ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/urology.2021-84243

Predictive Factors of Pathological Upgrading in Prostate Cancer Patients Treated by Radical Prostatectomy Who are Suitable for Active Surveillance

Aktif İzlem İçin Uygun Olan ve Radikal Prostatektomi ile Tedavi Edilen Prostat Kanserli Hastalarda Patolojik Yükselmeyi Gösteren Prediktif Faktörler

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ABSTRACT Objective: To evaluate the factors to predict Gleason score upgrading in prostate cancer patients who are suitable for active surveillance (AS) and the role of prostate-specific antigen (PSA) density in the management of these patients. **Material and Methods:** Seventy seven prostate cancer patients who had active surveillance criteria but preferred radical prostatectomy as the treatment instead of active surveillance protocol were included in the study. In our study, Gleason 3+3≤6 adenocarcinoma, positivity in maximum 2 biopsy cores in ≥12 core transrectal ultrasound guided systematic biopsy, PSA<10 ng/mL, and Clinical T Stage ≤2a were used as active follow-up criteria. Tumor grade in the radical prostate and prostate biopsy specimens were compared. Predictive factors of pathological upgrading after radical prostatectomy have been investigated. **Results:** There is statistically significant correlation between PSA density (p=0.042), prostate volume (p=0.010), maximum tumor length in a core (p=0.001), maximum percentage of tumor in a core (p=0.002), bladder neck involvement (p=0.023) and postoperative Gleason score upgrading in univariate analysis. The optimal cut-off values of PSA density and prostate volume were 0.12 ng/mL^2 and 48 cc, respectively. There isn't statistically significant correlation between PSA, free PSA, free/total PSA, the length of biopsy core, perineural invasion, apical involment and postoperative Gleason score upgrading in univariate analysis. Maximum tumor length in a core and prostate volume were independent predictors of pathological Gleason score upgrading on multivariate regression. **Conclusion:** Prostate volume and maximum tumor length in a core are independent predictors of pathological Gleason score upgrading in our study. These factors should also be included in current AS criterias in addition to PSA density and tumor percentage.

Keywords: Prostate specific antigen density; active surveillance; Gleason score upgrading; low risk prostate cancer; radical prostatectomy

ÖZET Amaç: Bu çalışmanın amacı, aktif izlem için uygun prostat kanseri hastalarında Gleason skor yükselmesini öngören faktörler ve bu hastaların yönetiminde prostat spesifik antijen (PSA) yoğunluğunun rolünü değerlendirilmektir. **Gereç ve Yöntemler:** Çalışmaya aktif izlem kriterlerine sahip olan ancak tedavi olarak aktif izlem yerine radikal prostatektomiyi tercih eden 77 prostat kanseri hastası dâhil edildi. Çalışmamızda, aktif izlem kriterleri olarak Gleason 3+3≤6 adenokarsinom, ≥12 kor transrektal ultrason kılavuzluğunda sistematik biyopside en fazla 2 biyopsi korunda pozitiflik, PSA<10 ng/mL ve Klinik T Evre ≤2a değerleri kullanılmıştır. Radikal prostatektomi piyesleri ve prostat biyopsi örneklerindeki tümör dereceleri birbiriyle karşılaştırılmıştır. Radikal prostatektomi sonrası patolojik evre yükselmesi ile ilgili prediktif faktörler araştırılmıştır. **Bulgular:** PSA yoğunluğu (p=0,042), prostat hacmi (p=0,010), bir kordaki maksimum tümör uzunluğu (p=0,001), bir kordaki maksimum tümör yüzdesi (p=0,002), mesane boynu tutulumu (p=0.023) ile Gleason skor yükselmesi arasında tek değişkenli analizde istatistiki olarak anlamlı fark bulundu. PSA yoğunluğu ve prostat hacminin optimal "kesme" değeri sırasıyla 0,12 ng/mL^2 ve 48 cc idi. Tek değişkenli analizde PSA, serbest PSA, serbest/total PSA, biyopsi kor uzunluğu, perinöral invazyon, apikal tutulum ile postoperatif Gleason skor yükselmesi arasında istatistiksel olarak anlamlı bir ilişki yoktur. Bir kordaki maksimum tümör uzunluğu ve prostat hacmi çok değişkenli regresyon analizinde Gleason skor yükselmesinde bağımsız prediktif faktör olarak tespit edilmiştir. **Sonuç:** Çalışmamızda prostat hacmi ve bir kordaki maksimum tümör uzunluğu, Gleason skor yükselmesinde bağımsız prediktör olarak tespit edilmiştir. Bu faktörler, PSA yoğunluğu ve tümör yüzdesine ek olarak mevcut aktif izlem kriterlerine de dâhil edilmelidir.

Anahtar Kelimeler: Prostat spesifik antijen dansitesi; aktif izlem; Gleason skor yükselmesi; düşük riskli prostat kanseri; radikal prostatektomi

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Peer review under responsibility of Journal of Reconstructive Urology.

Received: 03 May 2021 ***Received in revised form:*** 14 Nov 2021 ***Accepted:*** 18 Nov 2021 ***Available online:*** 26 Nov 2021

Prostate cancer (PCa) ranks second among all cancers seen in men.[1] Disease can be classified as localized (low, intermediate, high risk patients), locally advanced and metastatic.[2]

There are several strategies in the management of localized PCa patients.[3] One of these methods in low risk localized PCa is active surveillance (AS). AS criterias are: Gleason score (GS) ≤3+3, clinical stage ≤T2c, prostate-specific antigen (PSA) ≤10 ng/mL, 2 or fewer positive cores of PCa, and PSA density (PSAD) ≤0.2 ng/mL per cubic centimeter.[4] AS inclusion criteria and follow-up protocols differ among institutions.[5] The main purpose of AS protocol is reduce the overtreatment, prevention of morbidity and comorbidities like incontinence and erectile dysfunction which occurs in the radical treatment.

GS upgrading (GSU) defined as that GS of the radical prostatectomy (RP) specimen is higher than prostate biopsies GS. GSU in the literature changes between 30% and 40%.[6] 3-4% of patients with AS criteria who underwent RP had GS 8-10 in the final pathology.[7] PSAD was found as a significant predictor of GSU after RP.[8]

Our aim in this study is to evaluate the factors to predict GSU in PCa patients who are suitable for AS and role of PSAD in the management of these patients.

MATERIAL AND METHODS

This study was carried out in the Urology Department of University of Health Sciences, Prof. Dr. Cemil Taşcıoğlu City Hospital, İstanbul, Turkey. Seventy seven PCa patients who had AS criteria and preferred open RP for treatment between January 2014, and May 2020 were analyzed retrospectively.

Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee approval was obtained and all patients provided informed consent (date 17.03.2020, no: 90). The study was conducted in accordance with Helsinki Declaration.

Seventy seven patients with AS criteria underwent open RP within 3 months after the first diagnosis. They were not included in AS protocol, they preferred RP instead of AS. Patients who had clinical T stage ≤2a, PSA <10 ng/mL, biopsy GS 3+3≤6 and ≤2 positive biopsy cores in ≥12 multicore transrectal ultrasound (TRUS) guided systematic biopsy were included in this study. We used digital rectal examination (DRE), multiparametric magnetic resonance imaging (mpMRI), computed tomography and bone scan in local clinical tumor staging. We used mpMRI in most of our patients especially in recent years.

Data of the patients were collected and recorded. The clinical parameters: DRE, age, preoperative total PSA, TRUS prostate volume (PV), free PSA, PSAD (total PSA divided by TRUS volume), f/tPSA and histopathological findings of prostate biopsy (length of a core, maximum tumor length in a core, maximum percentage of tumor in a core) and RP pathologies were investigated and data were recorded.

We calculated preoperative PV (mililiter) of patients by TRUS during TRUS biopsy and used them in calculating PSAD (ng/mL^2). All of ≥12 multicore TRUS guided systematic biopsy in these patients were performed in our department.

We excluded the patients who were treated previously (hormone or radiation therapy), taken in AS protocol before, less than 12 core TRUS guided biopsy, patients with cT2b and cT2c disease, patients with missing data, patients whose prostate biopsy performed and evaluated histopathologically outside of our hospital.

Prostate biopsy and RP specimens were evaluated by 2 uropathology experts in our hospital using World Health Organization/International Society of Urological Pathology 2014 classifications system.[9] The prostate specimen was evaluated histopathologically after RP. If tumor focus number was one in the RP specimen the GS is given to this focus, if focus number was 2 then the highest GS between 2 values was reported as final GS. Tumor percentage also given for higher biopsy core specimen.

If GS was same both in RP specimen and biopsy, then this patient is categorized in Group 1 (Non-upgrading Group). If GS increases in RP specimen, then this patient is categorized in Group 2 (Upgrading Group).

Seventy seven patients were divided into 2 groups as Group 1 (n=48, 62.3% non-upgrading) and Group 2 (n=29, 37.7% upgrading) depending to GSU.

The clinical parameters, histopathological findings of biopsy and RP pathologies were compared between 2 groups by using statistical analysis.

STATISTICAL ANALYSIS

We used the Number Cruncher Statistical System (NCSS) statistical soft ware (NCSS, LLC, Kayville, Utah, USA) in all statistical analysis. Shapiro-Wilk test, box plot graphics, Student's t-test, Mann-Whitney U test, chi-squared test, Fisher's exact test, Fisher-Freeman-Halton test, receiver operating characteristic (ROC) curve analysis and backward logistic regression analysis were used in our study. p values were considered statistically significant if $p<0.05$.

RESULTS

Seventy seven patients were included in the study. Median values in our group were: age 68.29 years, tPSA 6.4 ng/mL, fPSA 1.19 ng/mL, f/tPSA 0.16, PV 48 cc, PSAD 0.14 ng/mL^2, tumor length in a core 3 mm, percentage of tumor 27.12%. GSU was detected 29 (37.7%) in overall cohort. 20 (26%), 6 (7.8%) and 3 (3.9%) patients were reported to GSU, 3+4, 4+3 and 4+4 respectively. In RP specimens, 39 (50.6%) patients were staged as pT2c and 9 (11.69%) patients were staged as pT3.

The comparative analysis of non-upgrading and upgrading groups of the overall cohort is shown in Table 1.

TABLE 1: The comparative analysis of non-upgrading and upgrading groups.

Parameters	Overall	Group 1 (Non-upgrading)	Group 2 (Upgrading)	p value
n	77	48	29	
Age (y): (Mean±SD)	68.29±6.96	68.96±6.95	67.17±6.96	0.278
Preoperative PSA (ng/mL): Median range	6.4 (5.3-9.9)	6.2 (4.7-9.9)	6.94 (5.7-9.1)	0.656
TRUS prostate volume (mL): Median range	48 (38.5-71.5)	60 (40-86.2)	40 (36-52,5)	0.010
PSAD (ng/mL^2): Median range	0.14 (0.08-0.18)	0.11 (0.08-0.18)	0.16 (0.12-0.23)	0.042
Free PSA (ng/mL): Median range	1.19 (0.77-1.72)	1.17 (0.72-1.81)	1.29 (0.78-1.51)	1.000
Free/Total PSA %: Median range	0.16 (0.12-0.21)	0.16 (0.13-0.23)	0.14 (0.11-0.1)	0.442
Maximum length of a core (mm): Median range	12 (10-15)	12 (10-15)	11 (10-19)	0.877
Maximum tumor length in a core mm: Median range	3.0 (2-4.6)	2.0 (2-4)	4.5 (3-6)	0.001
Maximum percentage of tumor length in a core %: Mean±SD	27.12±16.24	22.78±14.97	35.25±15.66	0.002
ASAP: n (%)	11 (14.3)	6 (12.5)	5 (17.2)	0.738
High PIN: n (%)	8 (10.4)	5 (10.4)	3 (10.3)	1.000
Perineural invasion in biopsy, n (%)	20 (26.0)	11 (22.9)	9 (31.0)	0.431
Gleason upgrading (RP), n (%)				
3+3	48 (62.3)	48 (100)	0 (0)	0.001
3+4	20 (26.0)	0	20 (69.0)	
4+3	6 (7.8)	0	6 (20.7)	
4+4	3 (3.9)	0	3 (10.3)	
Pathologic T Stage, n (%)				
pT2	68 (88.3)	49 (96.0)	19 (73.0)	0.026
pT3	9 (11.7)	2 (4.0)	7 (27.0)	
Extraprostatic involment, n (%)	6 (7.8)	3 (6.3)	3 (10.3)	0.667
Apical involment, n (%)	28 (37.3)	18 (37.5)	10 (37.0)	0.968
Bladder neck involment, n (%)	6 (7.8)	1 (2.1)	5 (17.9)	0.023
Seminal vesicle involment, n (%)	3 (3.9)	1 (2.13)	2 (6.9)	0.553
Perineural invasion in RP	37 (48.1)	24 (50.0)	13 (44.8)	0.660
High PIN, n (%)	39 (50.6)	24 (50)	15 (51.7)	0.883

SD: Standard deviation; PSA: Prostate-specific antigen; TRUS: Transrectal ultrasound; PSAD: Prostate-specific antigen density; RP: Radical prostatectomy; ASAP: Atypical small acinar proliferation; PIN: Prostatic intra-epithelial neoplasia.

There was a statistically significant difference between Group 1 and Group 2 with regard to PSAD (p=0.042), TRUS PV (p=0.010), maximum tumor length in a core (p=0.001), maximum percentage of tumor in a core (p=0.002) and bladder neck involvement (p=0.023) in univariate analysis.

There was a statistically insignificant difference between Group 1 and Group 2 in: fPSA (p=1.000), f/tPSA (p=0.442), maximum length of biopsy core (p=0.877), atypical small acinar proliferation (ASAP) (p=0.738), high prostatic intraepithelial neoplasia (PIN) (p=1.000), perineural invasion (p=0.431) in biopsy specimen, extraprostatic involvement (p=0.667), vesicle seminalis invasion (p=0.553) and perineural invasion (p=0.660) in RP specimen.

Median PSAD values in upgrade and non-upgrade group is 0.16 and 0.11, respectively (p=0.042). There is a statistically significant relation with both groups and cut-off value of PSAD≥0.12% ng/mL^2 (p=0.006) (Pearson chi-squared test). The ROC curve of PSAD is shown in Figure 1.

Diagnostic scan and ROC curve analysis of PSAD cut-off value ≥0.12: odds ratio is 4.582 [95% confidence interval (CI): 1.474-14.240]. Sensitivity was 80.76%, specificity was 52.17%, positive predictive value 48.83%, negative predictive value 82.76%, area 0.645, 95% CI: 0.514-0.776, p=0.042.

Median PV was 60 cc in non-upgrading and 40 cc in upgrading group p=0.010.

The relationship cut-off value of PV in groups was 48 cc (p=0.06). The ROC curve analysis of PV≤48 cc is shown in Figure 2. Odds ratio for PV is 5.731 (95% CI: 2.034-16.150). According to PV (cut-off value ≤48 cc), sensitivity, specificity, positive and negative predictive value were (75.86%, 64.58%, 56.41%, 81.58%) respectively p=0.010.

Logistic regression analysis of prognostic factors on GSU is shown in Table 2.

PV and maximum tumor length in a core are independent predictors of pathological GSU.

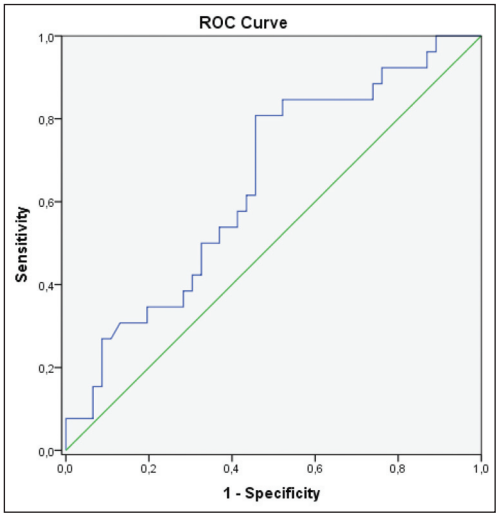

FIGURE 1: ROC curve showing the respective accuracies of PSAD in the prediction of GSU after RP.
ROC: Receiver operating characteristic; PSAD: Prostate-specific antigen density; GSU: Gleason score upgrading; RP: Radical prostatectomy.

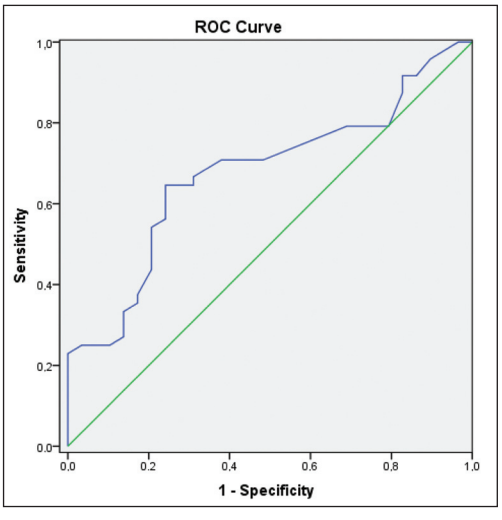

FIGURE 2: ROC curve of prostate volume according to the groups.
ROC: Receiver operating characteristic.

DISCUSSION

Cohen et al. found GSU after RP as 30% in patients with biopsy pathologies of GS 6.[11] Jin et al. found 24.0% of extracapsular extension in addition to 40% of GSU in his study.[12] GSU and upstaging to pT3a was 49.3% and 12.5%, respectively in Verep et al.'s study.[13] We found 37.7% GSU and 11.69% extracapsular extension in our study group. PCa sometimes exhibits aggressive behavior and this aggression affects disease management and treatment.

Clinically significant PCa sometimes can be underestimated in AS protocols.[13] In Grasso et al.'s

TABLE 2: Multivariate logistic regression analysis of prognostic factors of upgrading after radical prostatectomy.

		95% CI odds		
	p value	Odds	Lower	Upper
Maximum tumor length in a core (mm)	0.005	3.866	1.502	9.956
Prostate volume (≤48) cc	0.024	20.378	1.482	280.28
Maximum percentage of tumor length in a core (%)	0.848	1.016	0.860	1.201
PSAD (≥0.12) ng/mL^2	0.435	0.344	0.024	5.019
Post-up stage (pT3)	0.088	40.436	0.576	2,840.57

CI: Confidence interval; PSAD: Prostate-specific antigen density.

study, GSU and upstaging was reported as 47.3% and 59.7%, respectively.[14]

In Prostate Cancer Research International Active Surveillance (PRIAS) study, patients who switched to RP due to anxiety, 26% had intermediate (Gleason 3+4 and pT2) pathologic outcome and 17% had an unfavourable (Gleason ≥4+3 or ≥pT3) pathologic outcome.[4] In this study, only 25% of patients still be on AS after 10 year of follow-up. Of the initial chort, 60% had active treatment after 10 year of follow-up.[4] These findings show that switch to active treatment in AS protocol is higher than we expected.

Age is not an independent predictor of upstaging in our study (p=0.278) like most of studies in the literature.[13] De Nunzio et al. reported that age, PSA, PV and metabolic syndrome are independent predictors of upstaging.[15] GSU is 2 times more in patients over 70 years old than in those under 70 years old.[15]

We included ≥12 core TRUS biopsy patients in our study. The higher number of biopsies taken from suspicious areas using mpMRI reduces GSU.[15,16] We used mpMRI in most of our patients especially in recent years. mpMRI has become a part of AS protocole in recent years. In low risk PCa patients, if more biopsy cores (>18) were taken, GSU decreases from 47.9% to 23.5%.[17] The association between prostate size and GSU depends on the number of biopsy cores optained.[18]

PSAD is related with both PSA level and PV. It increases with higher PSA level with lower PV. The association between preoperative PSA and GSU varies in the literature. Mian et al. and Jin et al. did not show any association but Moussa et al. showed that PSA level was a statistically significant predictor of GSU.[12,20,21] Verep et al. found that preoperative PSA was statistically insignificant between 2 group (p=0.057).[13] There isn't a statistically significant difference between both groups in tPSA (p=0.656), fPSA (p=1.000) and fPSA/tPSA (p=0.442) in our study.

Oh et al. reported that PSA may not give as much information as PSAD in predicting outcomes after RP in patients with GS 6.[22] This finding is similar to our findings and it showed us that PV is a more significant factor than tPSA in predicting the outcomes after RP.

Gershman et al. found PV as a predictor in GSU (<40 cc).[23] Jin et al. observed that the prostate weight was lower in the upstaging group but this difference was not statistically significant in his study.[12] Verep et al. found median prostate weight as 52 g in upgrading and 58 g in non-upgrading group (p=0.69).[13] Several reports in the literature show that increasing of prostate weight reduces GSU.[20,23] Freedland et al. related this finding to the decreased androgens and low androgen environment.[24]

We observed lower PV in the upgrading group (p=0.010) and in the multivariate logistic regression analysis, PV was an independent predictor of GSU (p=0.010, odds ratio 5.731, 95% Cl: 2.034-16.150) in our study (cut-off of value of PV is ≤48 cc).

Magheli et al. found a strong correlation between PSAD and upgrading in GS 6 patients.[8] Sfoungaristos et al. found that PSAD was a predictor of GSU, although percentage of tumor and the number of cores were not predictors of GSU.[25] Sebastianelli et al. showed that higher PSAD values in low risk PCa had a ten fold risk of GSU and in this study, he

used cut-off value of PSAD as 0.185 ng/mL^2 to differentiate low and high risk PCa.[26] Magheli et al. found a strong correlation between PSAD and upgrade (p=0.037).[8] Verep et al. found median PSAD as 0.12 in upgrade and 0.08 in non-upgrade group (p=0.001).[13] Jin et al. found cut-off value of PSAD as 0.13 ng/mL^2.[12]

Gandaglia et al. added PSAD≤0.2 ng/mL^2 to the AS criteria and reported GSU rate as 46% in patients who have AS criteria at the time of RP.[27] PRIAS Protocol for AS has a PSAD cut-off 0.20 as one of the inclusion criteria.[28]

In our study, the median PSAD value was 0.16 in upgrade and 0.11 in non-upgrade group (p=0.042) in univariate analysis. In multivariate logistic regression analysis, PSAD was not an independent predictor of GSU (p=0.435). The cut-off value of PSAD in our study is ≥0.12 and odds ratio is 4.582: 95% CI: 1.474-14.240, p=0.006. We found that GSU is 4.582 fold higher if PSAD is ≥0.12 ng/mL^2 in our study (p=0.006).

There was a statistically significant difference between two groups in maximum percentage of tumor (p=0.002) and maximum tumor length in a core (p=0.001) in our study. Tumor percentage in the study of Verep et al. is median 21.6% in upgrading and 8.62% in non-upgrading group p=0.001.[13] Tumor percentage in upgrade group is median 35.25% and 22.78% in non-upgrade group in our study (p=0.002). Fiorentino et al. showed that length of biopsy cores and ratio of tumor volume in the biopsy and the volume of the corresponding tumor at RP can be helpful in correct estimation of GS.[29]

In backward logistic regression analysis in our study, 1 mm increase in tumor length in a core increases GSU 3.866 fold higher (p=0.005, odds ratio 3.866, 1.502-9.956). The odds ratio in PV≤48 cc is 20.378 (1.482-280.3, p=0.024).

Verep et al. found that the apical involment in RP specimen was significantly higher in upgrading group in his cohort (53% vs. 30.4%, p=0.013) but we didn't find similar findings in our groups (p=0.968).[13]

Being a single center study, including small number of patients and retrospective nature are the limitations of our study. However, further prospective and larger studies are needed about this issue.

We investigated the predictive factors and cut-off values of these in GSU patients who have AS criteria. We found that PSAD (cut-off value ≥0.12 ng/mL^2), PV (cut-off value ≤48 cc), maximum tumor length in a core (median 4.5 mm), maximum percentage of tumor (median 35.25%) are important factors in GSU and can be used in AS patients deciding whether or not to start a radical treatment initially. We can switch AS to active treatment in low-risk PCa patients using these predictive factors and cut-off values.

CONCLUSION

In this study, we demonstrated that maximum tumor length in a core and PV are more important predictive factors on GSU then PSAD and maximum tumor percentage in low-risk PCa patients. Maximum tumor length and PV should also be included in the current AS criteria. By using these predictive factors, we can better determine which patients will benefit from active treatment instead of AS initially and we can prevent GSU, and upstaging in these patients.

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: *Erkan Merder, Ahmet Arıman;* ***Design:*** *Mehmet Gökhan Çulha1, Fatih Altunrende;* ***Control/Supervision:*** *Fatih Altunrende, Erdal Abay;* ***Data Collection and/or Processing:*** *Osman Can, Musab Ümeyir Karakanlı, Recep Burak Değirmentepe, Muammer Bozkurt;* ***Analysis and/or Interpretation:*** *Erkan Merder, Ahmet Arıman;* ***Literature Review:*** *Erdal Abay, Erkan Merder;* ***Writing the Article:*** *Erkan Merder;* ***Critical Review:*** *Fatih Altunrende.*

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