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The Role of Urodynamics in the Evaluation of Lower Urinary Tract Symptoms After Postoperative Radiotherapy: A Retrospective Cross-Sectional Study

Postoperatif Radyoterapi Sonrası Alt Üriner Sistem Semptomlarının Değerlendirilmesinde Ürodinaminin Rolü: Retrospektif Kesitsel Çalışma

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ABSTRACT Objective: The aim of this study was to evaluate lower urinary tract symptoms (LUTS) and urodynamic parameters in patients with prostate cancer who received adjuvant radiotherapy (ART) or salvage radiotherapy (SRT) following open radical prostatectomy (RP) or robot-assisted radical prostatectomy (RARP) by using urodynamic parameters. **Material and Methods:** Patients who were treated with ART or SRT following RP or RARP due to prostate cancer were included. International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-SF) and International Prostate Symptom Score (IPSS) questionnaires were filled in for the evaluation of LUTS for each irradiated patient. Urodynamic parameters such as bladder pressure, maximum cystometric capacity, maximum urethral pressure, maximum urethral closure pressure used for diagnosis of intrinsic sphincteric deficiency (ISD), and urethral length were recorded. **Results:** Fifty patients had undergone open RP, while 48 had undergone RARP. ART and SRT was applied with 55 and 43 patients, respectively.There was no significant difference between the groups in terms of IPSS and ICIQ-SF scores, urgency-related measurements and maximum cystometric capacity values. Findings in filling cystometry were not significant in comparison of both RP and radiotherapy technique (p>0.05). Maximum urethral closure pressure values were significantly higher in RARP recipients, the frequency of ISD was significantly higher in the open RP group, and urethral length was longer in the RARP group. **Conclusion:** No significant difference was found in terms of LUTS in patients who underwent ART or SRT after RP. RARP had positive effects on functional urethral length, urethral closure pressures and ISD frequency, regardless of timing of radiotherapy.

Keywords: Prostate cancer; urodynamics; incontinence; radiotherapy; radical prostatectomy

ÖZET Amaç: Bu çalışmanın amacı, prostat kanseri nedeniyle açık radikal prostatektomi (RP) veya robot yardımlı radikal prostatektomi [robot-assisted radical prostatectomy (RARP)] sonrası adjuvan radyoterapi (ART) veya kurtarma radyoterapisi [salvage radiotherapy (SRT)] uygulanan hastalarda alt üriner sistem semptomları (AÜSS) ve ürodinamik parametreleri, ürodinamik testler kullanarak değerlendirmektir. **Gereç ve Yöntemler:** Prostat kanseri nedeniyle RP veya RARP sonrası ART veya SRT uygulanan hastalar dâhil edildi. AÜSS'nin değerlendirilmesi için Uluslararası İnkontinans Anketi-Üriner İnkontinans Kısa Formu [International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-SF)] ve Uluslararası Prostat Semptom Skoru [International Prostate Symptom Score (IPSS)] anketleri radyoterapi uygulanan her hasta için doldurduldu. Mesane basıncı, maksimum sistometrik kapasite, maksimum üretral basınç, intrinsik sfinkterik yetersizlik (ISD) tanısında kullanılan maksimum üretral kapanma basıncı ve üretral uzunluk gibi ürodinamik parametreler kaydedildi. **Bulgular:** Elli hastada açık RP ve 48 hastada RARP uygulandı. ART ve SRT sırasıyla 55 ve 43 hastaya uygulandı. Gruplar arasında IPSS ve ICIQ-SF skorları, ani sıkışma hissi ile ilgili hacimler ve maksimum sistometrik kapasite değerleri açısından anlamlı fark yoktu. Dolgu sistometrisindeki bulgular hem RP hem de RT tekniği karşılaştırıldığında anlamlı değildi (p>0.05).RARP uygulananlarda maksimum üretral kapanma basıncı değerleri anlamlı olarak daha yüksekti, açık RP grubunda ise ISD sıklığı anlamlı olarak daha yüksekti ve RARP grubunda üretral uzunluk anlamlı olarak daha uzundu. **Sonuç:** RP sonrası ART veya SRT uygulanan hastalarda AÜSS açısından anlamlı fark bulunmadı. Radyoterapi uygulama zamanından bağımsız olarak, RARP'nin fonksiyonel üretral uzunluk, üretral kapanma basınçları ve ISD sıklığı üzerinde olumlu etkileri olduğu bulundu.

Anahtar Kelimeler: Prostat kanseri; ürodinami; inkontinans; radyoterapi; radikal prostatektomi

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The most commonly used treatment modalities for the treatment of localized prostate cancer (PCa) are surgery and radiotherapy (RT).[1] Radical prostatectomy (RP) can be performed with open or robot-assisted techniques. Currently, robot-assisted RP (RARP) has been increasingly used despite a small improvement in erectile function and also without any satisfactory evidence of superiority over other techniques for maintaining urinary continence.[2] A multicentric prospective nonrandomized study comparing RARP and open RP reported no significant difference in achieving urinary continence between the surgical techniques.[3] However, when combined therapy (surgery and RT) is applied, the incidence of lower urinary tract symptoms (LUTS) increases, causing significant adverse impacts on both social and personal life of patients.[4]

The evidence for applying adjuvant RT (ART) after RP for high-risk of recurrence in patients defined as positive surgical margins, seminal vesicle involvement, extra-prostatic extension, high pathologic T stage, or high Gleason score derived from three prospective randomized controlled trials showed improvement in oncologic outcomes, while in several retrospective studies beneficial outcomes of salvage RT (SRT) have been revealed in cases with prostate-specific antigen (PSA) elevation or biochemical relapse during postoperative follow-up.[5]

Although new RT techniques have led to a significant reduction in gastrointestinal toxicity, the urinary side effects remain unchanged related to the inclusion of bladder neck and the vesicourethral anastomosis in the RT field.[6] However, LUTS are frequently seen in this population, there is a widespread belief that delaying post-prostatectomy RT until maintaining continence will reduce the risk of long-term RT induced urinary leakage.[7]

Prior studies investigated LUTS using questionnaires and symptom scoring systems and demonstrated the development of persistent post-prostatectomy incontinence (PPI) in patients who underwent ART and SRT after RP, however, limited data are available concerning urodynamic studies and alterations in urodynamic values in these patients.[8,9]

Although significant differences have not been detected between adverse events and the rates of long-term complications for postoperatively administered ART or SRT, the side effects of PCa treatments have been consistently demonstrated even so data concerning LUTS are rather limited concerning the effects of RT following surgical treatment (such as PPI and adverse LUTS findings).[10]

Therefore, this study aimed to evaluate LUTS, urodynamic parameters, and the frequency of intrinsic sphincteric deficiency (ISD) in patients who received either ART or SRT following open RP or RARP.

MATERIAL AND METHODS

The study designed in accordance with the relevant principles of Helsinki Declaration and its most recent amendments was approved by Prof. Dr. Cemil Tascioglu City Hospital Ethical Comittee (approval no: 451/2020, approval date: 15.12.2020). Informed consent was obtained from the study participants. The PCa patients were randomized into open and robot-assisted RP groups. All individuals had then received RT because of fulfilling high postoperative risk criteria or determination of biochemical recurrence during follow-up. The exclusion criterion was to have been treated for LUTS. The patients were grouped as ART (<6 months after surgery) or SRT (>6 months after surgery). The demographic and clinical data of these patients (age, height, weight, PSA, RP technique, lymph node count, T stage, Gleason score, surgical margin positivity, application of ART or SRT) were recorded. Comorbidities of the patients were identified as hypertension, diabetes mellitus, and coronary artery disease. The urodynamic examination was performed on each patient. Also, the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-SF) and International Prostate Symptom Score (IPSS) questionnaires were utilized for the evaluation of LUTS in each subject. The ICIQ-SF inquiry form consists of 4 questions.

Its Turkish validation was performed by Çetinel et al.[11] The IPSS form consists of 7 questions.[12] The total score ranges from 0 to 35 points and a score of >19 points is associated with the presence of severe LUTS.

RADIOTHERAPY TECHNIQUE

For the treatment of the patients, the volumetric arc therapy (VMAT) technique was applied using a linear accelerator (Varian RapidArc, Palo Alto, CA, USA). All patients were placed in a suitable fixation device with knee and foot support, and a computerized tomography simulation was performed with a comfortably full bladder and empty rectum in the supine position. For all patients, the clinical target volume 1 (CTV1) included the prostate bed and the seminal vesicles, while the lymph nodes below the aortic bifurcation were delineated within the CTV2. The CTV1 was delineated using the Radiation Therapy Oncology Group consensus guidelines, modified according to each patient's postoperative pathological findings.[13] The planning target volume 1 (PTV1) was defined as CTV1, and an additional margin of 10 mm in every direction except 6 mm posteriorly for rectal dose reduction. PTV2 was obtained by expanding the CTV2 with an isotropic margin of 7 mm.

Organs at risk were defined as the rectum, bladder, femoral heads, large and small bowel, and the penile bulb. A total RT dose of 66-72 Gy was delivered to PTV1 in 33-36 fractions with 2 Gy per daily fraction. The pelvic nodes were irradiated with a total dose of 50 Gy in 25 fractions with daily fractional doses of 2 Gy. The VMAT was planned using the Aria 11.0 system. The target coverage on CTV was defined as V95% > 99% and as 95% on PTV.

URODYNAMIC ANALYSES

A double lumen urethral catheter with 6 Fr and a rectal balloon catheter with 9 Fr were used to assess intravesical and abdominal pressures.

During urodynamic evaluation, filling cystometry, urethral pressure profile (UPP), pressure flow study and uroflowmetric parameters were examined. The UPP was performed with at least 50 mL of fluid in the bladder in the supine position. Urethral pressure uroflowmetry was performed using the same catheter after the pressure-flow study was complete. While the fluid was instilled at a rate of 2 mL/min through the lumen of the urethral catheter with the help of a pump, the catheter was pulled from the proximal to the distal urethra at a constant speed of 60 mL/min with the help of a motor, and the following parameters were recorded: pressure in bladder (Pbladder), maximum urethral pressure (MUP), maximum urethral closure pressure (MUCP) (MUP-Pbladder) and urethral length from the bladder to MUP. Determination of an MUCP value of <35 cmH_2O was used to define ISD.

STATISTICAL ANALYSIS

The SPSS v21.0 program (IBM, Armonk, NY, USA) was used for statistical analysis The Kolmogorov-Smirnov test was used to determinate the variables distribution. The independent samples t-test or the Mann-Whitney U test were used to compare quantitative variables between the 2 groups, depending on the normality of distribution. Chi-square tests were used to evaluate the differences between groups in terms of categorical variables. The p value <0.05 was defined as significant statistically.

RESULTS

In the present study, a total of 98 patients, including 50 patients in the open RP and 48 in the RARP group, were involved. While the nerve-sparing surgical approach was performed in 32 patients in the robot-assisted group, the nerve-sparing approach was performed in 26 patients in the open RP group (p=0.568). These patients, underwent ART (n=55; 56.1%) or SRT (n=43; 43.9%). The median time period elapsed from prostatectomy to RT was 4 months (range 1-6 months) in the ART and 28 months (range 6-180 months) in the SRT group. There was no significant difference between the ART and SRT groups in terms of follow-up times after RT (p=0.252). The mean age was found 65.2±7.1 years. The initial mean PSA value was 11.75±9.59 ng/dL. The follow-up period was median 9.5 months after RT (range 2-36). The mean dose of RT applied to the prostatic bed was calculated as 70.08±1.07 Gy (Table 1).

When symptom scores were examined, the mean ICIQ-SF scores of the patients who underwent open (11.61±5.81) or RARP (13.05±5.34) were similar (p=0.223). Likewise, the mean IPSS scores were also similar among the groups (p=0.470). When the urodynamic findings were compared, no significant differences were found between the volumes determined for first urination urge, first urgency, final urgency, maximum capacity, and the detrusor pressure at max-

imum flow (PdetQmax) value of patients (p>0.05). However, MUCPs and urethral lengths were statistically significant in the RARP group compared to the open RP group of patients (37.81±37.59 vs. 66.32±53.70 cmH_2O, p=0.005 and 26.68±2.54 vs. 28.12±2.71 cm, p=0.015; respectively) (Table 2).

TABLE 1: Patient characteristics.

	Mean±SD
Age	65.18±7.13
PSA	11.75±9.59
Hypertension (yes/no)	44/54
Diabetes mellitus (yes/no)	22/76
Coronary artery disease (yes/no)	14/84
Radical prostatectomy	
Open	50 (%51)
Robotic-assisted	48 (%49)
Lymph node	8.67±7.65
T stage	
T2a	14 (%14.3)
T2b	16 (%16.3)
T2c	30 (%30.6)
T3a	26 (%26.5)
T3b	12 (%12.2)
RT dose	70.08±1.07
Pre-RP PSA	
<10	22 (%22.4)
10-20	45 (545.91)
>20	31 (%31.6)
Surgical margin	
Negative	66 (%67.3)
Positive	32 (%32.7)

SD: Standard deviation; PSA: Prostate-specific antigen; RT: Radiotherapy; RP: Radical prostatectomy.

A total of 51 patients had been diagnosed with ISD according to MUCP values. It was determined that the incidence of ISD was greater in the open RP group compared to the RARP group (66% vs. 37.5%, p=0.008; chi-square test). A moderately significant inverse relationship was found between urethral length and ICIQ-SF questionnaire scores (r=-0.411, p<0.001) (Table 3 and Figure 1).

Subgroup analysis was examined and it was observed that there was no significant difference when surgical techniques were examined in terms of urodynamic parameters (Table 4).

DISCUSSION

In the present study, LUTS of the patients with PCa who received RT (ART or SRT) after RP were evaluated in terms of the surgical method used (open vs. robot-assisted), and MUCP and urethral length were found to be significantly lower in the open RP group compared to RARP group. Additionally, when diagnosed according to MUCP values, ISD was found to have developed more frequently in the open RT group. However, lack of significant differences between ART vs. SRT group of patients in terms of these parameters meant that the timing of RT after RP had no influence on the recovery of continence.

TABLE 2: Comparison of urodynamic parameters.

	Open RP	RARP	p value	ART	SRT	p value
ICIQ-SF	11.61±5.81	13.05±5.34	0.223	11.00±4.08	12.30±5.30	0.425
IPSS	12.98±4.65	12.23±5.21	0.470	11.14±3.86	11.96±4.98	0.577
First sensation volume (mL)	141.88±71.75	137.20±72.64	0.767	130.14±32.85	152.29±86.39	0.355
First desire to void volume (mL)	217.19±86.45	194.80±87.52	0.242	203.29±50.44	205.10±97.92	0.948
Urgency volume (mL)	284.47±102.48	258.68±94.06	0.234	301.00±44.72	261.76±99.52	0.161
MCC volume (mL)	308.98±99.86	281.41±92.83	0.194	313.86±38.67	288.67±107.94	0.399
MUCP (cmH_2O)	37.81±37.59	66.32±53.70	0.005	99.10±79.09	62.78±47.18	0.124
ISD diagnosis, n (%)	26.68±2.54	28.12±2.71	0.015	28.24±1.78	28.55±2.30	0.619
PdetQmax (cmH_2O)	38.48±21.02	41.39±24.38	0.553	29.01±11.61	40.81±24.87	0.094

ICIQ-SF: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form; IPSS: International Prostate Symptom Score; MCC: Maximum cystometric capacity; MUCP: Maximum urethral closure pressure; ISD: Intrinsic sphincteric deficiency; PdetQmax: Detrusor pressure at maximum flow; RP: Radical prostatectomy; RARP: Robot-assisted radical prostatectomy; ART: Adjuvant radiotherapy; SRT: Salvage radiotherapy.

TABLE 3: Relationship of urethral length with symptom scores and urethral pressures.

		ICIQ-SF	IPSS	MUCP	PdetQmax
Urethral length	Pearson correlation	-0.411**	-0.156	0.127	0.211
	p value	0.000	0.162	0.256	0.057

ICIQ-SF: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form; IPSS: International Prostate Symptom Score; MUCP: Maximum urethral closure pressure; PdetQmax: Detrusor pressure at maximum flow.
** p<0.05.

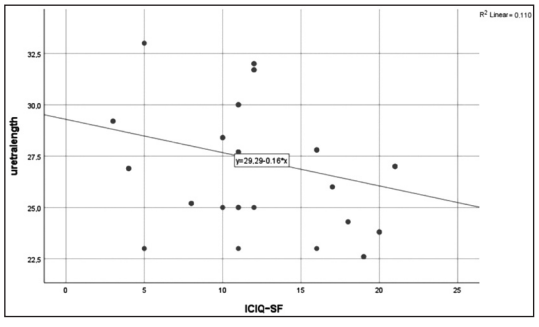

FIGURE 1: Correlation graphics between urethra length and ICIQ-SF scores. ICIQ-SF: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form.

The previous prospective, randomized clinical trials have shown that ART was associated with a reduced risk of recurrence in patients at risk, however, only one study revealed an overall survival improvement rates in ART group of patients.[14,15] Recently published non-inferiority Phase III trials (RAVES, RADICALS, GETUG-17) and a meta-analysis (ARTISTIC) have pointed out that SRT may be regarded as a reliable option at the onset of recurrence.[16-19]

The primary goal of therapy is undoubtedly the effectiveness of the treatment in PCa patients; however, unfortunately, the evaluation of adverse events related to the treatment that affect the quality life of the patients is often ignored.[20] The cause of PPI is multifactorial, and the most common factors are bladder abnormalities such as sphincteric insufficiency, excessive detrusor activity, overactive bladder, decreased bladder compliance, and impaired detrusor contractility.[21]

Thanks to technological developments, the advantages of RARP have drawn attention. Important improvements have been experienced in robotic surgery in terms of preserving both erectile functions and urethral length and minimizing neuropraxia. As a result of a meta-analysis, it was reported that the function of urinary continence was regained at a greater frequency in patients who underwent RARP compared with open RP.[22] Urodynamic studies are considered as a standard method for evaluating LUTS and have been used in previous studies evaluating PPI development. In clinical practice, urodynamic studies can only be performed in patients with urinary incontinence or de novo LUTS following RP, therefore it is difficult to achieve large-scale data on function of the bladder and urethra that may occur immediately after RP.[23]

Scarce number of urodynamic studies evaluating patients treated with RP alone have mostly found

TABLE 4: Subgroup analysis of the patients.

	RARP Group (n=50)			Open RP Group (n=48)		
	ART (n=22)	SRT (n=28)	p value	ART	SRT	p value
ICIQ-SF	14.70±4.37	13.19±6.21	0.509	12.68±5.02	10.08±6.15	0.065
IPSS	13.00±6.13	12.38±6.35	0.807	12.95±4.82	12.12±3.57	0.459
First sensation volume (mL)	130.44±80.30	149.07±97.34	0.634	135.85±62.65	143.71±67.58	0.653
First desire to void volume (mL)	192.78±100.54	203.80±101.47	0.798	195.41±83.20	213.95±77.48	0.085
Urgency volume (mL)	247.89±100.92	251.00±107.33	0.945	269.95±93.49	309.29±86.96	0.052
MCC volume (mL)	267.00±96.03	280.73±123.95	0.779	294.23±86.31	303.29±86.96	0.436
MUCP (cmH_2O)	73.32±65.06	65.49±59.74	0.785	73.08±60.81	67.15±41.65	0.534
PdetQmax (cmH_2O)	33.56±20.86	34.80±16.79	0.874	41.11±24.91	43.55±22.61	0.701

ICIQ-SF: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form; IPSS: International Prostate Symptom Score; MCC: Maximum cystometric capacity; MUCP: Maximum urethral closure pressure; PdetQmax: Detrusor pressure at maximum flow; RARP: Robot-assisted radical prostatectomy; RP: Radical prostatectomy; ART: Adjuvant radiotherapy; SRT: Salvage radiotherapy.

that weakness of the urinary sphincter along with impaired detrusor activity and decreased compliance of the bladder, were the most common causes of urinary incontinence.[24-27] In most patients, the main cause of stress incontinence after RP is associated with the development of weakness of the sphincter.[26]

Although many urodynamic studies have been carried out after RP, a few number of urodynamic studies have been performed following RT. The symptoms associated with the disorders of the bladder, prostate gland, prostatic urethra, or any combination of these may be seen in these cases. In a systematic review evaluating the impact of RT in localized PCa patients, decreased bladder compliance, bladder capacity, and de novo detrusor overactivity were found in urodynamic studies.[28] In addition, investigation of urodynamic changes on long-term functional effects in patients treated with primary RT revealed that maximal bladder capacity and volume at first urge to void will decrease at 3 months.[29] However, at 18-month follow-up, while the decrease in bladder capacity persisted, other urodynamic parameters were unaffected.[30] The RTOG 94-08 and RTOG 96-01 trials comparing primary RT to an intact prostate with postprostatectomy RT respectively, demonstrated that due to postoperative inferior transposition of the anastomosis to the external sphincter LUTS are mainly related with the exposure of prostatic fossa to higher doses of RT rather than the prostate gland and prostatic urethra.[31] Ervandian et al. examined urodynamic parameters in patients who received SRT after RP and stated that LUTS were compatible with urodynamic findings, especially concerning its effects on maximal cystometric bladder capacity, bladder compliance, and bladder outlet obstruction.[20]

On the other hand; delivery of ART following RP was found to be an independent predictor of decreased improvement in the recovery of urinary continence.[8] In our study, we compared the patients who received ART vs. SRT following open RP or RARP in terms of symptom scores and urodynamic parameters, and found relatively lower MUCP values in the open RP group compared to the RARP group. This suggests that ISD may be associated with urinary incontinence in this group of patients.

The median time elapsed between prostatectomy and RT in the ART and SRT arms was 4 months and 28 months, respectively. In the study of Munoz et al, improvement in urinary recovery was shown in the first period of 7-8 months after RP which was a longer period than ours. However, the time from prostatectomy to RT in terms of ART vs. SRT did not affect the outcomes of urodynamics in this study.[32] No difference was found between the groups regarding the first urge to urinate, severe urge to urinate, and maximum bladder capacity. However, significant differences were observed in MUCP values (and ISD frequency) and urethral lengths and robotic-assisted RP was found to be beneficial in this respect. In a recently published meta-analysis, it was found that each extra millimetric membranous urethral length detected on preoperative magnetic resonance imaging was associated with improvement in early recovery of continence after RP.[33] Our study also supports current evidence that suggests maintaining urethral length is important in the mechanism of continence. That is, the significantly longer urethral length in the RARP group was associated with improved continence and a lower likelihood of ISD.

The present study has some limitations. The first one is the small number of patients enrolled. However excluding considerable number of patients that were not receiving treatment for LUTS was necessary for accurate analysis. Another limitation is the fact that the urodynamic parameters of the patients before RP and immediately after the surgery were not known. Not using a questionnaire for overactive bladder is another limitation. The short follow-up time after RT may also be considered to be a limitation because of the time-bound changes had been demonstrated in prior studies.

CONCLUSION

A statistically significant difference was not found in terms of urodynamic parameters in patients who underwent ART or SRT after RP. In patients who received ART or SRT following RP, it was found that utilization of RARP had positive effects on functional urethral length, urethral closure pressures, and ISD frequency, regardless of the timing of RT.

Further studies with a larger number of patients are needed to evaluate the urodynamic alterations in patients receiving RT after RP which will play an important role in making treatment decisions in terms of RT timing.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Selvi Dinçer;* ***Design:*** *Selvi Dinçer, M. Gökhan Çulha;* ***Control/Supervision:*** *Selvi Dinçer, M. Gökhan Çulha;* ***Data Collection and/or Processing:*** *Selvi Dinçer, M. Gökhan Çulha;* ***Analysis and/or Interpretation:*** *Selvi Dinçer, M. Gökhan Çulha;* ***Literature Review:*** *Selvi Dinçer, M. Gökhan Çulha;* ***Writing the Article:*** *Selvi Dinçer, M. Gökhan Çulha;* ***Critical Review:*** *Selvi Dinçer, M. Gökhan Çulha.*

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