Original Paper

Histopathological Study of the Prostate Cancer Growth Patterns in Relation with the Grading Systems

TUDOR CRISTIAN TIMOTEI POPESCU[1], ALEX EMILIAN STEPAN[2], MIRELA MARINELA FLORESCU[2], CRISTIANA EUGENIA SIMIONESCU[2]

[1]*PhD Student, Department of Pathology, University of Medicine and Pharmacy of Craiova, Romania*

[2]*Department of Pathology, University of Medicine and Pharmacy of Craiova, Romania*

ABSTRACT: Prostate adenocarcinomas are common lesions with a high incidence and variable prognosis, which can be assessed using tumor grading systems. In this study, we analyzed 329 prostate adenocarcinomas in relation to tumor variants, growth patterns, classical and updated grading systems. The study indicated statistical associations of atrophic, pseudohyperplastic and microcystic variants with low grading scores, the associations of glomeruloid, cribriform with or without necrosis and signet ring-like cell variants with high grading scores, and also of single growth patterns with intermediate scores, which supports the accordance and usefulness of existing grading systems for the identification of aggressive prostate tumor lesions.

KEYWORDS: *Prostate adenocarcinoma, histological patterns, ISUP groups.*

Introduction

Although prostate adenocarcinoma (PA) has a relatively good prognosis compared with other malignant tumors, it raises major problems in clinical practice through the incidence and possible aggressive evolution of some histological subtypes.

Therefore, the individual assessment of the aggressive potential of each tumor is indispensable in the evaluation of clinical decisions in these patients.

The Gleason scoring system introduced by more than half a century ago, has remained one of the strongest prognostic and predictive factors of PA, hence of clinical therapeutic decisions [1].

One of the strengths of the traditional Gleason classification is that it takes into account the lesional heterogenity of PA.

Gleason scores (GS) are based on the classification of architectural patterns of tumors, being a sum of major and minor architectural models, appreciated on the prostate specimen, which varies from 2-10.

Due to this wide range of scores, the International Society of Urological Pathology (ISUP) and the World Health Organization (WHO) have introduced a new grading concept, with GS being assigned grade groups from 1 to 5 [2,3], to better reflect the prognostic implications, with a good reproducibility in the pathological reporting [4].

In reality, this is a different way of grouping GS than a whole new scoring system [2].

Modified Gleason grade has been shown to be one of the strongest prognostic indicators of clinically localized tumors and is one of the best factors used in establishing the management of these patients [5].

The present study aims to identify the different architectural patterns of the PA according to the modified GG and to place them in the corresponding ISUP groups.

Materials and Methods

The present study included a number of 329 cases of PA, the biological material being represented by tissue fragments obtained during prostate biopsy or prostate tumor transurethral resection (TURP), from patients hospitalized to the Urology Clinic of the Emergency County Clinical Hospital Craiova for a period of 4 years (2018-2021).

The tumor fragments were fixed in 10% buffered formalin, processed by the usual paraffin embedding technique and stained with Hematoxylin-Eosin in the Pathology Department of the same hospital.

We aimed to quantify the growth patterns in relation to the ISUP groups, according to the WHO/ISUP recommendations [2,3].

For the statistical analysis we used comparison tests ($\chi 2$ test) within the SPSS 10 software (Statistical Package for the Social Sciences), the p values <0.05 being considered significant.

The study was approved by the Ethics Committee of the University of Medicine and Pharmacy of Craiova, and written informed consents were obtained from patients.

10.12865/CHSJ.48.01.14

Results

The study included 329 PAs that corresponded: 109 cases to GS 6/ISUP 1, 41 cases to GS 7/ISUP 2, 25 cases to GS 7/ISUP 2, 69 cases to GS 8/ISUP 4 and 85 cases to GS 9 and 10/ISUP 5 (Table 1).

Table 1. Distribution of cases related to PA variants and grading systems.

Gleason grading scores/ growth patterns	**6/ 3+3**	**7/ 3+4**	**7/ 4+3**	**8/ 3+5**	**8/ 5+3**	**8/ 4+4**	**9/ 4+5**	**9/ 5+4**	**10/ 5+5**	**Total**
ISUP grading groups	**1**	**2**	**3**		**4**			**5**		
Conventional (acinar)	51	23	14	12	2	22	22	7	35	**188**
Foamy gland	19	10	7	3	1	12	-	-	7	**59**
Conventional/ foamy gland	15	3	2	2	-	10	-	4	-	**36**
Conventional/ atrophic	14	3	2	-	-	-	-	-	-	**19**
Conventional/ microcystic	6	-	-	-	-	-	-	-	-	**6**
Conventional/ pseudohyperplastic	4	2	-	-	-	-	-	-	-	**6**
Conventional/ cribriform	-	-	-	-	3	-	-	-	-	**3**
Conventional/ glomeruloid	-	-	-	-	2	-	-	-	-	**2**
Conventional/ cribriform/comedonecrosis	-	-	-	-	-	-	-	3	2	**5**
Conventional/ signet ring-like cell	-	-	-	-	-	-	-	-	5	**5**

The analysis of the architectural and cytological patterns of PA indicated in 247 (75%) cases the presence of single patterns, for the remaining 82 (25%) cases two histological patterns being associated.

In 109 cases (33.1%) we identified PAs corresponding to GS 6 (3+3)/ISUP 1.

In 70 cases we found the presence of single patterns, represented by the conventional or foamy gland type (Figure 1A).

In 39 cases associated patterns were present, respectively conventional and foamy gland, conventional and atrophic, conventional and microcystic, conventional and pseudohyperplastic.

We found 41 cases (12.5%) for PAs corresponding to GS 7 (3+4)/ISUP 2.

The single patterns were present in 33 cases, also with conventional or foamy gland appearance (Figure1B-C).

We identified the associated patterns in 8 cases, represented by the coexistence of the conventional pattern with foamy gland, conventional and atrophic, conventional and pseudohyperplastic.

For the PAs corresponding to GS 7 (4+3)/ISUP 3 we identified 25 cases (7.6%).

The single patterns were present in 21 cases, with a conventional or foamy gland appearance (Figure 1D).

We observed the associated patterns only in 4 cases, represented by the coexistence of the conventional with foamy gland or atrophic patterns.

For PAs corresponding to GS 8/ISUP 4 we found 69 cases (21%), which included for GS (3+5) 17 cases, GS (5+3) 8 cases and GS (4+4) 22 cases.

Single tumor patterns were observed in 57 cases, which had a conventional or foamy gland appearance (Figure 1E).

The associated patterns were present in 17 cases, in which there were conventional aspects with foamy gland, conventional and cribriform, conventional and glomeruloid (Figure 1F-G).

For PAs corresponding to GS 9 and 10/ISUP 5 we found 85 cases (25.8%), which included for GS (4+5) 22 cases, GS (5+4) 14 cases and for GS (5+5) 49 cases.

Single tumor patterns were observed in 71 cases, which present a conventional or with foamy gkland pattern.

The associated patterns were present in 14 cases, in which there were conventional aspects with foamy gland, conventional and cribriform with comedonecrosis, conventional and with signet ring-like cells (Figure 1H).

10.12865/CHSJ.48.01.14

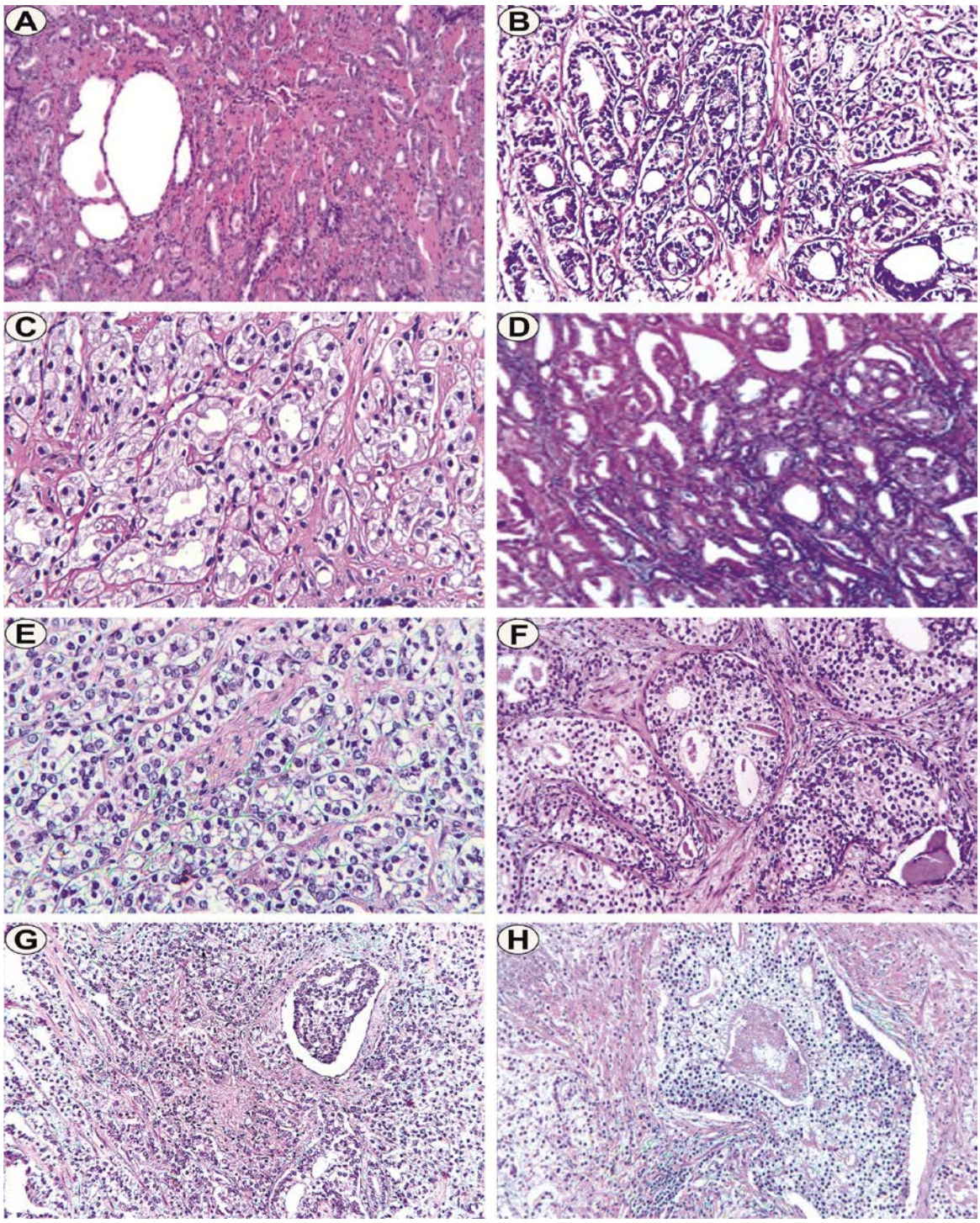

Figure 1. Prostate adenocarcinoma. A. Conventional and atrophic patterns, GS 6 (3+3)/ISUP 1, HE staining, x200; B. Conventional pattern, GS 7 (3+4)/ISUP 2, HE staining, x400; C. Foamy gland pattern, GS 7 (3+4)/ISUP 2, HE staining, x400; D. Conventional pattern, GS 7 (4+3)/ISUP 3, HE staining, x200; E. Foamy gland pattern, GS 8 (4+4)/ISUP 4, HE staining, x400; F. Conventional and cribriform patterns GS 8/ISUP 4, HE staining, x200; G. Conventional and glomeruloid patterns GS 8/ ISUP 4, HE staining, x200; H. Conventional and cribriform wirh comedonecrosis patterns, GS 10/ ISUP 5, HE staining, x200.

Statistical analysis of the investigated PA typs indicated the association of low 6/7 Gleason scores with adenocarcinomas with atrophic, pseudohyperplastic and microcystic patterns and of high Gleason scores 8-10 with those with glomeruloid component, cribriform with or without comedonecrosis and signet ring-like cell, while single pattern conventional tumors or those with foamy gland showed variable scores ($p<0.001$, test $\chi 2$) (Figure2A), aspects that were also observed in the case of associations with growth patterns ($p<0.001$, test $\chi 2$) (Figure2B) and with ISUP grading groups ($p<0.001$, test $\chi 2$) (Figure2C).

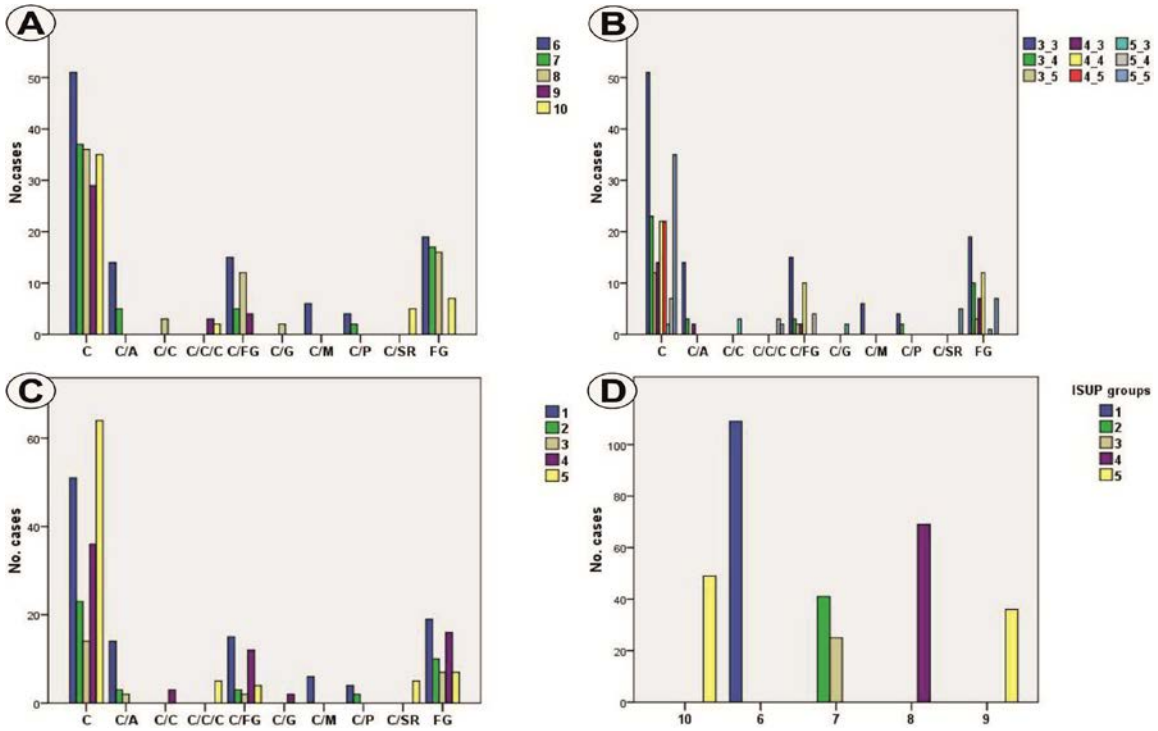

Figure 2. A. Distribution of cases in relation to the PA variants and Gleason Score; B. Distribution of cases in relation to the PA variants and the growth pattern; C. Distribution of cases in relation to PA variants and ISUP grading groups; D. Distribution of cases in relation to the Gleason Score and ISUP grading groups.

Note* C=conventional; C/A=conventional/atrophic; C/C=conventional/cribiform; C/C/C=conventional/cribiform/ comedonecrosis; C/FG=conventional/foamy glands; C/G=conventional/glomeruloid; C/M=conventional/microcystic; C/P=conventional/pseudohyperplastic; C/SR=conventional/signet ring-like cells; FG=foamy glands.

At the same time we found the association of low Gleason scores 6/7 with ISUP groups 1-3 and of the Gleason high scores 8-10 with ISUP groups 4-5 ($p<0.001$, test $\chi 2$) (Figure2D), which supports the utility of these systems for identifying aggressive PAs.

Discussion

Despite the interobserver variation between pathologists, the histopathological gradation of PA remains the strongest prognostic indicator of disease recurrence and death, as well as the main tool for stratifying patients for different treatment options [6].

The classification of PA has changed considerably over time, mainly due to major advances in diagnostic approaches and procedures, as well as early detection of the disease.

Several changes have been made to improve the prognostic significance of various tumor groups, in order to reduce interobserver variability and to increase the agreement between prostate biopsy and radical prostatectomy [7].

During the 2014 ISUP Consensus Conference on PA Classification, a number of amendments were adopted and subsequently included in the 2016 WHO Classification [3].

Thus, the latest classification according to the groups of degrees recommended by the WHO/ISUP is based on GS, which is evaluated on the basis of architectural models.

The prognostic use of ISUP degrees has been validated by several studies [8-14].

One of the most important reasons of using ISUP terminology, is the acceptance of active surveillance by patients with PAs with ISUP grade 1, equivalent to GS 6.

In the case of PAs with GS 6, the assessment is made on a scale between 1-10 which suggests an intermediate grade, these tumors being more suitable classified by ISUP grading in the lowest grade group, respectively group 1 out of 5.

Such an approach informs both physicians and patients about the relatively indolent nature of this PA group [11], therefore, it reduces the overtreatment of indolent prostate cancer.

Also, the application of these groups is helpful to clinicians in the management of heterogeneous PAs with variable prognosis, such as those with GS 7 that can be included in ISUP groups 2 or 3, groups associated with different prognosis and therefore with different therapeutic approaches [7].

10.12865/CHSJ.48.01.14

ISUP grade 3 is defined by the presence of well-differentiated glands, often with variable-sized and tubular architecture, separated from each other by stroma.

A particular aspect of this group, which should not be underestimated, is the evaluation of specific PA variants, which can look deceptively benign, respectively the atrophic, pseudohyperplastic or foamy gland variant, similar situations being observed in the case of micronodular architecture, or similar variants of PIN (prostate intraepithelial neoplasia), mucinous or collagenous (mucinous fibroplasia) [11,15-18].

The most recent WHO classification emphasizes that atrophic, pseudohypertrophic, with foamy and microcystic glands, which may have a deceptively benign appearance, are attributed to pattern 3 [3,18].

In our study, the atrophic, pseudohyperplastic and microcystic variants were identified only in patterns associated with the conventional acinar appearance, which imposed the final Gleason score, most cases being ISUP group 1 or 2.

The same ISUP classification was present in the case of the foamy gland variant, which was observed as a single pattern in 17.9% of cases, and in a pattern associated with the conventional one in 10.9% of cases.

ISUP grade 4 includes fused glands with small and large sizes, poorly formed, as well as tumors with glomeruloid and cribriform architecture [11,19].

In one study, the prevalence of pattern 4 submodels in prostate biopsies it was: 75% merged pattern, 64% undefined, 48% cribriform and 25% glomeruloid [6].

Several models of tumor growth initially considered as pattern 3, have been redefined as pattern 4 [20].

Thus, the small cribriform glands and the glomeruloid appearance were reconsidered and it is recommended that both models be classified as pattern 4 [21-23].

Several studies have shown that the glomeruloid model, considered specific for PA, is associated with a reduced risk of biochemical recurrence after radical prostatectomy [24,25], but compared with pure pattern 3 the prognosis was unfavorable, justifying the inclusion in pattern 4 category [20,25].

In our study, in the ISUP 4 group, the single or associated conventional or with foamy glands patterns predominated, as well as a limited number of PAs that associated to the conventional pattern the cribiform or glomeruloid aspects.

Several studies have indicated a more unfavorable evolution and biochemical recurrence for GS 4+3 compared to GS 3+4 [11,26].

As a result, by separating PA with GS 7 into 2 categories, 3+4=7 (ISUP grade 2) and 4+3=7 (ISUP grade 3), the proportion of ISUP grade 4 was at least partially included in the patient management algorithms [26-28], several studies reporting clinical significance for ISUP group 4 quantification [29-34].

A number of studies have shown that patients with the cribriform model [35] have survival without biochemical relapses, survival without metastases, and cancer-specific survival is more unfavorable than those without this pattern [19].

The value of this pattern has been studied especially for patients with GS 7, but has been shown to have independent prognostic value in PA GS 8 with pattern 4 [36], unlike PA with GS 9 in which its role remains uncertain [33].

ISUP grade 5 includes PAs without glandular features or lumen formation.

Several particular patterns can be distinguished, such as comedonecrosis, infiltrative cords, and the solid pattern [37,38].

The presence of comedonecrosis even in a single gland (focal comedonecrosis) [37], as well as signet ring-like cell with unicellular aspects or in larger cell groups, are also considered pattern 5.

In prostate biopsies the patterns with infiltrative cords without formation of lumens and single cells have been reported as the most common grade patterns 5, the most uncommon being comedocarcinoma [39].

With the reclassification of PA with GS 8-10 (considered a single high-grade subgroup), in two specific 4-5 patterns, clinicians can better differentiate the prognosis and clinical risk associated with the disease [11,26].

In this study, in the ISUP 5 group, in addition to the conventional pattern, we found a significant number of cases of PA with mixed patterns, rspectively conventional in association with cribriform with comedonecrosis and signet ring-like cell patterns.

While for less than half of patients with PA, the tumor can be life-threatening (Gleason score ≥7), many patients have low-risk disease and are still undergoing radical prostatectomy [3].

For the latter, active surveillance has become a widely used alternative after the diagnosis of PA, even if up to 33% of patients in active

surveillance need therapeutic intervention after a period of 1.2-3.5 years [4-8].

Therefore, a better stratification of PA patients in terms of clinical decision is needed, especially in the predominant group of low-and medium-risk of the PA.

Conclusions

In this study, we found the association of prostate adenocarcinoma variants with classic and updated Gleason growth patterns and ISUP grading systems.

Statistical concordance of lesion grading systems indicates their usefulness for identifying aggressive prostate tumors in determining the management of these patients.

Conflict of interests

None to declare.

References

1. van Santvoort BWH, van Leenders GJLH, Kiemeney LA, van Oort IM, Wieringa SE, Jansen H, Vernooij RWM, Hulsbergen-van de Kaa CA, Aben KKH. Histopathological re-evaluations of biopsies in prostate cancer: a nationwide observational study. Scand J Urol, 2020, 54(6):463-469.
2. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA; Grading Committee. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol, 2016, 40(2):244-252.
3. Moch H, Humphrey PA, Ulbright TM, Reuter VE, editors. Tumors of the prostate. In: International Agency for Research on Cancer (Eds.): WHO Classification of Tumours of the Urinary System and Male Genital Organs, IARC Press, 2016, Lyon, France, 135-183.
4. Khochikar M. Newly Proposed Prognostic Grade Group System for Prostate Cancer: Genesis, Utility and its Implications in Clinical Practice. Curr Urol Rep, 2016, 17(11):80.
5. Humphrey PA. Histopathology of Prostate Cancer. Cold Spring Harb Perspect Med, 2017, 7(10):a030411.
6. Kweldam CF, van Leenders GJ, van der Kwast T. Grading of prostate cancer: a work in progress. Histopathology, 2019, 74(1):146-160.
7. Cimadamore A, Scarpelli M, Raspollini MR, Doria A, Galosi AB, Massari F, Di Nunno V, Cheng L, Lopez-Beltran A, Montironi R. Prostate cancer pathology: What has changed in the last 5 years. Urologia, 2020, 87(1):3-10.
8. Delahunt B, Egevad L, Srigley JR, Steigler A, Murray JD, Atkinson C, Matthews J, Duchesne G, Spry NA, Christie D, Joseph D, Attia J, Denham JW. Validation of International Society of Urological Pathology (ISUP) grading for prostatic adenocarcinoma in thin core biopsies using TROG 03.04 'RADAR' trial clinical data. Pathology, 2015, 47(6):520-525.
9. Samaratunga H, Delahunt B, Gianduzzo T, Coughlin G, Duffy D, LeFevre I, Johannsen S, Egevad L, Yaxley J. The prognostic significance of the 2014 International Society of Urological Pathology (ISUP) grading system for prostate cancer. Pathology, 2015, 47(6):515-519.
10. Berney DM, Beltran L, Fisher G, North BV, Greenberg D, Møller H, Soosay G, Scardino P, Cuzick J. Validation of a contemporary prostate cancer grading system using prostate cancer death as outcome. Br J Cancer, 2016, 114(10):1078-1083.
11. Epstein JI, Zelefsky MJ, Sjoberg DD, Nelson JB, Egevad L, Magi-Galluzzi C, Vickers AJ, Parwani AV, Reuter VE, Fine SW, Eastham JA, Wiklund P, Han M, Reddy CA, Ciezki JP, Nyberg T, Klein EA. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. Eur Urol, 2016, 69(3):428-435.
12. Spratt DE, Cole AI, Palapattu GS, Weizer AZ, Jackson WC, Montgomery JS, Dess RT, Zhao SG, Lee JY, Wu A, Kunju LP, Talmich E, Miller DC, Hollenbeck BK, Tomlins SA, Feng FY, Mehra R, Morgan TM. Independent surgical validation of the new prostate cancer grade-grouping system. BJU Int, 2016, 118(5):763-769.
13. Spratt DE, Jackson WC, Abugharib A, Tomlins SA, Dess RT, Soni PD, Lee JY, Zhao SG, Cole AI, Zumsteg ZS, Sandler H, Hamstra D, Hearn JW, Palapattu G, Mehra R, Morgan TM, Feng FY. Independent validation of the prognostic capacity of the ISUP prostate cancer grade grouping system for radiation treated patients with long-term follow-up. Prostate Cancer Prostatic Dis, 2016, 19(3):292-297.
14. Gordetsky J, Epstein J. Grading of prostatic adenocarcinoma: current state and prognostic implications. Diagn Pathol, 2016, 11:25.
15. Humphrey PA. Variants of acinar adenocarcinoma of the prostate mimicking benign conditions. Mod Pathol, 2018, 31(S1):S64-S70.
16. Arista-Nasr J, Martínez-Benítez B, Aguilar-Ayala EL, Aleman-Sanchez CN, Bornstein-Quevedo L, Albores-Saavedra J. Pseudohyperplastic prostate carcinoma: histologic patterns and differential diagnosis. Ann Diagn Pathol, 2015, 19(4):253-260.
17. Hameed O, Humphrey PA. Stratified epithelium in prostatic adenocarcinoma: a mimic of high-grade prostatic intraepithelial neoplasia. Mod Pathol, 2006, 19(7):899-906.
18. Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part B: Prostate and Bladder Tumours. Eur Urol, 2016, 70(1):106-119.
19. Iczkowski KA, Paner GP, Van der Kwast T. The New Realization About Cribriform Prostate Cancer. Adv Anat Pathol, 2018, 25(1):31-37.
20. Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL; ISUP Grading Committee. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol, 2005, 29(9):1228-1242.
21. Epstein JI. An update of the Gleason grading system. J Urol. 2010, 183(2):433-440.

 10.12865/CHSJ.48.01.14

22. Latour M, Amin MB, Billis A, Egevad L, Grignon DJ, Humphrey PA, Reuter VE, Sakr WA, Srigley JR, Wheeler TM, Yang XJ, Epstein JI. Grading of invasive cribriform carcinoma on prostate needle biopsy: an interobserver study among experts in genitourinary pathology. Am J Surg Pathol, 2008, 32(10):1532-1559.
23. Lotan TL, Epstein JI. Gleason grading of prostatic adenocarcinoma with glomeruloid features on needle biopsy. Hum Pathol, 2009, 40(4):471-477.
24. Kweldam CF, Wildhagen MF, Steyerberg EW, Bangma CH, van der Kwast TH, van Leenders GJ. Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer. Mod. Pathol, 2015, 28:457-464.
25. Choy B, Pearce SM, Anderson BB, Shalhav AL, Zagaja G, Eggener SE, Paner GP. Prognostic Significance of Percentage and Architectural Types of Contemporary Gleason Pattern 4 Prostate Cancer in Radical Prostatectomy. Am J Surg Pathol, 2016, 40(10):1400-1406.
26. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU Int, 2013, 111(5):753-760.
27. Sakr WA, Tefilli MV, Grignon DJ, Banerjee M, Dey J, Gheiler EL, Tiguert R, Powell IJ, Wood DP. Gleason score 7 prostate cancer: a heterogeneous entity? Correlation with pathologic parameters and disease-free survival. Urology, 2000, 56(5):730-734.
28. Chan TY, Partin AW, Walsh PC, Epstein JI. Prognostic significance of Gleason score 3+4 versus Gleason score 4+3 tumor at radical prostatectomy. Urology, 2000, 56(5):823-827.
29. Cole AI, Morgan TM, Spratt DE, Palapattu GS, He C, Tomlins SA, Weizer AZ, Feng FY, Wu A, Siddiqui J, Chinnaiyan AM, Montgomery JS, Kunju LP, Miller DC, Hollenbeck BK, Wei JT, Mehra R. Prognostic Value of Percent Gleason Grade 4 at Prostate Biopsy in Predicting Prostatectomy Pathology and Recurrence. J Urol, 2016, 196(2):405-411.
30. Dean LW, Assel M, Sjoberg DD, Vickers AJ, Al-Ahmadie HA, Chen YB, Gopalan A, Sirintrapun SJ, Tickoo SK, Eastham JA, Scardino PT, Reuter VE, Ehdaie B, Fine SW. Clinical Usefulness of Total Length of Gleason Pattern 4 on Biopsy in Men with Grade Group 2 Prostate Cancer. J Urol, 2019, 201(1):77-82.
31. Huang CC, Deng FM, Kong MX, Ren Q, Melamed J, Zhou M. Re-evaluating the concept of "dominant/index tumor nodule" in multifocal prostate cancer. Virchows Arch, 2014, 464(5):589-594.
32. Kır G, Seneldir H, Gumus E. Outcomes of Gleason score 3+4=7 prostate cancer with minimal amounts (<6%) vs≥6% of Gleason pattern 4 tissue in needle biopsy specimens. Ann Diagn Pathol, 2016, 20:48-51.
33. Iczkowski KA, Torkko KC, Kotnis GR, Wilson RS, Huang W, Wheeler TM, Abeyta AM, La Rosa FG, Cook S, Werahera PN, Lucia MS. Digital quantification of five high-grade prostate cancer patterns, including the cribriform pattern, and their association with adverse outcome. Am J Clin Pathol, 2011, 136(1):98-107.
34. Billis A, Guimaraes MS, Freitas LL, Meirelles L, Magna LA, Ferreira U. The impact of the 2005 international society of urological pathology consensus conference on standard Gleason grading of prostatic carcinoma in needle biopsies. J Urol, 2008, 180(2):548-552; discussion 552-553.
35. Cheng L, Davidson DD, Lin H, Koch MO. Percentage of Gleason pattern 4 and 5 predicts survival after radical prostatectomy. Cancer, 2007, 110(9):1967-1972.
36. Harding-Jackson N, Kryvenko ON, Whittington EE, Eastwood DC, Tjionas GA, Jorda M, Iczkowski KA. Outcome of Gleason 3+5=8 Prostate Cancer Diagnosed on Needle Biopsy: Prognostic Comparison with Gleason 4+4=8. J Urol, 2016, 196(4):1076-1081.
37. McKenney JK, Wei W, Hawley S, Auman H, Newcomb LF, Boyer HD, Fazli L, Simko J, Hurtado-Coll A, Troyer DA, Tretiakova MS, Vakar-Lopez F, Carroll PR, Cooperberg MR, Gleave ME, Lance RS, Lin DW, Nelson PS, Thompson IM, True LD, Feng Z, Brooks JD. Histologic Grading of Prostatic Adenocarcinoma Can Be Further Optimized: Analysis of the Relative Prognostic Strength of Individual Architectural Patterns in 1275 Patients From the Canary Retrospective Cohort. Am J Surg Pathol, 2016, 40(11):1439-1456.
38. Fajardo DA, Miyamoto H, Miller JS, Lee TK, Epstein JI. Identification of Gleason pattern 5 on prostatic needle core biopsy: frequency of underdiagnosis and relation to morphology. Am J Surg Pathol, 2011, 35(11):1706-1711.
39. Shah RB, Li J, Cheng L, Egevad L, Deng FM, Fine SW, Kunju LP, Melamed J, Mehra R, Osunkoya AO, Paner GP, Shen SS, Tsuzuki T, Trpkov K, Tian W, Yang XJ, Zhou M. Diagnosis of Gleason pattern 5 prostate adenocarcinoma on core needle biopsy: an interobserver reproducibility study among urologic pathologists. Am J Surg Pathol, 2015, 39(9):1242-1249.

Corresponding Author: Alex Emilian Stepan, Department of Pathology, University of Medicine and Pharmacy of Craiova, 66 1 May Avenue, 200628 Craiova, Romania, e-mail: astepan76@yahoo.com