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Frequency of ISUP 2014 Grade Group Upgrading in Radical Prostatectomy Patients and Associated Risk Factors: A Retrospective Study and Multivariate Analysis

Radikal Prostatektomi Hastalarında ISUP 2014 Grade Grup Yükselmesi Sıklığı ve İlişkili Risk Faktörleri: Retrospektif Bir Çalışma ve Çok Değişkenli Analiz

Emre Salabas[1], Huseyin Cihan Demirel[2], Ozlem Ton Eryilmaz[3]

[1]Department of Urology, University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey
[2]Department of Urology, Aydin University Faculty of Medicine, VM Medical Park Florya Hospital, Istanbul, Turkey
[3]Department of Pathology, University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey

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Corresponding Author: Emre Salabas / University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital, Department of Urology, Istanbul, Turkey / emresalabas@gmail.com / ORCID ID: 0000-0002-8663-2476

Abstract

Objective: The primary aim of this study is the determination of International Society of Urological Pathology (ISUP) grade group (GG) upgrading prevalence and its risk factors in prostate cancer patients.
Materials and Methods: This study was conducted on 117 patients who all underwent open radical prostatectomy in our institution between 2011 and 2020. Patients who received neoadjuvant therapy prior to surgery and had metastasis in lymph nodes or bones were excluded from the study.
Results: In 28 (23.9%) cases ISUP GG had upgraded in final pathology. While grade group of 81 (69.2%) patients did not change, it was downgraded in the remaining 8 (6.8%) cases. In the univariate analysis for the predictors of ISUP GG upgrade, ISUP GG distribution in biopsy pathology (OR: 0.46, 95% CI: 0.26-0.82, p=0.009), positive core fraction (PCF) (OR: 0.07, 95% CI 0.01-0.85, p=0.037), greatest positive core percentage (GPC) (OR: 0.12, 95% CI: 0.02-0.68, p=0.016) and extraprostatic invasion extended (EPI-extended) (OR: 2.95, 95% CI: 1.16-7.49, p=0.023) were all identified as significant factors. When these significant factors were analyzed in multivariate logistic regression analysis, biopsy ISUP grade (OR: 0.38, 95% CI: 0.18-0.79, p=0.01), greatest percentage of cancer (GPC) (OR: 0.10, 95% CI 0.01-0.78, p=0.027) and EPI-extended (OR 14.9, 95% CI:3.1-71.9, p=0.01) were shown as independent predictors.
Conclusion: ISUP GGs of a significant number of patients upgrade in the final pathology. Initial biopsy ISUP score and greatest positive core percentage in the biopsy are independent predictors of ISUP GG upgrade risk. EPI-extended was also significantly higher in ISUP upgrade group. Tumor upgrade risk should be considered prior to prostate cancer treatment.

Keywords: prostate neoplasms, urologic surgical procedures, male, pathology

Öz

Amaç: Çalışmamızın ana amacı prostat kanseri hastalarında, ISUP Grade Grup (GG) yükselmesi oranının tespiti ve ilgili risk faktörlerinin tanımlanmasıdır.
Gereçler ve Yöntemler: Bu çalışma, 2011-2020 yılları arasında, hastanemizde açık radikal prostatektomi ve bilateral lenfadenektomi operasyonu geçiren 117 hastada gerçekleştirilmiştir. Cerrahi öncesi neoadjuvan tedavi alan, lenf nodu pozitifliği ya da uzak metastazı olan hastalar çalışma dışı bırakılmıştır.
Bulgular: Hastaların 28'inde (%23,9), ISUP grade grubu final patolojisinde yükselmiştir. Grade grubu değişmeyen veya azalan hastaların sayısı ise 81 (%69,2) ve 8'dir (%6,8). ISUP GG yükselmesinin tek değişkenli analizinde, biyopsideki ISUP GG`u (OR 0.46, 95% CI 0.26-0.82, p=0.009), pozitif kor oranı (OR 0.07, 95% CI 0.01-0.85, p=0.037), en yüksek pozitif kor yüzdesi (OR 0.12, 95% CI 0.02-0.68, p=0.016) ve geniş ekstra prostatik invazyonu (OR 2.95, 95% CI 1.16-7.49, p=0.023) prediktif faktörler olarak belirlenmiştir. Bu faktörlere çok değişkenli analiz uygulandığında, biyopsi ISUP grubu (OR 0.38, 95% CI 0.18-0.79, p=0.01), GPC (OR 0.10, 95% CI 0.01-0.78, p=0.027) ve geniş ekstra prostatik invazyonu (OR 14.9, 95% CI 3.1-71.9, p=0.01) bağımsız prediktif faktörler olarak bulunmuştur.
Sonuç: Final patolojide önemli bir sayıda hastanın ISUP grade grubu artmaktadır. İlk biyopsi ISUP grade grubu ve en yüksek pozitif kor yüzdesi, ISUP GG yükselmesinin bağımsız prediktörleridir. Ekstra prostatik invazyon da ISUP yükselme grubunda anlamlı oranda daha fazla görülür. Prostat kanseri tedavisi öncesinde tümör grubu yükselme ihtimali değerlendirilmelidir.

Anahtar kelimeler: prostat kanseri, ürolojik cerrahi işlemler, erkek, patoloji

ORCID ID: H.C. Demirel 0000-0001-7378-5599 **O. Ton Eryilmaz** 0000-0002-6499-7298

Introduction

Prostate cancer is the most common malignancy of men except skin cancers and causes significant mortality and morbidity [1]. There is a wide variety of therapy options for prostate cancer ranging from conservative managements like watchful waiting and active surveillance to definitive treatments such as radical prostatectomy, radiotherapy and brachytherapy [2]. Gleason score (GS) classification of prostate biopsy specimens is a vital part of management algorithm [2,3]. GS is especially important for choosing between active surveillance and definitive treatment options like surgery or radiotherapy [2]. However, upgrade of Gleason scores has been reported in subjects who underwent radical prostatectomy following an active surveillance protocol period. The discrepancies between pathologic upgrade rates ranged between 14-55% in different series [4-8]. Furthermore, this pathologic upgrade rate has been increasing in recent years [9]. This phenomenon may lead to either overtreatment (surgery or radiotherapy) of subjects as a result of overgrading of needle biopsy specimens or under treatment (active surveillance) of them following an understaged biopsy [4]. Gleason grading system was modified by the grading group classification in order to improve identification of low-grade cancers [10,11]. The 2014 International Society of Urological Pathology (ISUP) grading system classifies Gleason grades into 5 tiers with corresponding Gleason scores as follows: Grade group 1 (ISUP GG 1): GS< 6; GG 2: GS 3+4=7 ; GG 3: GS 4+3=7; GG 4: GS 4 and GG 5: GS 9 and 10. The stratification of GS 7 into two separate parts with different survival outcomes and treatment requirements as well as comforting patients by naming GS≤ 6 cancers as GG 1 are important aspects of this classification system [12].

The primary aim of this study is the determination of ISUP GG upgrading prevalence and its risk factors in a group of cases who underwent prostate needle biopsy or radical prostatectomy. Investigation of prostate cancer grade group upgrading using a relatively recent system (ISUP 14 GG) encompassing all risk groups is the essence of this article.

Material and Methods

This study was conducted on 117 patients who all underwent open radical prostatectomy with bilateral lymphadenectomy in University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital between 2011 and 2020 after approval of Clinical Research Ethics Board was obtained (date and number: 2021/3156). Patients who received any kind of neoadjuvant therapy prior to surgery and had metastases in lymph nodes or bones were excluded (n=25). Patients from all risk groups were included in the research since our objective was the investigation of ISUP GG upgrade in non-metastatic surgery candidates in prostate cancer group. However, majority of the cases (75%) were still in low-risk group with PSA levels <10 ng/dl, ISUP grade 1 or 2 and clinical stage of T1c or T2a. The data were analyzed retrospectively. Demographic, and clinical data of the patients including age, preoperative PSA levels, prostate volumes (cc) measured by ultrasound (formula=length x width x height x 0.52) and clinical stage of the cancer were investigated and recorded. PSA density was calculated by dividing PSA values with prostate volumes in cc.

Postoperative pathology reports were used for this retrospective analysis without re-examining pathology slides. Histopathologic examinations of all the surgical, and the majority of the needle biopsy specimens were performed in our institution by the same pathologists. Our analysis included external needle biopsy specimens having at least 12 biopsy cores in which number of positive cores and tumor length/percentage, Gleason grades and patterns were recorded. Assessment of pathologies was performed according to Gleason score classification, including primary and secondary Gleason patterns. Pathologies were also stratified according to the new ISUP 2014 grading group system [11]. Any transition from lower ISUP group to a higher one was accepted as ISUP GG upgrading. Needle biopsy pathology parameters may be listed as: ISUP grade grouping (determined from Gleason grades recorded in the original pathology reports), number of positive cores (PCN), positive core fraction (PCF: number of positive cores/total number of cores), extended PCF (PCF >50%), greatest percentage of cancer cells in a single core (GPC), total sum of positive core percentages (TPC), biopsy core ratio of percentages (BCR%: TPC/ (Core number x100)), total core length with cancer (TCL), biopsy core ratio of length (BCR mm: TCL/total biopsy length in mm) and absence/presence of prostatic intraepithelial neoplasia (PIN) and high grade PIN (HGPIN). Postoperative pathology parameters included ISUP grade grouping, weight of the specimen, calculated volume (volumetric calculation from the 3 dimensions of prostate specimen in cc, presence/absence of PIN and HGPIN, extraprostatic capsule invasion (EPI) and extended EPI (EPIe), seminal vesicle invasion (SVI), lymphovascular invasion (LVI), apex invasion, bladder neck invasion (BNI), lymph node metastasis [13,14]. Unilateral/bilateral nature of the cancer was assessed in histopathological examinations of both biopsy and surgical specimens. Patients with ≤pT2 and ≥pT3 tumors detected in surgical specimens were classified as cases with local and locally advanced prostate cancers, respectively.

Statistical Method

Statistical analysis was performed with IBM SPSS Statistics 15.0.0 (Chicago, IL). Descriptive analysis of categorical parameters was reported as numbers and percentages while continuous data were given either as mean and standard deviations (SD) or median and interquartile range (IQR) for variables with normal and abnormal distribution, respectively. In cases of abnormal distribution, numerical differences between two dependent groups were estimated with Mann-Whitney U test. In case of normal distribution, numerical differences were compared by independent samples t-test. Ratio differences between two dependent groups were compared by McNemar and McNemar-Bowker tests. Correlation of nonparametric numerical variables was determined using Spearman correlation analysis. Binary univariate and multivariate logistic regression analysis was utilized in order to estimate predictive factors. Fraction and ratios were sometimes expressed as a number fraction between 0, and 1 and sometimes as a percentage. Statistical significance was assumed in cases of $p<0.05$.

Results

A total of 117 patients were included in this study. **Table 1** shows the baseline demographics, clinical, and pathology features of the cohort. Median age at surgery was 63 (interquartile range (IQR) 57-67 years), PSA and PSA density were 8.7 ng/ml (IQR: 5.8-22) and 0.21 (IQR: 0.13-0.60), respectively. Median positive core fraction (PCF) and greatest percentage of a single core (GPC) were 33% (IQR: 17%-50%) and 60% (IQR: 40%-90%), respectively. In addition, biopsy core ratio of length (BCR mm) and percentages (BCR%) were found as 8% (4-19%) and 10% (5-20%), respectively. Median total length of positive cores (TCL mm) was 10.1 mm (IQR: 2.9-20.3). The rate PIN positivity was 23.9% (n=28) and 87.2% (n=102) for biopsy and surgical pathology specimens, respectively whereas the corresponding rates were 15.3% (n=18) and 78.6% (n=92) for high grade prostatic intraepithelial neoplasia (HGPIN). In 76 of 89 patients without perineural invasion (PNI) detected in their biopsy specimens, PNI was revealed in the surgical pathology material with a statistically significant (23.9% vs 87.2%, p<0.001) intergroup difference. Furthermore, HGPIN was detected in the final pathology of 77 patients who had not HGPIN in biopsy specimens, and the HGPIN was disclosed in the final pathology of 78.6% the patients. The differencein the rates of HGPIN detected in biopsy and surgical pathology specimens was statistically significant (15.3% vs 78.6%, p<0.001). In addition, 40 (34.2%) of these 117 patients had extraprostatic invasion (EPI), including 27 (23.1%) cases with extended EPI. Seminal vesicle invasion was detected in 10 (8.6%) patients, whereas surgical margin positivity and apex positivity were present in 41 (35%) and 54 (46.6%) cases, respectively.

The distribution of ISUP grade groups detected in biopsy specimens in the indicated number of patients was as follows: GG 1, n=38 (32%); GG 2, n=49 (31.9%); GG 3, n=21 (17.9%); GG 4, n=8 (6.8%, and GG 5, n=1 (0.9%), while their distribution in surgical pathology specimens of these patients changed as shown: GG 1, n=23 (19.7%); GG 2, n=57 (48.7%); GG 3, n=25 (21.4%); GG 4, n=7 (6.0%), and GG 5, n=5 (4.3%). The difference in ISUP GG distribution estimated for biopsy, and surgical pathology specimens was statistically significant (p=0.03). In other words, in 28 (23.9%) cases, ISUP upgrading was observed in the final surgical pathology compared to biopsy pathology. Furthermore, there was no change in ISUP scores in 81 (69.23%) patients, and downgrading was observed in the final pathology scores in 8 (6.84%) cases (**Table 2**).

When the patients were classified into ISUP upgrading (Group 2) and non-upgrading (Group 1) groups, which also included downgraded cases; groups 1 and 2 had 89 (76.1%) and 28 (23.9%) patients, respectively. These two groups were compared using chi-square, and Mann-Whitney U tests, and statistically significant intergroup differences were found as for the distribution of ISUP GGs (p=0.01), positive core fractions, greatest percentage of cancer and EPI extended. PCF (33% vs 25%, p=0.05) and GPC (70% vs 45%, p=0.01) were both statistically lower in the upgrading group, while EPI extended was detected in significantly higher rates in the upgrading group (18.0% vs 39.3%, p=0.02). In the univariate analysis of the same parameters in biopsy pathology specimens, ISUP GG

Table 1. The overall patient and pathology characteristics

Descriptive (n=117)	Median (IQR)
Age at surgery (years)	63 (57-67)
PSA (ng/ml)	8.7 (5.8-22)
PSA density (ng/ml^2)	0.21 (0.13-0.60)
US volume (cc)	40 (30.5-58.5)
Calculated volume (cc)	41.6 (31.1-62.2)
Specimen weight (g)	45 (34.75-56.25)
Positive core number (PCN)	4 (2-6)
Positive core fraction (PCF)	0.33 (0.17-0.50)
Greatest percentage of single core (GPC)	0.60 (0.40-0.90)
Total sum of positive core percentages (TPC)	1.15 (0.60-2.60)
Biopsy core ratio of length (BCR, mm)	0.08 (0.04-0.19)
Biopsy core ratio of % (BCR %)	0.10 (0.05-0.20)
Total core length with cancer (TCL, mm)	10.1 (2.9-20.3)
ISUP GG upgrade +	28 (23.9%)
ISUP GG upgrade -	89 (76.1%)
Biopsy PIN +	28 (23.9%)
Surgery PIN +	102 (87.2%)
Biopsy HGPIN +	18 (15.3%)
Surgery HGPIN +	92 (78.6%)
EPI +	40 (34.2)
EPI extended +	27 (23.1%)
SVI +	10 (8.6%)
LVI +	5 (4.3%)
Margin +	41 (35.0%)
Apex invasion +	54 (46.2%)
BNI+	15 (12.8%)
Biopsy bilateral	42 (35.9%)
Surgery bilateral	82 (70.1%)
Local advanced	47 (40.2%)
Lymph node +	6 (5.1%)

All the continuous data with abnormal distribution according to Kolmogorov-Smirnov and Shapiro-Wilk test were expressed as median value and interquartile range. Interquartile range in parenthesis were the 25th and 75th percentile values of the data. US: ultrasound; BCR mm: biopsy core ratio of length (total positive core length in mm/total core length); BCR%: biopsy core ratio of percentages (BCR%: TPC/ (core number x100)); ISUP GG: international society of urological pathology 2014 grade group; PIN: prostatic intraepithelial neoplasia; HGPIN: high grade PIN; EPI: extra prostatic capsule invasion; SVI: seminal vesicle invasion; LVI: lenfo-vascular invasion; BNI: bladder neck invasionw

Table 2. The distribution of ISUP Gleason groups in biopsy and surgery pathologies

		ISUP GG Surgery					
		1	**2**	**3**	**4**	**5**	**Total**
ISUP GG Bx	**1**	21	14	1	1	1	**38 (32%)**
	2	2	40	5	2	0	**49 (41.9%)**
	3	0	3	16	1	1	**21 (17.9%)**
	4	0	0	3	3	2	**8 (6.8%)**
	5	0	0	0	0	1	**1 (0.9%)**
	Total	**23 (19.7%)**	**57 (48.7%)**	**25 (21.4%)**	**7 (6.0%)**	**5 (4.3%)**	**117**

distribution (OR 0.46, 95% CI 0.26-0.82, p=0.009), positive core fraction (PCF) (OR 0.07, 95% CI 0.01-0.85, p=0.037) greatest positive core percentage (OR 0.12, 95% CI 0.02-0.68, p=0.016) and extraprostatic invasion extension (EPI-extended) (OR 2.95, 95% CI 1.16-7.49, p=0.023) were all identified as significant factors (**Table 3**). When these significant factors were analyzed in multivariate logistic regression analysis (backward method), biopsy ISUP grade (OR 0.38, 95% CI 0.18-0.79, p=0.01), GPC (OR 0.10, 95% CI 0.01-0.78, p=0.027) and EPI extended (OR 14.9, 95% CI 3.1-71.9, p=0.01) were shown as the independent predictors of ISUP GG upgrade from biopsy to surgery (**Table 4**).

Discussion

Since the development of prostate cancer grading system by Donald Gleason 50 years ago, Gleason grading system has been a controversial issue among urologic pathologists. Grading system, classification of atypical lesions and the discrepancy between the histopathologic reports of biopsy and surgical specimens may be counted among these contradictory topics [5,15,16]. Epstein et al. explained the reasons of these differences as pathology errors, borderline grades and sampling error [4]. Furthermore, Gleason score of 7 encompassed both 3+4 and 4+3 pathologies, which may require different managements with their differentiating risk factors. Therefore, in the year 2014 a new grading grouping system was proposed by a pathology consultation in which all GS≤ 6 was classified as ISUP G1 and GS 7 was divided into two compartments as ISUP GG 2: 3+4, and ISUP GG 3: 4+3. This new system (ISUP GG 2014), which was a modification of 2005 updates, allowed an accurate stratification of tumors, described the lowest grade as 1 instead of 6 and thereby reduced patient anxiety [17]. This system also classified some of the atypical lesions such as cribriform glands, glomeruloid glands and mucinous carcinoma as Gleason pattern of 4 and thus increased their risk factor [11].

In the light of all these developments, we deemed the usage of ISUP GG system to assess the Gleason grade upgrade from biopsy to surgery. Furthermore, accurate GG identification is necessary not only for the decision of active surveillance and definitive treatment but also for the correct risk stratification of the cancer, informing patient and planning the definitive post-treatment options in advance. As a result, we preferred to report GG upgrading in a heterogeneous cohort who underwent open radical prostatectomy in our hospital. ISUP GG upgrade was observed in 23.9% of our 117 patients. While in our univariate analysis, biopsy ISUP grade, PCF and GPC were significant parameters, only biopsy ISUP GG and GPC kept their significance in the multivariate analysis. In addition, extended EPIe was the only significant surgical pathology parameters which was significantly associated with upgrading in both univariate and multivariate analysis.

Independent predictors of pathology grade upgrading identified in different studies may be listed as non-white race, older age, higher PSA levels, cancer positive biopsy fraction, prostate volume, prostate density and tumor percentage of >50% per core [18-23]. In a recent study, cancer upgrade has been shown to have a positive correlation with increased levels of TNF-alpha and a negative correlation with high levels of IL-6 (24). In an article by Epstein al., GS upgrading from ≤6 to a higher grade happened in 36.3% of 7643 cases [4]. Even after multidisciplinary consultations, tumor upgrades remained high ranging from 43% to 63.8% (20, 21). In their study of 7643 patients, they identified increasing age, PSA levels, maximum percentage of cancer, per core number and decreasing radical prostatectomy specimen weight as predictors of biopsy upgrade from GS of 5-6 (ISUP 1). Greatest percentage of prostate cancer, showing the extension of the tumor in prostate was identified as a significant predictor of upgrading in our investigation, similar to other studies [4,21,23,25]. In a multicenter study of 1159 patients, PSA levels, percent of positive biopsy cores and small prostate volumes were suggested as predictive factors for upgrading [23]. Schiffmann et al. indicated tumor involvement per core (≥50%) as the most strong predictor for upgrading besides the number of positive cores, PSA values and age in their study of 1331 cases [21]. Although positive core fraction could not keep its significance in our multivariate analysis, several studies reported it as a significant predictor [4,18,21]. In another study by Brasetti et al., GG upgrade was reported in 41.4% of the patients with a number of positive biopsy cores and PSA density as the predictors [26]. The relation between positive cores and upgrade of GG 1 cancers was confirmed again in a study of 1966 patients with an upgrade rate of 40% and 59% for very low and low-risk cancers, respectively [27]. Finally Capitanio et al., reported that Gleason upgrade rate was reduced by half (23.5% vs 47.9%, p<0.001) when greater number of biopsy cores were obtained (18 cores vs 10-12 cores) [28].

Extended extraprostatic extension (EPIe) was the only

Table 3. The comparison of ISUP GG upgrading and non-upgrading groups in terms of clinical, biopsy and surgical pathologic parameters

	ISUP Upgrade (-)	ISUP Upgrade (+)	p
n (%)	89 (76.1%)	28 (23.9%)	
Age (years)	61.4 ± 6.9	65.0 ± 6.3	0.8
Clinical stage (Pt1c vs T2)	48 (68.6%) 22 (31.4%)	15 (75%) 5 (25%)	0.58
PSA ng/ml [1]	6.9 (5.7-15)	8.3 (5.2-13.4)	0.54
PSAd [1] (ng/ml^2)	0.19 (0.14-049)	0.19 (0.11-0.38)	0.68
US vol [1] (cc)	39.0 (30.0-50.3)	40.0 (33.0-60.0)	0.85
Calculated vol [1] (cc)	40.5 (29.2-56.4)	39.3 (33.5-62.5)	0.51
Specimen weight [1] (gr)	41.5 (33.5-55.2)	46.5 (36.3-69.7)	0.99
Biopsy ISUP 1 2 3 4 5	 21 (23.6%) 42 (47.2%) 19 (21.3%) 6 (6.7%) 1 (1.1%)	 17 (60.1%) 7 (25.0%) 2 (7.1%) 2 (7.1%) 0 (0%)	**0.01**
PCN [1]	4 (2-6)	3.0 (1.25-5.0)	0.13
PCF [1]	0.33 (0.19-0.44)	0.25 (0.11-0.42)	**0.05**
PCF >50 %	23 (25.8%)	5 (17.9%)	0.38
GPC (%) [1]	0.70 (0.40-0.90)	0.45 (0.3-0.67)	**0.01**
TPC (mm) [1]	1.15 (0.69-2.60)	0.85 (0.36-1.30)	0.06
BCR % [1]	0.09 (0.06-0.20)	0.08 (0.03-0.11)	0.06
TCL (mm) [1]	12.2 (5.7-27.1)	8.6 (2.2-13.1)	0.06
BCR mm [1]	0.09 (0.05-0.23)	0.08 (0.03-0.09)	0.06
Biopsy PIN +	23 (25.8%)	5 (17.9%)	0.38
Surgery PIN +	76 (85.4%)	26 (92.9%)	0.52
Biopsy HGPIN +	11 (12.4%)	7 (25.0%)	0.13
Surgery HGPIN +	68 (76.4%)	24 (85.7%)	0.29
EPI total +	27 (30.3%)	13 (46.4%)	0.11
EPI extended +	16 (18%)	11 (39.3%)	**0.02**
SVI +	6 (6.8%)	4 (14.3%)	0.24
LVI +	3 (3.3%)	2 (7.2%)	0.59
Margin +	30 (33.7%)	11 (39.3%)	0.59
Apex invasion +	41 (46.1%)	13 (46.4%)	0.97
BNI +	10 (11.3%)	5 (17.9%)	0.34
Biopsy bilateral	32 (35.9 %)	10 (35.7 %)	0.98
Surgery bilateral	60 (67.4%)	22 (78.6%)	0.26
Local advanced +	33 (37.1%)	14 (50%)	0.22
Lymph node +	3 (3.4%)	3 (10.7%)	0.15

All the continuous data with abnormal distribution according to Kolmogorov-Smirnov and Shapiro-Wilk test were expressed as median value and interquartile range. Interquartile range in parenthesis were the 25th and 75th percentile values of the data. Continuous data with normal distribution was expressed as mean value and standard deviation (only age in this group US: ultrasound; PCN: positive cores number; PCF: positive core fraction; GPC: greatest percentage of cancer cells in a single core; TPC: total sum of positive core percentages; BCR mm: biopsy core ratio of length (total positive core length in mm/total core length); BCR%: biopsy core ratio of percentages (BCR%: TPC/ (core number x100)); TCL: total core length with cancer; ISUP GG: international society of urological pathology 2014 grade group; PIN: prostatic intraepithelial neoplasia; HGPIN: high grade PIN; EPI: extra prostatic capsule invasion; SVI: seminal vesicle invasion; LVI: lenfo-vascular invasion; BNI: bladder neck invasion

1: The continuous data showed non-normal distribution and therefore expressed as medians (IQR)

Table 4. Binary logistic regression analysis for ISUP upgrade (univariate and multivariate)

	Univariate Analysis		Multivariate Analysis	
	OR (95% CL)	**p**	**OR (95% CL)**	**p**
Biopsy ISUP	0.461 (0.26-0.82)	0.009	0.38 (0.18-0.78)	0.01
Positive core Ffraction (PCF)	0.066 (0.01-0.85)	0.037		
Greatest positive core (GPC)	0.120 (0.02-0.68)	0.016	0.10 (0.02-0.78)	0.03
EPI extended +	2.952 (1.16-7.49)	0.023	14.9 (3.01-71.9)	0.001

Only statistically significant data in the univariate analysis was shown in this table. Binary univariate and multivariate logistic regression analysis was utilized in order to estimate predictive factors. PCF: positive core fraction; GPC: greatest percentage of cancer in a single core; ISUP GG: international society of urological pathology 2014 gradeg; EPI: extra prostatic capsule invasion

significantly associated surgical pathology factor with upgrading in our study. When compared with the non-upgrading group other factors such as SVI (6.8% vs 14.3%), LVI (4.1% vs 9.1%), lymph node positivity (3.9% vs 12%), and surgical pT3 vs pT2 (37.1% vs 50%) showed much higher prevalence in the upgrading group, without any statistical significance. Tilki et al. demonstrated a significantly higher prevalence of these factors (EPE, SVI, LVI, margin positivity) in the upgrading group [5]. In another study by Abedi et al., 32.8% of patients had a Gleason score upgrade, and also they histopathologically detected significantly higher rates of EPI, SVI and positive lymph node invasion in surgical specimens [16]. These results support the idea that Gleason score upgrading in PCa indicates a tendency to become invasive/locally advanced cancers. Some of our results might not attain a level of statistical significance probably due to limited number of patients, but may achieve statistical significance if the study could be performed with larger number of patients.

Limitations of this study are its retrospective nature, inclusion of pathology reports of multiple surgeons and pathologists in the study. The relatively subjective sampling procedure of needle biopsy, especially when performed by different surgeons, may increase heterogeneity of the biopsy group. While all of our identified predictive parameters (PCF, GPC, EPIe) are in accordance with literature, the rates of PCF and GPC were paradoxically lower in the upgrade group. While this finding is in contrast with previous literature which indicates high volume/ extension of tumor leads to tumor upgrading, our data is consistent in its own accord. Total tumor length, BCR% and BCR mm were also lower in the upgrade group in addition to PCF and GPC. As a hypothesis, this discrepancy might be due to the inclusion of all risk groups instead of only lower tier ones. Otherwise, this might also be due to accurate identification of Gleason grade in the biopsy as a result of higher cancer tissue available.

Conclusion

ISUP Grade Groups may allow better understanding of prostate cancer pathologies for both surgeons and pathologists. However, discrepancy between histopathological classifications of biopsy and surgical specimens in terms of PIN, HGPIN, ISUP grade groups still continues. A significant number of patients with low-grade ISUP scores are upgraded in the final pathology. Initial ISUP score and greatest percentage of cancer-positive cores in the biopsy specimens were independent predictors of ISUP upgrade risk. Extended extraprostatic invasion was also significantly higher in the IUSP upgrade group. Tumor upgrade risk should be considered prior to prostate cancer treatment.

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