,28). In a meta-analysis focusing on the relationship between 25-hydroxyvitamin D and mortality in PC, a study of 7808 participants was conducted, and the results calculated from seven eligible studies showed a significant correlation with higher vitamin D levels and a reduction in all-cause mortality and a reduction in PC-related mortality. Other dose-response analysis showed that every 20 nmol/L increase in 25-hydroxyvitamin D level was associated with a 9% lower risk of all-cause mortality and PC-related mortality. It was concluded that high levels of circulating vitamin D were associated with a lower risk of PC-related mortality (29).

A meta-analysis of 21 studies by Xu et al. (30) found a high risk of developing PC in patients with a high level of 25-hydroxyvitamin D in the serum. Sixteen studies showed a positive correlation between serum vitamin D level and PC [odds ratio (OR)=1.17, 95% confidence interval: 1.08-1.27].

Table 1. Comparison of prostate cancer and benign prostate hyperplasia patients

	PC (n=128)	BPH (n=128)	p value
	Mean ± SD	Mean ± SD	
Age (years)	67.70±7.74	67.03±7.89	**0.498**
1,25-hydroxyvitamin D (ng/mL)	29.42±13.99	31.28±13.64	**0.283**
25-hydroxyvitamin D (ng/mL)	19.45±7.24	26.15±8.80	**0.000***

Independent samples t-test *p<0.05
PC: Prostate cancer, BPH: Benign prostate hyperplasia, SD: Standard deviation

Table 2. Comparison of prostate cancer subgroups

	ISUP 1 (n=64)	ISUP 2,3,4 (n=64)	p value
	Mean ± SD	Mean ± SD	
1,25-hydroxyvitamin D (ng/mL)	30.86±11.49	27.99±16.07	**0.247**
25-hydroxyvitamin D (ng/mL)	22.13±7.26	16.76±6.20	**0.000***

Independent samples t-test *p<0.05
ISUP: International Society of Urological Pathology, SD: Standart deviation

In one study, it was shown that the incidence of PC was high and vitamin D level was low in the black race compared to other races (31). Selenium and vitamin E cancer protection research found an inverse relationship between plasma vitamin D levels in high-grade cancers with a Gleason score of 7-10 (32).

In our study, there was a statistically significant difference between patients with PC and BPH in terms of mean 25-hydroxyvitamin D levels (p=0.000). In the PC group, 25-hydroxyvitamin D levels were significantly lower. When the patients diagnosed with PC were examined according to their subgroups, the mean 25-hydroxyvitamin D levels of 64 patients with ISUP Grade I tumors were significantly higher than the remaining 64 patients with ISUP Grade II, III and IV tumors (p<0.01). As the Gleason score of cancer increased, a significant decrease was found in vitamin D levels.

In a study conducted since the functions of the VDR and associated vitamin D metabolic enzymes are associated with vitamin D levels, it was shown that nucleotide polymorphisms alone in the 3'-untranslated region of the *VDR* gene were associated with PC risk in men with low vitamin D levels (31).

In a meta-analysis of 19 prospective studies, epidemiological evidence of the tumor-promoting effect of vitamin D in PC was provided, but the effect was modest (32). However, no clear biological relationship was found between high levels of vitamin D and increased risk of PC. We can only speculate about the cause of the tumor-stimulating effect of vitamin D in PC (33). One reason for this may be that 25-hydroxyvitamin D is a sign of other factors related to PC risk. For example, insulin-like growth factor-I (IGF-1) is associated with PC (34,35) and a relationship between 25-hydroxyvitamin D and IGF-1 has been reported. In another study, each 10 ng/mL 25-hydroxyvitamin D increase was associated with an increased risk of PK of 23% (5). In the meta-analysis of Gilbert et al. (36), it was shown that there was a low level of evidence between low exposure to sunlight and the risk of PC (37,38).

Conclusion

According to our results, vitamin D levels were found to be significantly lower in patients with PC than in patients with BPH. In addition, when the cancer group was evaluated among themselves, a significant decrease was found in vitamin D levels as the Gleason score increased. Although there is no relationship between vitamin D and PC in most studies, there are studies in the literature showing an inverse relationship. Since PC has a high prevalence and heterogeneous geographical distribution, randomized controlled trials are needed in order to demonstrate the relationship between vitamin D and cancer.

Ethics

Ethics Committee Approval: This case-control study was initiated with the approval of Fatih Sultan Mehmet Training and Research Hospital Ethics Committee (Number: FSMEAH-KAEK 2017/6, date: 12.01.2017).

Informed Consent: Each patient included in the study signed informed consent form.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

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

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Review

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Does Robot-assisted Surgery in Urology Has Benefits? The Current Status

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Abstract

Minimally invasive surgery has gradually replaced the conventional surgery with the introduction of laparoscopy. Subsequently, with intensive advertisement and marketing strategies, robot-assisted surgery became popular and robot-assisted surgery has been used in almost every surgical procedure. Despite its high cost, the robotic platform, which has proven its general advantages such as less hospital stay and less blood loss, has become controversial in the literature in terms of cost effectiveness. In this study, the advantages and disadvantages of the robot-assisted surgery in urology have been reviewed in the light of current literature.

Keywords: Robotic surgery, cost-benefit, urology

Introduction

The word robot was first used by Karel Capek in 1921 in Rossum's Universal Robots (1). The term is derived from the word "Robota", which means forced labor in the Czech language. In Capek's play, robots used to help people in all their jobs, but then the robots took the place of their owners and tried to dominate the world (2).

EndoAssist, probably the first surgical robot, was used in 1990 (2). The first robot-assisted hip replacement was performed in 1992 with Robodoc in California (3). AESOP 1000, the first commercial robot, was used in laparoscopic surgery in 1993 to hold the endoscopic camera. It has been shown that the robot uses the camera more efficiently with less shaking than the human (4). The Zeus robotic surgical system was first used transatlantically in 2001 by a surgeon in New York during a cholecystectomy procedure in France (5).

In the 2000s, with the development of the Da Vinci surgical system, there was a huge leap in the use of robots in surgery. The basic principle of the robot system, which is based on the surgeon's handling of three or four robotic arms in the console, has three main components: Surgeon console, patient-side cart and vision system. Although the first literature studies on robotic surgery have been reported in the field of cardiac surgery, most of the operations have been performed in the field of urology recently (2).

Robot has been used in the field of urology in many operations such as adrenalectomy, simple and radical nephrectomy, partial nephrectomy, vena cava thrombectomy, nephroureterectomy, live donor nephrectomy, renal transplantation, pyeloplasty, ureter surgery, radical and partial cystectomy, bladder augmentation, simple and radical prostatectomy, retroperitoneal lymph node dissection, varicocelectomy, testicular sperm extraction, re-anastomosis after vasectomy and spermatic cord denervation (6). Aside from this wide range of applications, robot has been questioned in terms of cost effectiveness even in areas such as radical prostatectomy, radical and partial nephrectomy, where it is used most.

The first robot-assisted radical prostatectomy was quickly accepted by urologists after its description in 2000 and it has become the most widely used field of robotic surgery today (6,7). In a systematic review, robot-assisted radical prostatectomy, laparoscopic prostatectomy and conventional surgery were compared, and there was no difference in terms of complications, oncologic outcomes, erectile dysfunction and urinary incontinence, but the laparoscopic and robot-assisted groups were similar in terms of blood transfusion rates and short duration of hospital stay, however, robot-assisted group was found to be more advantageous than the surgical group (8). In a study of 2625 patients comparing robot-assisted and conventional prostatectomy, no statistically significant difference was found in terms of urinary incontinence and surgical margins; however, a statistically significant difference was observed in favor of the robot in terms of erectile dysfunction (9). Canada Ontario Health Technology Advisory Committee compared robot-assisted radical prostatectomy with conventional radical prostatectomy in terms of cost and benefit. In conclusion, they stated that there was no high-quality evidence that robot-assisted prostatectomy had a benefit to explain the additional cost of $6000 per patient for cure rate, urinary incontinence and erectile dysfunction compared to conventional surgery (10).

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Another area where robotic surgery is widely used in urology is radical nephrectomy. In a meta-analysis of 23,753 patients by Jeong et al. (11), 18,573 patients underwent laparoscopic radical nephrectomy and 5,180 patients underwent robotic radical nephrectomy between 2003 and 2015. In the study, it was reported that both methods were similar in terms of the incidence of major complications, blood transfusion rate, length of hospital stay, but robotic surgery was disadvantageous in terms of operative time and hospital cost. The use of the robot in radical nephrectomy does not provide the advantage of easier resection as in partial nephrectomy. Since there is no need for more comfortable intracorporeal suturing such as in radical prostatectomy and pyeloplasty, no superiority to conventional laparoscopy has been demonstrated. However, it has been reported that the number of robotic radical nephrectomies has increased considerably in recent years compared to laparoscopic surgery. In the guidelines, there are increasing studies reporting that robotic surgery makes a difference in the treatment of T3 tumors, although laparoscopic radical nephrectomy is routinely recommended in T1 renal tumors (11-16).

Robotic partial nephrectomy is also one of the popular uses of robotics. In a meta-analysis by Shen et al. (17), conventional partial nephrectomy was compared with robotic partial nephrectomy in 3024 patients. As a result, the advantages of robot-assisted partial nephrectomy such as less hospital stay, less perioperative complications and less blood loss were demonstrated, however, operative time and warm ischemia time were longer. There were no differences in criteria such as transfusion rates, positive surgical margins, and postoperative glomerular filtration rate changes. In a meta-analysis comparing robotic and laparoscopic partial nephrectomy in T1a tumors, two methods were found equivalent (18). In a series of 216 patients published by Wang et al. (19), patients with a RENAL nephrometry score of 7 or more were evaluated and the peri-operative, functional, and oncologic results were found to be similar.

In 2003, after the first robot-assisted radical cystectomy was described by Menon et al. (20), the use of the robot in this field increased rapidly over the years. In a non-systematic analysis, robot-assisted radical cystectomy was found to be superior to conventional radical cystectomy in terms of estimated blood loss, transfusion rate, gastrointestinal recovery, narcotic analgesic requirement, and hospital stay. The cost, operative time, and metastasis to extra-pelvic lymph nodes and peritoneum were more likely to occur in patients undergoing robot-assisted surgery. There was no difference in terms of urinary incontinence, postoperative quality of life, positive surgical margin, number of removed lymph nodes, and recurrence (21). An analysis from randomized controlled studies indicated that robot-assisted cystectomy did not reduce postoperative complication rate and length of hospital stay, and postoperative quality of life was similar to conventional radical cystectomy (22).

In a meta-analysis of 1162 patients by Economopoulos et al. (23) evaluating laparoscopic and robot-assisted adrenalectomy, there was no difference in terms of intraoperative and postoperative complications, mortality, shift to laparotomy and hemorrhage. Operative time in the robotic arm was longer but the hospital stay was shorter. In a systematic analysis performed by Tang et al. (24), robot-assisted adrenalectomy was reported to be a safe alternative with the advantage of less hemorrhage and less hospital stay compared to laparoscopy.

In recent years, robotic surgery has been used in pediatric patients, especially in pyeloplasty operations. In a study conducted in public and training hospitals in the USA, a total of 12,662 pediatric pyeloplasty operations, including conventional, laparoscopic and robotic, were compared, and similar complication rates were reported in all three methods. The cost of robotic surgery was significantly higher than conventional and laparoscopic surgery. The operative time of robotic and laparoscopic pyeloplasty was longer than that of conventional pyeloplasty, but the mean length of hospital stay was same for all methods. Although it did not reach statistical significance, the mean length of hospital stay in robotic surgery was reported to be 17 hours less than conventional surgery. It was commented that this period did not have a significant financial advantage, but that it might have prevented possible loss of work wages by assuming that parents stayed with the children. The study suggested laparoscopic pyeloplasty as the most suitable method among these three methods because of being minimally invasive, having perioperative results similar to conventional pyeloplasty, and similar or lower cost (25).

Today, with the advertising and marketing strategy of the robot, the perception that surgeons who do not perform robotic surgery is a 2nd class surgeon and that every operation can be performed with the robot has been created (26). The popularity of robotic surgery has also affected physicians. In a recent survey of 238 urology physicians, a large number of physicians reported that robot-assisted surgery was not the gold standard for prostatectomy, cystectomy, and nephrectomy, but that they could recommend this method for themselves or their families if necessary (27). Similarly, robot-assisted surgery has altered the patient's perception of operation. In a study, it was found that patients with robot-assisted radical prostatectomy surgery were emotionally more peaceful and comfortable than those who underwent conventional surgery, and those who had open surgery were more anxious (28).

One of the most important advantages proved in favor of robotic surgery in the above- mentioned studies is the shorter hospital stay. However, in countries like ours with low minimum wages and cheap labor, the economic disadvantage of short hospital stay is very insignificant compared with the high cost of the robot. On the other hand, even in developing countries, which lack access to effective health services and where even a clean water supply and sewerage network are not sufficient, robots have been purchased. Ten Da Vinci robotic systems were installed in public hospitals in South America, including four in Brazil, three in Mexico, two in Argentina and one in Venezuela. In a study evaluating the results of these clinics, it was concluded that half of these programs were stopped temporarily or permanently due to the cost of disposable instruments, and that these programs could not be sustained with the financing of social security institutions and the robotic surgery program was likened to a sand castle (26). Cost is also an important burden for hospitals. Some studies have shown that performing more operations reduces the cost of the robotic

system. In other words, using the robotic system more makes the system more profitable for the hospital. In a study, it was calculated that it is necessary to make an average of 150-250 robotic cases per year in order to obtain a Da Vinci system and meet its sustainable cost within 6 years (29).

Conclusion

Other important advantages of robotic surgery over conventional surgery are less bleeding and better cosmetic appearance. However, laparoscopic surgery provides similar results with less cost, less bleeding, short hospital-stay and cosmetic advantage. For this reason, widespread use of laparoscopic surgery, which can be applied in almost every hospital condition in our country, will be a very appropriate health policy both in terms of access to quality health care of the society and national economy. For this purpose, both residents and urologists should be prepared with periodic courses and practical trainings to be equipped to perform this surgery.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Ablation Therapies in Small Renal Masses

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Abstract

Small renal masses are defined as renal neoplasms with the largest diameter less than 4 cm and the incidence of renal malignancies is increased with the widespread use of cross-sectional imaging methods. One of the options for disease management in small renal masses is ablation therapy. Ablation therapies include options such as radiofrequency ablation, cryoablation and irreversible electroporation. In this review, outcomes and comparisons of ablation therapies used in small renal masses are discussed together with current approaches and studies.
Keywords: Ablation, small renal mass, radiofrequency ablation, cryotherapy

Introduction

Small renal masses are defined as renal neoplasms with the largest diameter less than 4 cm and they express T1a tumors in tumor, nodes, metastases (TNM) staging (1). Today, with the widespread use of cross-sectional imaging methods, the majority of renal masses are incidentally detected. As a result, the incidence of primary renal malignancies increases over the years (2). There is a wide range of options from active follow-up to radical nephrectomy in the management of small renal masses. One of these options is ablation therapy. According to the American Urological Association (AUA) guidelines, the gold standard treatment for T1a renal masses is partial nephrectomy, and ablation therapies are offered as treatment options (3).

In this review, outcomes and comparisons of ablation therapies used in small renal masses are discussed together with current approaches and studies.

Patient Selection

As with all treatment options, the most important point in the planning of ablation therapy is the selection of the appropriate patient. Ablative therapies are a good option, especially in patients with contraindicated surgical treatment, patients with severe comorbidities, or those who do not consent surgery (4). In addition, it may be considered as a treatment method in patients with conditions such as solitary kidney, transplanted kidney, underlying renal failure, multiple renal tumors, and recurrent tumor in the nephrectomy bed (5).

Basic Information about Ablation Therapies

Ablation therapy in patients with small renal masses should be performed only in cases where the treatment of the whole lesion is technically feasible and renal biopsy is required before the procedure (6).

Tumor ablation is essentially the process of causing necrosis of tumor cells by energy transfer to the target with the help of imaging. These energy sources are roughly divided into thermal and non-thermal sources. Radiofrequency ablation (RFA) that provides high-temperature necrosis of tumor cells and cryotherapy method that provides freezing necrosis of the cells can be cited as examples of thermal ablation. Electroporation, which causes cell death by causing permanent pores in the cell membrane, is an example for non-thermal ablation (7,8).

Among the ablation therapies, thermal ablation methods are used more commonly and the most prominent methods are RFA and cryotherapy.

Ablation Methods

Radiofrequency Ablation

RFA is based on the generation of heat by means of an alternating electric current used at different frequencies and consequently cell death occurs in the exposed area (9). This alternating electric current is transferred to the tissue with the aid of a probe placed in the center of the target tissue, and these systems are generally monopolar.

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RFA-induced cellular damage is based on a time-temperature curve where less time is required at higher temperatures (9). In a study, cellular damage was shown to develop after 60 minutes exposure to 45°C, 5 minutes exposure to 55°C, and 1-minute exposure to 70°C (10). When the temperature exceeds 60°C, the cell loses its intracellular buffering ability, thereby increasing intracellular calcium levels, resulting in cellular death. Subsequently, acidosis and coagulation necrosis develop with increasing local inflammation (11).

In thermal ablation, cellular damage develops in different phases according to temperature rise. At temperatures of 50-80°C, coagulation and cellular damage due to protein denaturation develops within seconds or minutes. Tissue ablation is observed with dehydration and vacuolization at temperatures above 100°C, while carbonization and melting are finally observed in the tissue when 150-300°C is reached (9).

Although there is no definite consensus on this issue in the literature, it is stated that it is necessary to reach a temperature of at least 60°C for irreversible cellular damage and necrosis (9). In another publication, it is reported that at least 70°C temperature should be reached (4). It has also been reported that better and more effective cellular death can be achieved with two cycles of active ablation phase with a short-term cooling phase between them (12).

Cryoablation

Cryotherapy is another method of thermal ablation, which uses freezing temperatures instead of extremely high temperatures. It is known that the first modern cryotherapy probes worked with liquid nitrogen in the 1960s, followed by the more effective argon gas-based probes (4).

In animal models, tissue has been shown to be destroyed by cryoablation at temperatures between -19.4°C and -50°C. In cancer tissues, it is stated that the target temperature should be -40°C to ensure cellular death (4).

Larger areas of cellular necrosis have been reported to occur with multiple freezing and thawing cycles rather than a one-time freezing. It is stated that the risk of bleeding increases if the duration of the freezing cycle is 5 minutes, and the risk of tumor breakage increases when it is 15 minutes. Therefore, it was concluded that the ideal period of freezing should be between 8-10 minutes (13,14).

Similar to RFA, two cycles of freezing and thawing are applied in cryoablation to ensure that cellular death is more effective (4).

Application Methods in Ablation Therapies: Laparoscopic and Percutaneous Approaches

Ablation treatments can be performed by laparoscopic or percutaneous approach. The most important factor in choosing the method is the location of the tumor. Percutaneous approach is ideal for lateral and posterior tumors that are further away from vital organs. Laparoscopic method is more suitable for anterior tumors, especially because it allows dominating the surrounding anatomy (9). However, RFA is often performed with a percutaneous approach, whereas cryoablation is usually performed laparoscopically (4).

During percutaneous application of RFA, methods such as ultrasound, CT, CT fluoroscopy, MRI can be used for guiding and placement of the needle.

In a meta-analysis comparing percutaneous and surgical methods for renal tumor ablation, a total of 46 cases were included in the study, and 28 of them underwent percutaneous ablation. In 28 case series with percutaneous approach, RFA was reported as ablative therapy in 21 patients and cryotherapy was reported in only seven patients. Regarding 18 patients with surgical approach, only three patients underwent RFA and cryotherapy was performed in 15 cases (15).

According to many studies in the literature, when the percutaneous or laparoscopic thermal ablation procedures were compared, similar results were found at both primary endpoints. No significant difference was observed in primary efficacy, disease-specific survival and complication rates (16,17,18). In contrast, in a meta-analysis, the primary efficacy of the percutaneous approach was reported to be significantly lower than that of the surgical approach (87% vs 94%). There was no significant difference in secondary efficacy. In the same meta-analysis, the rate of major complications was reported to be significantly lower in the percutaneous approach than in the surgical approach (3.1% vs 74%) (15).

Outcomes of Ablative Treatments

Currently, there are no randomized controlled trials comparing ablation and surgical treatments. Most of these publications are retrospective or observational studies. According to current guidelines, the gold standard in small renal masses is reported as partial nephrectomy (19). According to European guidelines, ablation therapies in small renal masses are recommended in cases where the patient is not suitable for surgical treatment and has a multifocal malignant tumor as mentioned above in the patient selection section (7,20).

According to a recent meta-analysis comparing treatments in renal tumors less than 7 cm, 5-year cancer-specific survival and metastasis-free survival were reported to be similar between partial nephrectomy and thermal ablation (21). In contrast, in another meta-analysis, laparoscopic cryoablation was compared with laparoscopic and robotic partial nephrectomy, where it was shown that there was a significantly higher risk of local recurrence and metastasis in the cryoablation group (22).

Ablation treatments have been reported to be less invasive, less associated with perioperative complications, cause less blood loss and shorter hospital stay than surgical treatments. In addition, renal function loss and the cost of the procedure are also reported to be less than surgery (4,7). In addition to these, ablation therapies are appealing treatment modalities in suitable patients with other advantages such as the fact that it is a procedure that usually requires a day or overnight stay and can be applied more safely than the surgery, especially in patients with high comorbidities.

There is no randomized controlled trial comparing ablation treatments and surgical treatments, nor is there a randomized controlled clinical trial comparing these two basic ablation methods. Most publications in the literature are retrospective and include a small number of patients. In the UK, both

cryotherapy and RFA are recommended for small renal masses according to NICE (National Institute for Health and Care Excellence) guidelines (23).

According to a meta-analysis in 2008, local recurrence was found to be higher in RFA compared to cryoablation and it was stated that the need for a second ablation was higher in RFA (24). Another meta-analysis involving 20 cryoablation and 11 RFA case series was published in 2012. In this meta-analysis published by El Dib et al. (24), 457 patients undergoing cryoablation and 426 patients undergoing RFA were studied. The mean tumor size was 2.5 cm in the cryoablation group and 2.7 cm in the RFA group. Among the cryotherapy group, the surgical method was laparoscopic in 13 of the 20-case series, percutaneous in six and conventional in one. In 11 studies in the RFA group, seven were reported to be performed percutaneously, one by laparoscopy, and three by both. In this meta-analysis, the clinical efficacy of cryotherapy in 457 patients was found to be 89%. The clinical efficacy of RFA in 426 patients was reported to be 90%. According to these data, similar oncologic and clinical outcomes have been reported in both treatment modalities (25). In a more recent observational study, cryotherapy has been reported to have superior outcomes compared to RFA in metastasis-free survival. In the same study, no significant difference was found between the two groups in local recurrence-free survival (26).

The rate of renal function preservation in the kidney after any surgical treatment is directly related to the remaining renal volume after the procedure. Since normal renal parenchymal loss is minimal in ablative therapies, long-term renal functions are better than surgical treatments (27). In a study comparing renal functions after cryoablation, RFA and partial nephrectomy, it was reported that both renal parenchymal volume and glomerular filtration rate decreased significantly in partial nephrectomy compared to ablation methods. In the same study, no difference was found between the two ablation methods (28).

The most common complications in ablative treatments are bleeding and post-ablation hemorrhage. Since radiofrequency ablation already involves high temperatures, hemorrhage is less common and hemorrhage occurs more often after cryotherapy. In addition, ureteral or renal pelvic injuries are rarely seen. If thermal ablation extends beyond the target tissue and reaches the collecting system, urine leakage may be observed. More rarely, bowel injury, seeding in the treatment tract and pneumothorax may be observed (risk <0.01%) (9). According to a meta-analysis, the complication rate was 19.9% in cryotherapy patients and 19% in the RFA group. It has been concluded that there are similar results between the two treatment methods in terms of complication rates (25).

Follow-up after Ablative Therapy

The success of the treatment after ablation is determined by radiological findings. The absence of contrast enhancement in tumor tissue and the cessation of tumor growth (MRI or CT) at 3 months after the procedure are evaluated as successful ablation (29). According to the AUA guidelines, it is recommended that the patient be followed up by cross-sectional imaging at 3 and 6 months after ablation and annually for 5 years thereafter (30).

Other Methods in Ablation Therapies

In addition to RFA and cryoablation, different ablation methods are available. Microwave ablation, high intensity focused ultrasound (HIFU) and irreversible electroporation are examples.

Microwave Ablation

Microwave ablation is based on high temperature production similar to RFA. With the help of probes, electromagnetic energy is transferred to the tumor tissue at frequencies between 900 Mhz and 2.5 GHz and consequently high temperatures leading to coagulation necrosis and cell death are obtained (10). Results have been reported that microwave ablation can achieve higher temperatures, higher volume ablation and shorter treatment time than RFA (10).

There are several studies on the results of microwave ablation. In a study of the results of 12 patients who underwent percutaneous microwave ablation, no residual tumor or recurrence was reported during the median follow-up period of 11 months (31). In a randomized prospective study of 102 patients, Guan et al. (31) compared microwave ablation and partial nephrectomy, and reported that estimated blood loss, complication and renal function loss were significantly better in microwave ablation. In another report, the results of 10 patients who underwent laparoscopic microwave ablation were examined and a high recurrence rate of 38% was found (32).

Variable results with microwave ablation are available and larger, randomized controlled trials are needed.

HIFU (High Intensity Focused Ultrasound)

HIFU is based on high heat generation by sending high intensity ultrasound waves to the target tissue. As in other ablation methods, coagulation necrosis in tumor cells is created by this high energy in HIFU. The major advantage of HIFU over other methods is that it is completely noninvasive, but its oncologic results are not optimal (4).

Irreversible Electroporation

Unlike other ablation methods, irreversible electroporation is a non-thermal ablation method and no temperature is used for this procedure. Instead, electrical currents are sent to the cell membranes to form pores in the membrane. As a result, cell homeostasis deteriorates and cellular death occurs (10).

Muscle contractions and severe arrhythmias due to the energy currents applied in electroporation have been reported to increase concerns in this approach (27). There are few reports on the efficacy and safety of electroporation and large series of randomized trials are needed.

Conclusion

There are various ablation methods, including thermal and non-thermal. Ablation therapies have been found to be preferred in the appropriate patient group because of their satisfactory oncologic outcomes, short hospital stay and low complication rates in small renal masses.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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Case Report

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A Rare Case of Granulomatous Hepatitis After Intravesical BCG Treatment

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Abstract

Tumor recurrence following transurethral resection is common in non-muscle invasive urothelial cancers of the bladder. Intravesical Bacillus Calmette-Guerin (BCG) is frequently used in urology practice to prevent this recurrence and tumor progression. In this study, we present a case of Granulomatous Hepatitis that rarely develops during intravesical BCG application and that improved with anti-tuberculosis treatment.
Keywords: BCG, Hepatititis, bladder cancer

Introduction

Bacillus Calmette-Guerin (BCG), an attenuated live strain of Mycobacterium bovis, was first administered intravesically by Morales et al. (1) in 1976 for high-risk superficial bladder cancer. BCG, which is applied intravesically to prevent tumor recurrence in the treatment of superficial bladder cancer, is thought to have an anti-tumor effect by creating an immune response through T-cell in the bladder (2). Local and systemic side effects may occur after intravesical BCG administration. Although these side effects are generally mild, they can rarely be serious and life-threatening. Cystitis, dysuria, pollakiuria and fever are the most common side effects and systemic side effects such as myalgia, headache, arthralgia, anorexia, malaise, diarrhea, chills, tremors, fatigue, high fever, arthritis, pneumonia, hepatitis, renal abscess, cytopenia and sepsis may also be seen (3).

In this article, a case of superficial bladder tumor with granulomatous hepatitis developed after intravesical BCG administration is presented.

Case Report

A 70-year-old male patient underwent transurethral resection with the diagnosis of bladder tumor. The pathology was superficial transitional cell carcinoma with no muscle invasion (pT1G2) and the patient was given intravesical BCG treatment once a week for six weeks starting four weeks after the operation (4). Three days after the sixth dose, the patient presented with severe headache, frequent urination, 39°C fever, chills and tremor. The laboratory tests were as follows: blood leukocyte count=6000/mm^3, erythrocyte count=4750000/mm^3, CRP=109 mg/dL, Aspertate aminotransferage (AST)=311 U/L, Alanine amino transferase (ALT)=330 U/L, total protein=5.53 g/dL, albumin=3.8 g/dL. Hepatitis A virus, Hepatitis C virus, Human immunodeficiency virus and Brucella tube agglutination tests were negative. There was no pathological finding on chest X-ray. No growth was detected in blood and urine cultures. Abdominal ultrasonography, and cranial and abdominal tomography were unremarkable.

The patient underwent liver biopsy and histopathological examination revealed granulomatous lesions characterized by the collection of mononuclear cells, mainly macrophages, in the portal areas and surrounded by fibroblasts and lymphocytes, and granulomatous hepatitis was diagnosed (Figure 1). ARB tests in sputum and urine were negative. Granulomatous hepatitis was thought to occur due to intravesical BCG instillation and the patient was consulted to Department of Infectious Diseases. Triple anti-tuberculosis treatment (Rifampicin 600 mg/day, INH 300 mg/day and Ethambutol 1200 mg/day) was started. Fever returned to normal 15 days after the initiation of treatment. All laboratory tests returned to normal six weeks later, and the patient is still being followed up by Urology and Infectious Diseases clinics.

Discussion

BCG, an attenuated live strain of M. bovis, was first administered intravesically by Morales et al. (1) in 1976 for high-risk superficial bladder cancer (5). Intravesical BCG administration reduces bladder tumor recurrence through anti-tumor effect. Following administration, T-lymphocyte infiltration occurs in the lamina propria layer of the bladder, which causes an increase in cytotoxic T cells. The resulting local inflammation causes damage to tumor cells and anti-tumoral effect is observed (2,6).

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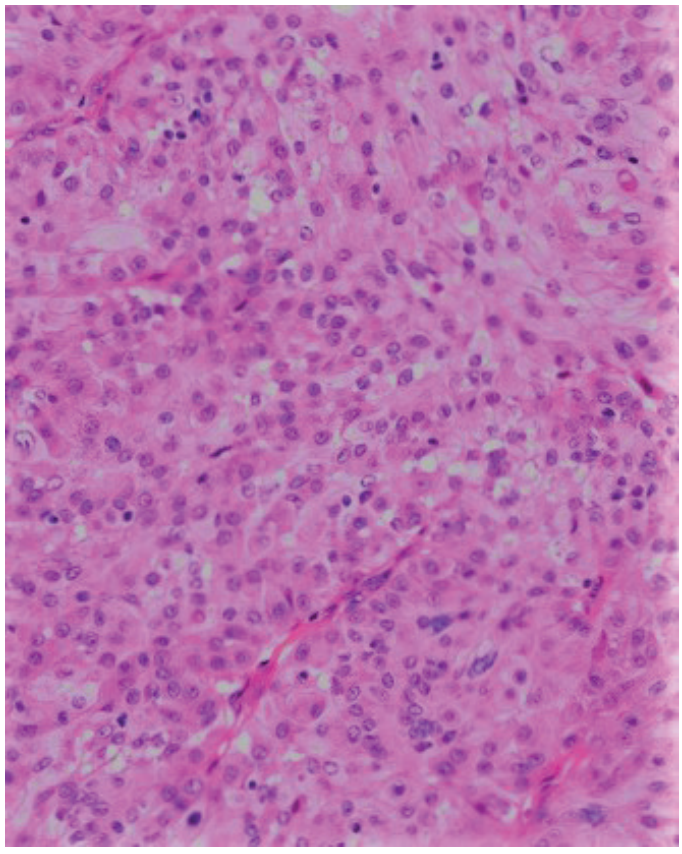

Figure 1. Granulomatous structures consisting of polymorphonuclear leukocytes in portal areas was observed. (Stained with hemotoxylin-eosine, H&Ex40)

Local and systemic side effects may occur after intravesical BCG administration. Although these side effects are generally mild, they can rarely be serious and life-threatening (7). The most common local side effects after application are cystitis, dysuria, pollakiuria and fever, while systemic side effects such as myalgia, headache, arthralgia, anorexia, malaise, diarrhea, chills, weakness, high fever, arthritis, pneumonia, hepatitis, renal abscess, cytopenia and sepsis may also occur. Systemic side effects are less common than local side effects. In a study by Steg et al. (2), the rate of systemic side effects was reported as 3%. There are those who argue that systemic complications are due to immunoallergic reaction after intravesical BCG application, as well as there are authors suggesting hematogenous spread of bacteria due to damaged urothelium secondary to traumatic catheterization, bladder perforation and excessive tumor resection (8,9).

Intravesical BCG should be discontinued in patients with systemic side effects. In particular, patients with high fever should be followed closely, and patients with fever above 39°C should be hospitalized (10). In a study by Paterson et al. (10), patients with fever above 39°C within 48 hours following intravesical BCG treatment were hospitalized. Patients with no bacterial growth in blood and urine cultures despite ongoing fever were given 300 mg isoniazid treatment, and a rapid response was observed and fever decreased.

Impaired liver function tests and high fever during intravesical BCG therapy should be considered for granulomatous hepatitis. Anti-tuberculosis treatment should be started at the first stage in cases with confirmed granulomatous hepatitis. Steroid should be added to the treatment in patients whose liver function tests do not improve despite six months of treatment (2). In our case, cure was achieved with anti-tuberculosis treatment without the need for steroid treatment.

In order to prevent complications after intravesical BCG administration, Lamm et al. (8). reported that prophylactic isoniazid administration, which was started on the morning of treatment and used for three days, could prevent severe irritative symptoms and systemic complications.

Conclusion

Local and systemic side effects of intravesical BCG can be seen in the treatment of superficial bladder cancer and carcinoma in situ. Although local side effects are more frequent, they are better tolerated by patients. Although systemic side effects are rare, such patients should be closely monitored, and liver biopsy should be initiated for definitive diagnosis, especially in patients with impaired liver function.

Ethics

Informed Consent: Informed consent was obtained from all the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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