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UROONCOLOGY
Original Article

The effect of the presence of a high-grade tertiary Gleason pattern in radical prostatectomy specimens on histopathological results and failure of biochemical treatment

Radikal prostatektomi spesmenlerinde yüksek tersiyer gleason patern bulunmasının histopatolojik sonuçlar ve biyokimyasal başarısızlık üzerine etkisi

Mehmet Giray Sönmez, Ahmet Hakan Haliloğlu, Erhan Demirelli, Orhan Göğüş

ABSTRACT

Objective: The aim of this study was to analyze the effect of a high-grade tertiary pattern in radical prostatectomy (RP) specimens on the histopathological results and PSA progression.

Material and methods: In this study, specimens from 71 patients with clinically localized prostate cancer who underwent RP between January 2007 and January 2011 in our department, who regularly attended their follow-up visits and who had a Gleason score of 5-8 (5 and 8 included) were reanalyzed by a single pathologist. The patients were evaluated for the presence of a high-grade tertiary Gleason pattern (Gleason 4 or 5). We investigated the effect of the tertiary pattern on the histopathological results and PSA progression. The patients were followed with testing for the free and total levels of PSA and given a digital rectal examination quarterly for the first two years, semiannually for the next 2 years, and annually for the remaining period. An increase in the serum total PSA count of 0.2 ng/mL or more was considered to represent PSA progression. The statistical analysis in this study was performed with SPSS for Windows Version 15.0 (Inc., Chicago, IL). $p<0.05$ was accepted as significant.

Results: The incidence of a high-grade tertiary pattern in RP specimens was found to be 15.4%. The patients were categorized into groups that were positive or negative for a tertiary pattern. When compared with the other group, the tertiary pattern positive group had higher preoperative PSA levels (p=0.469), more frequent extracapsular extension (p=0.031), more frequent lymph node (p=0.05) and seminal vesicle invasion (p=0.022) and more advanced disease in terms of the pathological stage (p=0.005). The patients were followed up for an average of 36,3 months postoperatively. PSA recurrence was found to be significantly higher in the tertiary pattern positive group (p=0.001), and the PSA progression time was shorter (p=0.001). There was no statistically significant difference between the two groups in terms of preoperative age, clinical stage, Gleason score and surgical margin positivity. When we investigated the effects of a high-grade tertiary pattern, extracapsular extension, seminal vesicle invasion, surgical margin positivity and Gleason scores on PSA recurrence according to the multivariate Cox regression analysis, only the presence of a high-grade tertiary pattern had a significant effect on PSA recurrence (p=0.034).

Conclusion: The presence of a high-grade tertiary pattern in the Gleason scores of RP specimens is associated with poor histopathological results and with postoperative biochemical failure. We believe that prospective studies with a higher number of patients and longer follow-up periods will more distinctly reveal the prognostic value of the tertiary pattern.

Key words: Gleason score; prostate cancer; PSA; radical prostatectomy; tertiary Gleason pattern.

ÖZET

Amaç: Bu çalışmada amaç, radikal prostatektomi (RP) spesmenlerinde yüksek tersiyer patern bulunmasının histopatolojik sonuçlar ve PSA progresyonu üzerine etkisini değerlendirmektir.

Gereç ve yöntemler: Çalışmada kliniğimizde ocak 2007-ocak 2011 tarihleri arasında klinik lokalize prostat kanseri tanısı ile radikal prostatektomi operasyonu uygulanmış ve günümüze kadar takibe düzenli olarak gelmiş olan, gleason skoru 5-8 (5 ve 8 dahil) olan, 71 hastanın spesmenleri tek patolog tarafından tekrar incelenmiştir. Hastalar yüksek tersiyer gleason patern (gleason 4 veya 5) bulunması açısından değerlendirildi. Tersiyer paternin bulunmasının histopatolojik sonuçlar ve PSA progresyonu üzerine etkisi araştırıldı. Hastalar ilk iki yıl 3 ayda bir, sonraki 2 yıl 6 ayda 1, sonrasında yılda bir serbest ve total PSA ölçümü ve dijital rektal muayene yapılarak takip edildi. PSA progresyonu serum total PSA değerinin 0.2 ng/mL ve

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daha üzerindeki artışı olarak kabul edildi. Bu çalışmada istatistiksel analiz SPSS for Windows Version 15.0 paket programında yapıldı. Sonuçlar da, anlamlılık p<0.05 düzeyinde değerlendirilmiştir.

Bulgular: RP spesmenlerinde yüksek tersiyer patern bulunma oranı %15.4 olarak saptandı. Hastalar tersiyer patern pozitif ve negatif olarak sınıflandırıldı. Tersiyer patern pozitif grupta diğer gruba göre preoperatif PSA değerinin yüksek olduğu (p=0.469), extrakapsüler yayılım (p değeri=0.031), lenf nodu invazyonu (p=0.05), seminal vezikül invazyonunun (p=0.022) daha fazla görüldüğü, patolojik evrenin daha yüksek olduğu (p=0.005) saptandı. Hastalar postoperatif ortalama 36,3 ay takip edildi. Tersiyer patern pozitif grupta anlamlı olarak PSA rekkürensi daha fazla (p=0.001) ve PSA progresyon zamanı daha kısa olarak (p=<0.001) tespit edildi. Her iki grupta da preoperatif yaş, klinik evre, gleason skorları, cerrahi sınır pozitifliği açısından istatistiksel olarak anlamlı fark olmadığı bulundu. Çok değişkenli Cox regresyon analizde yüksek tersiyer patern, ekstrakapsüler yayılım, seminal vezikül invazyonu , cerrahi sınır pozitifliği ve gleason skorların PSA rekkürensi üzerine etkisi incelendiğinde sadece yüksek tersiyer patern bulunmasının PSA rekkürensi üzerine anlamlı etkisi olduğu belirlendi (p=0.034).

Sonuç: Radikal prostatektomi spesmenlerinde tüm gleason skorlarda yüksek tersiyer patern bulunması kötü histopatolojik sonuçlar ve postoperatif biyokimyasal başarısızlık ile ilişkilidir. Bu konuda daha fazla sayıda hasta ile yapılan ve daha uzun takip süresi olan prospektif çalışmaların tersiyer paternin prognostik değerini daha net ortaya koyacağı düşüncesindeyiz.

Anahtar sözcükler: Gleason skoru; prostat kanseri; PSA; radikal prostatektomi; tersiyer gleason skoru

Introduction

Prostate cancer (PCa) is the most frequently diagnosed cancer among men. In Turkey, it ranks the 5th in the general cancer incidence. The incidence increases in parallel to the increase in age. Particularly after the age of 50, the incidence increases almost exponentially.[1]

Currently, the gold standard treatment method for prostate cancer at the clinical local stage is radical prostatectomy (RP) for patients with the appropriate general condition and life expectancy. The goal of RP is to leave no cancer tissues behind. For that reason, all of the prostate tissue, periprostatic adipose tissue, seminal vesicles, ejaculatory canals and pelvic lymph nodes should be removed.[2]

In prostate adenocarcinoma, identification of the biological behavior of the tumor is particularly important in the selection of the correct treatment method. The histological pattern of prostate cancer is closely related to the biological potential of the tumor.[3-7] The most widely used grading system in prostatic adenocarcinoma is the Gleason grading system, which is based on the degree of differentiation of glandular structures. The Gleason score (GS) is a widely used system that is calculated by adding the primary and secondary grades obtained through the histological evaluation of prostate cancer.[3,8,9] The tertiary pattern is described by the third most frequently observed Gleason pattern, which is different than the primary and secondary patterns.

Prostate cancer is a heterogeneous disease. Many different, aggressive tumor foci can be observed in the prostate tissue.[10]

The tertiary grade definition and its negative biological effects were first described in 2000 by Pan et al.[8] The authors stated that the presence of the tertiary Gleason grade in tumors with a Gleason score of 6 and 7 had a negative effect on the pathological stage and biochemical relapse-free survival. In many studies that have been conducted subsequently, the presence of a tertiary pattern has been found to be associated with poor histopathological results and increased PSA recurrence.[11]

Modified Gleason score (mGS) is a scoring system that is defined by taking into consideration the primary and high-grade tertiary pattern.[9-13] Recently some, modifications to the prostatic adenocarcinoma grading system have been proposed, and the presence of a high tertiary component (Gleason pattern 4 or 5) is reported to be correlated with the pathological stage and progression rates.[3,6] In addition, it is known that the heterogeneity of the histomorphological image of the carcinoma of the prostate can cause inconsistency between the scores of prostate needle biopsy and radical prostatectomy materials.[4,5]

In this study, the relationship between the presence of the tertiary Gleason pattern and age, the preoperative PSA, clinical stage, biopsy scores, postoperative pathology results (Gleason score, pathological stage, extracapsular extension, seminal vesicle invasion, lymph node invasion, surgical margin positivity), and postoperative PSA levels were analyzed.

Material and methods

Selection of the patients

One hundred twenty-one localized prostate cancer (clinical stage T1 and T2) patients, who were diagnosed with prostate adenocarcinoma by means of transrectal prostate biopsy and who underwent radical retropubic prostatectomy in our department between January 2007 and January 2011 were enrolled. Transrectal prostate needle biopsy was performed according to the elevated PSA levels and rectal examination results, and then the diagnosis was made. Clinical staging of the patients was performed by digital rectal examination, the serum PSA level, chest X-ray, whole body bone scintigraphy and pelvic radiological imaging (CT or MR). Radical retropubic prostatectomy was performed on patients with localized prostate cancer with more than 10 years of life expectancy and without any comorbidity that would cause contraindication for the surgery.

Pelvic lymphadenectomy was performed on patients who had a high risk for lymph node invasion according to the Partin nomogram, those who had a total PSA level of 10 ng/mL or higher, those with lymph nodes that were 1 cm or larger according to the radiological imaging of the pelvis, and those who had palpable lymph nodes intraoperatively.

In total, 71 patients, who did not receive preoperative neoadjuvant hormone ablation therapy, whose radical prostatectomy specimens could be recollected, who attended the follow-ups regularly and who had a total postoperative Gleason score of 5-8 (5 and 8 included), were included in the study.

Patients who received neoadjuvant hormone therapy, whose pathology preparations could not be recollected, who did not regularly attend the postoperative follow-ups, and who had a total postoperative Gleason score of less than 5 and more than 8, were excluded.

Histopathological examination

The tumor type, Gleason score, tertiary pattern, perineural invasion, extraprostatic extension, seminal vesicle invasion, surgical margin, lymph nodes, pathological stage, vascular invasion, tumor location, non-neoplastic prostate tissue, high-grade PIN and tumor volume were investigated and reported.

All of the radical prostatectomy specimens were analyzed by a single pathologist who is experienced in uro-oncology. Pathological staging was classified according to the 2002 TNM staging system. All the microscopic pathological findings of the patients were noted. The grading was performed using the Gleason grading system according to the 2005 İSUP consensus conference. The most frequently observed Gleason pattern was recorded as the primary pattern, and the 2nd most frequently observed pattern was recorded as the secondary pattern. The specimens were reevaluated retrospectively by a single pathologist for tertiary grade positivity.

If the third most frequently observed high-grade pattern was less than 5% of the total tumor volume, it was reported as the tertiary pattern; if it was more than 5%, then it was accepted as the secondary pattern.

Patients with a tertiary Gleason pattern higher than the primary and secondary patterns (tertiary Gleason pattern 4 or 5) were accepted to be tertiary grade positive. Those with a Gleason pattern lower than the primary and secondary patterns were accepted to be tertiary pattern negative.

With regard to the positivity of the surgical margin, patients who had tumor positivity with in less than 1 mm of the margin were also included.

Postoperative follow-up

The patients were examined for their free and total PSA levels and by digital rectal examination on a quarterly basis for the first two years, semiannually for the following 2 years, and annually for the remaining period. The patients were followed up for an average of 36.3 months (6-54 months).

PSA progression was defined as an increase of 0.2 ng/mL or more in the serum total PSA level. None of the patients received adjuvant therapy before recurrence.

Statistical analysis

The statistical analyses were performed with SPSS for Windows Version 15.0. Quantitative variables are expressed as the average±standard deviation or as the median (min-max). The qualitative variables were summarized with numbers and percentages. The effect of the presence of the tertiary score on age, preoperative PSA and postoperative PSA was analyzed with the Mann Whitney test. The effect of the presence of the tertiary score on the biopsy and postoperative Gleason score, clinical stage, pathological stage, surgical margin positivity, extracapsular extension, seminal vesicle invasion and lymph node invasion was investigated with the Chi-square test. The coherence between the biopsy score and the postoperative score was evaluated with the Kappa coefficient. Kaplan Meier survival analysis was used to investigate whether the progression time was affected by the presence of the tertiary grade. Factors effecting the PSA progression were evaluated with the Cox regression analysis. The level of significance was accepted as $p<0.05$.

Results

A tertiary Gleason pattern was identified in 11 of the 71 patients (15.5%) analyzed in the study. The average age of the 71 patients was 63.5 years (range 47-74 years). While the average age of the tertiary grade positive group was 64.5 years (range 52-71 years) and that of the Tertiary Grade (-) group was 63.4 years (range 47-74 years), the age difference between the groups was not statistically significant (p=0.469).

When the total PSA levels of the patients were analyzed, the average total PSA level of 71 patients was reported as 7.93 ng/mL (2.82-34 ng/mL). The Tertiary Grade (+) group had an average total PSA level of 8.93 ng/mL (4.07-14 ng/mL), the Tertiary Grade (-) group, on the other hand, had an average total PSA level of 7.75 ng/mL (2.82-34 ng/mL) according to the calculations. The difference between the two groups was found to be statistically significant (p=0.028).

According to the evaluation of the biopsy Gleason scores, 7 patients (9.9%) had a Gleason score of (3+2), 38 patients (53.4%) had a Gleason score of (3+3), 7 patients (9.9%) had

Turkish Journal of Urology 2012; 38(4): 177-84
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(3+4), 11 patients (15.5%) had (4+3), 7 patients (9.9%) had (4+4), and 1 patient (1.4%) had a Gleason score of (4+5). It was noted that there was no significant difference among the biopsy Gleason scores in terms of the rate of the occurrence of a tertiary grade (p=0.162). There were no bone metastases or distant organ metastases and no significant lymph node involvement in any patients in the preoperative period.

According to the postoperative Gleason score analysis, 12 patients (17%) had a Gleason score of (3+2), 34 patients (47.9%) had (3+3), 4 patients (5.6%) had (3+4), 15 patients (21.1%) had (4+3), and 6 patients (8.4%) had a Gleason score of (4+4). There was no significant difference among the postoperative Gleason scores in terms of the occurrence of a tertiary grade (p=0.276) (Figure 1).

No statistically significant difference was found between the biopsy and the postoperative group in terms of their Gleason scores (p=0.213).

According to the clinical staging, 66 of the patients (92.9%) were T1c and 5 of them (7.1%) were T2. Eleven patients in the Tertiary (+) group (100%) were defined as clinical stage T1c. The difference in the clinical stages between the two groups was not reported to be statistically significant (p=1.0) (Table 1).

When the pathological results were postoperatively analyzed, 46 patients out of the entire population (64.8%) were pT2, 23 patients (32.4%) were pT3a, and 2 patients (2.8%) were pT3b. In the Tertiary Grade (+) group, 2 patients (18.2%) were pT2, 7 patients (63.6%) were pT3a, and 2 patients (18.2%) were pT3b. In the Tertiary Grade (-) group, on the other hand, 44 patients (73.3%) were pT2 and 16 patients (26.7%) were pT3a. The pathological stage was statistically higher in the Tertiary Grade (+) group (p=0.005).

Pelvic lymphadenectomy was performed in 34 of 71 patients. In 2 lymphadenectomies out of 8, which were performed in the Tertiary Grade (+) group (25%), lymph node invasion was found to be positive. There was no lymph node invasion detected in the 26 lymphadenectomies carried out in the Tertiary Grade (-) group (p=0.05).

Surgical margin positivity was detected in 6 patients out of the entire group of patients (8.5%). Surgical margin positivity was identified in 1 patient (9.1%) in the Tertiary Grade (+) group and in 5 patients (8.4%) in the Tertiary Grade (-) group (p=1.0).

Twenty-three patients in total (32.4%) had extracapsular involvement. Seven patients (63.6%) in the Tertiary Grade (+) group and 16 patients (26.7%) in the Tertiary Grade (-) group had extracapsular involvement (p=0.031).

Table 1. The difference in the clinical stages between the Tertiary Grade positive and Tertiary Grade negative groups

	Total	Tertiary Grade (+)	Tertiary Grade (-)	p
Number	71	11 (15.5%)	60 (84.5%)	
Age	63.5 (47-74)	64.5 (52-71)	63.4 (47-74)	0.469
Pre-op PSA	7.93 ng/mL (2.82-34)	ng/mL 8.93 (4.07-14)	7.75 ng/mL (2.82-34)	0.028
Biopsy Gleason Score				0.162
3+2	7 (9.9%)	1 (9.1%)	6 (10%)	
3+3	38 (53.4%)	4 (36.4%)	34 (56.8%)	
3+4	7 (9.9%)	1 (9.1%)	6 (10%)	
4+3	11 (15.5%)	1 (9.1%)	10 (16.6%)	
4+4	7 (9.9%)	4 (36.3%)	3 (5%)	
4+5	1 (1.4%)		1 (1.6%)	
Post-op Gleason Score				0.276
3+2	12 (17%)	1 (9.1%)	11 (18.4%)	
3+3	34 (47.9%)	4 (36.4%)	30 (50%)	
3+4	4 (5.6%)	1 (9.1%)	3 (5%)	
4+3	15 (21.1%)	2 (18.2%)	13 (21.6%)	
4+4	6 (8.4)	3 (27.2%)	3 (5%)	
Clinical Stage				1.0
T1c	66 (92.9%)	11 (100%)	55 (91.6%)	
T2	5 (7.1%)	0	5 (8.4%)	

Table 2. Pathological results

	Total	Tertiary Grade (+)	Tertiary Grade (-)	p
Pathologic Stage	71	11	60	0.005
pT2	46 (64.8%)	2 (18.2%)	44 (73.3%)	
pT3a	23 (32.4%)	7 (63.6%)	16 (26.7%)	
pT3b	2 (2.8%)	2 (18.2%)		
N Stage	34 lymphadenectomy			0.05
N0	32 (94.2)	6 (75%)	26 (100%)	
N1	2 (5.8%)	2 (25%)	0	
Surgical Margin				1
Positive	6 (8.5%)	1 (9.1%)	5 (8.4%)	
Negative	65 (91.5%)	10 (90.9%)	55 (91.6%)	

Table 3. Prognostic pathologic results

		Tertiary Grade (+)	Tertiary Grade (-)	p
Organ confined	46/71 (64.8%)	2/11 (18.2%)	44/60 (73.3%)	
Extracapsular involvement	23/71 (32.4%)	7/11 (63.6%)	16/60 (26.7%)	0.031
Seminal vesicle invasion	2/71 (2.8%)	2/11 (18.2%)	0	0.022
Lymph node invasion	2/71 (2.8%)	2/11 (18.2%)	0	0.05
Surgical margin positivity	6/71 (8.5%)	1/11 (9.1%)	5/60 (8.4%)	1

Seminal vesicle invasion was found in 2 patients (2.8%). Both of those patients (100%) belonged to the Tertiary Grade (+) group. There was no lymph node invasion observed in the Tertiary Grade (-) group (p=0.022).

When the two groups were compared, lymph node invasion, seminal vesicle invasion and extracapsular involvement were significantly higher in the Tertiary Grade (+) group. On the other hand, surgical margin positivity did not change significantly between the two groups (p=1.0) (Table 2, 3).

According to the analysis of the tertiary scores and tertiary score percentages of all the Gleason scores, for the Gleason scores of 3+2 and 3+3, pattern 4 was identified and for the Gleason scores of 3+4, 4+3, and 4+4, pattern 5 was identified. The average tumor volume with a tertiary score was found to be 3.18% on average among all Gleason scores. The tertiary score prevalence in patients with a Gleason score 4+4 (50%) was reported to be higher than for the other scores.

For the postoperative analysis of PSA levels, the patients were followed for an average of 36.3 months (6-54) postoperatively. PSA recurrence was defined in 12 patients in total (16.9%). PSA recurrence was defined in 7 patients (63.6%) in the Tertiary Grade (+) group and in 5 patients (8.3%) in the Tertiary Grade (-) group. PSA recurrence was found to be significantly higher in the Tertiary Grade (+) group (p=0.001).

According to the evaluation of the PSA progression time based on the Kaplan Meier survival analysis, the progression time in the Tertiary Grade (+) group was significantly shorter than the Tertiary Grade (-) group (p value: <0.001). According to the Log rank analysis, the presence of the tertiary Gleason pattern was defined as a significant independent variable for PSA recurrence (p=<0.001) (Figure 2).

In the multivariate Cox regression analysis, the effect of the tertiary grade, extracapsular extension, seminal vesicle invasion, surgical margin positivity and Gleason scores of 3+2, 3+3, 3+4, 4+3, and 4+4 on PSA recurrence was investigated. We found that only the presence of the tertiary grade had a significant impact on PSA recurrence (p=0.034). Other variables did not have any statistical effect on recurrence.

Discussion

The Gleason score is composed of the sum of the two most frequently observed dominant Gleason patterns (grade). In 1992, Gleason reported that there were two patterns in more than 50% of the tumors.[14] Prostate cancer is a heterogeneous disease. Many distinct and aggressive tumor foci can be observed in the prostate tissue.[10] Therefore it is not surprising that in the Gleason grading system, the 3rd most frequent pattern, in addition to the 1st and the 2nd most frequent patterns, also affects the course and prognosis of the disease.

In 1994 Aihara et al.[15] reported 3 different Gleason patterns in more than 50% of the cases in their series of 101 patients with radical prostatectomy. Therefore, the presence of a tertiary Gleason grade in the pathological specimens is not uncommon. That is the reason why recently there have been there have been an increasing number studies conducted focusing on the impact of the tertiary Gleason grade on the clinical behavior of prostate cancer.

The definition of the tertiary grade and its negative biological effects was first proposed by Pan et al.[8] in 2000. The authors reported that in Gleason score 6 and 7 tumors, the presence of the tertiary Gleason grade had a negative impact on the pathological stage and biochemical relapse-free survival.

Rasiah et al.[16] reported a higher rate of biochemical recurrence and a shorter biochemical progression time in patients with a Gleason score (GS) of 4+3 in the presence of a tertiary Gleason grade (TGG) 5. Mosse et al.[13] stated that the negative impacts of the presence of the tertiary Gleason grade 5 were more explicit in tumors with low Gleason scores but that the effect was naturally decreased in aggressive tumors. In our study, as opposed to the studies of Mosse and Rasiah's, the presence of the tertiary grade is found to be associated with poor histopathological results and PSA recurrence in all Gleason scores.

There are studies in the literature suggesting that the presence of tertiary grades 4 and 5 is an independent predictor of biochemical recurrence.[17,18] In contrast to these studies, Van Oort et al.[19] argued that the presence of any high tertiary Gleason grade was an independent predictor for PSA recurrence and treatment failure in all patterns. As in the study of Van Oort et al.,[19] in our study, according to the log rank analysis, the presence of the tertiary grade was defined as an independent variable for PSA recurrence.

Turkish Journal of Urology 2012; 38(4): 177-84
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Sim et al.[20] found that the presence of the tertiary Gleason grade is directly associated with biochemical recurrence, and there is a high progression rate in the presence of the tertiary Gleason grade.

Whittemore et al.[21] detected a tertiary Gleason grade in 36 patients (16.8%) out of 214 patients with a Gleason score 7, and despite the lower rate of biochemical recurrence-free survival in the tertiary Gleason grade positive group, there was no significant difference between the 2 groups.

The prevalence of a tertiary Gleason grade in the study of Isbarn et al. was higher than in other studies. In their study, statistically significant poor pathological features were identified in patients with tertiary Gleason grades of more than 5%, on the other hand, in opposition to Mosse et al.,[22] there was no correlation between the presence of the tertiary Gleason grade and poor pathological features in the group with less than 5%. Consistent with the studies of Sim and Whitmore, according to our results, tertiary Gleason grade positivity was reported as 15.5%. This rate was clearly higher in the study of Isbarn et al. (22.5%). In our study, the average tertiary grade tumor volume was 3.18%. Therefore, no interpretation could be made for values of 5% and higher in terms of the tumor volume and the tertiary grade.

According to all the above-mentioned studies, the tertiary Gleason grade is an indication of the aggressiveness of the biological behavior of the tumor. Therefore, as per the 2005 ISUP consensus conference, the tertiary Gleason grade should not be ignored by the pathologist and should absolutely be included in pathology reports.[23] In biopsy specimens, the needle biopsy materials, including the various rates of 3, 4 and 5 grade tumors, should be reported as the primary pattern + high grade. For example, a tumor with a Gleason score of 3+4=7 and a tertiary pattern of 5 should be reported as Gleason score 3+5=8. The high-grade tertiary pattern should directly be included in the scoring system according to the intensity. In the determination of the tertiary pattern, data from specialized pathologists are needed. The presence of the tertiary pattern may cause serious concerns about surgery for patients with borderline indications. For this reason, patients with a high likelihood of undergoing surgery can be directed to other treatment protocols by means of thorough tertiary reports.

The presence of a tertiary Gleason pattern in radical prostatectomy specimens has been interpreted in 2 ways in many studies. According to the first interpretation, if the third most frequently observed high-grade pattern corresponds to less than 5% of the entire tumor volume, it should be reported as the tertiary pattern; if it is more than 5%, it should be accepted as the secondary pattern. On the other hand, according to the second interpretation, regardless of the percentage, the third most frequently observed pattern should be accepted as the tertiary pattern, and the percentage should be reported.[24]

According to the study conducted by Trock et al.,[25] the presence of a Gleason score of 3+3=6 + TGG 4 leads to a worse prognosis than a Gleason score of 6 and a better prognosis than a Gleason score of 7. Similarly, the presence of Gleason score of 4+4=8 + TGG 5 indicates a less aggressive disease than a Gleason score of 9. For that reason, due to the need for a modified Gleason scoring system, in this study, in addition to the normal scores, the presence of Gleason scores of 3+3=6 + TGG 4; 6.5, 3+4=7 + TGG 5; 7.25, 4+3=7 + TGG 5 and 7.5, 4+4=8 + TGG 5 are defined as a Gleason score of 8,5. However, this modification does not lead to a dramatic change in clinical practice.

It has been suggested that tertiary scores increase the grade in approximately 37% of the patients, but this increase in the histopathological grade is not associated with the clinical stage. On the other hand, tertiary scores can be statistically correlated with the age of the patients, serum PSA levels, number of positive cores in the biopsies, cancer/core ratio within the cores, and the weight of the pathological specimens.[26]

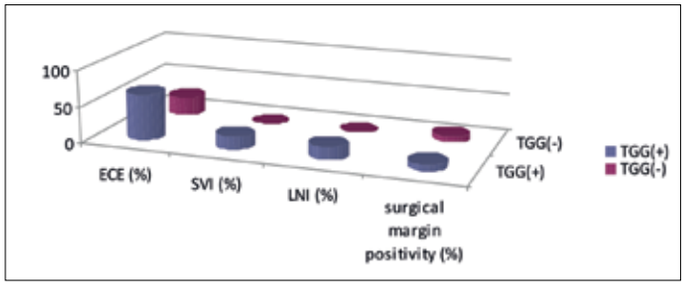

Figure 1. Incidence of pathological results.

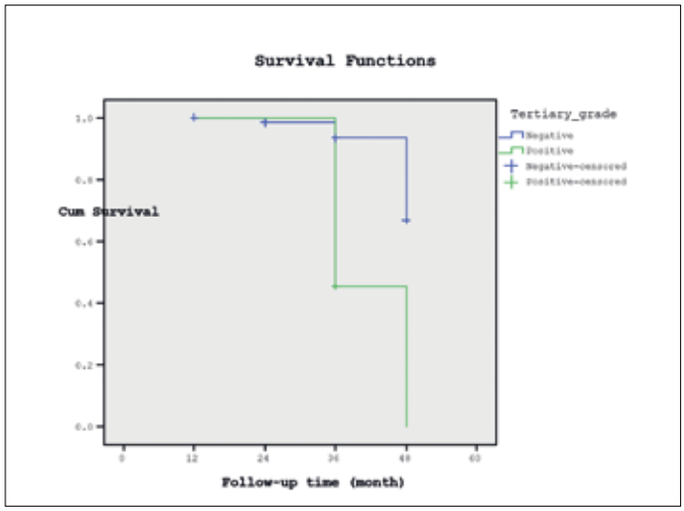

Figure 2. Kaplan-Meier survival analysis with time to PSA progression.

In our study, analysis of the specimens by a single pathologist provided us with sounder results in the evaluation of the tertiary Gleason pattern due to the lack of different subjective interpretations. A tertiary Gleason pattern was identified in 11 patients (15.5%) out of 71. This rate is consistent with the literature. We did not find a significant difference between the tertiary Gleason pattern positive and negative patients in terms of preoperative age, clinical stage, biopsy or postoperative Gleason score. However, as in the study of Trock et al.,[25] the preoperative PSA level was found to be higher in the tertiary Gleason pattern positive group (p=0.028).

With regard to the pathological features, pathological stage, extracapsular invasion, seminal vesicle invasion, and lymph node invasion were reported to be significantly higher in the tertiary Gleason pattern positive group, which is consistent with the literature. However, surgical margin positivity was not significantly different between the two groups (p=1.0).

In our study, as recommended in the European Association of Urology (EAU-2011) guidelines, the PSA relapse threshold after radical prostatectomy was determined to be 0.2 ng/mL. The PSA relapse rate was found to be higher (p=0.001) and the PSA progression time was shorter (p<0.001) in the tertiary Gleason pattern positive group. These results are also in compliance with many other studies carried out on the tertiary Gleason pattern.

There are some limitations of our study. First, as the patients included in the study were those who had undergone a radical prostatectomy only at our clinic within a period of 4 years, the number of the patients does not ensure the reliability of a subanalysis or the statistical significance in the investigation of the presence of a tertiary Gleason pattern for each Gleason score separately. Therefore, the patients were analyzed in only two groups, namely, the tertiary Gleason pattern positive and negative groups. The low number of patients and the tertiary Gleason pattern positive patients diminished the statistical strength of the study.

Secondly, due to the retrospective structure of the study, its sensitivity is prejudiced. Therefore, it is important that the findings be confirmed with prospective studies.

Thirdly, the median follow-up period for the patients is 36 months. However, statistically significant PSA progression develops after the 40th month. The follow-up of the patients is still underway.

Fourthly, in contrast to our expectations, the surgical margin positivity was not found to be associated with PSA recurrence in either group. The reason for this may be the inclusion of tumor positivity within less than a 1-mm distance from the surgical margin.

Our study confirms that the presence of a high-grade tertiary pattern is associated with negative pathological features and a high risk for PSA progression. For that reason, in the biopsy specimens and radical prostatectomy specimens, the presence of the tertiary pattern, the grade and percentage of the tertiary pattern should be reported by a pathologist who is specialized in this topic. Particularly in radical prostatectomy specimens, the modified Gleason score, which includes the tertiary pattern, should be calculated. Therefore, we should be more cautious in the postoperative follow-up of patients. However, this modification does not seem to cause any dramatic change in clinical practice.

Gleason score 4+4 was higher when compared with the other scores. This finding may be interpreted as follows: with the increase in score, the aggressiveness of the tumor increases as expected; therefore, the prevalence of a high-grade tertiary pattern would also increase.

The presence of the high-grade tertiary pattern in addition to the current Gleason score in radical prostatectomy specimens was associated with a high preoperative PSA level. No statistically significant difference was found between the groups in terms of preoperative age, clinical stage and Gleason score.

The presence of the tertiary pattern was associated with a high pathological stage, extracapsular extension, seminal vesicle invasion and lymph node invasion.

The presence of the tertiary grade had a significant effect on PSA recurrence, and the PSA progression time was significantly shorter in these patients.

Prospective studies involving large series are needed to confirm these findings.

Conflict of interest

No conflict of interest was declared by the authors.

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Turkish Journal of Urology 2012; 38(4): 177-84
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