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EDITORIAL

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Parallel Processing of Biopsies Increases Precision of Diagnosis in Prostate Cancer

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ABSTRACT

Introduction: The Gleason classification system for prostate cancer is the most widely used method worldwide in both research and clinical practice. This study aims to evaluate the upstaging vs downstaging given to the Gleason score from conventional needle biopsy vs radical prostatectomy and BxChip™ biopsy vs radical prostatectomy.

Material and methods: This study was conducted in the Clinical Hospital of Urology "Prof. Dr. Theodor Burghel" and 341 prostate cancer patients were admitted to the clinic between 2010 and 2016, out of which 51 (2010-2011) had conventional biopsies performed and 291 (2012-2016) underwent biopsies with BxChip™. The collected cores were processed individually for the patients analyzed in 2010 and 2011. Starting in 2012 the biopsies were placed directly in the LUMEA BxChip™, which allows parallel processing, sectioning, staining and microscopic analysis.

Results: A symmetrical approximation of the Gleason score differences is observed for the BxChip group with a marked trend for the lack of difference ($\cong 69\%$), while for the Classic group the median trend is also for the lack of differentiation, but with a significantly lower weight ($\cong 43\%$) and a high weight for undervaluation (down 1 and 2) of $\cong 43\%$. Following the analysis of the ordinal logistic regression, a 1.5 (C.I. 95% 1.24 ÷ 1.84) times higher chance of obtaining under valuations was identified in the Classic group than in the group where the biopsy was performed with the BxChip™. The trend is statistically significant for a Wald test value $\chi^2=16.60$, $df=1$, and $p.<001$

Conclusion: Gleason biopsy scores were compared, and the logistic regression analyzes showed greater consistency in the BxChip™ group compared to the conventional biopsy group, the difference being statistically significant in all categories (Gleason score, Major and Minor patterns, ISUP Score). We conclude that the use of BxChip™ in medical practice of is a real innovation in the correct classification of prostate cancer.

Keywords: gleason score, ISUP score, LUMEA BxChip™, prostate cancer.

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Introduction: The Gleason classification system for prostate cancer is the most widely used method worldwide in both research and clinical practice. It is based on the glandular architecture and must be applied on all prostate tissue samples, including prostate needle biopsies (PNB) and radical prostatectomy (RP) specimens [1,2]. The Gleason classification system shows a reasonable degree of correlation between biopsy samples and radical prostatectomy. However, discrepancies have been identified between these 2 types of specimens and further clinical practice studies are needed to reach a better consensus and accuracy in using the Gleason system. The International Society of Urological Pathology (ISUP) decided to change the 2005 Gleason score at the 2014 Consensus Conference, clarifying the morphological criteria. In addition to compulsory reporting of Gleason scores, they also recommended that Gleason scores ≤ 6 , $3+4 = 7$, $4+3 = 7$, 8, and 9-10 respectively, be reported as five groups, *i.e.*, ISUP classes 1-5. This new classification system has the dual advantage of predicting the patient's prognosis, as well as facilitating communication with the patient [3-5].

Purpose: In medical practice, the use of the Gleason score is essential for the treatment decision in prostate cancer. The BxChip™ was initially validated for reducing the escalating costs of the ever increasing number of cores per patient collected during prostate biopsy [6,7]. However, it became quickly apparent [8] that the BxChip™: *i)* reduces linear fragmentation of biopsy cores, *ii)* eliminates completely non-linear fragments, and *iii)* increases tissue yield of every core being present on the diagnostic microslides, *iv)* has the potential to increase the accuracy of the diagnostic.

This study aims to evaluate the upstaging vs downstaging given to the Gleason score from conventional needle biopsy vs radical prostatectomy and BxChip™ biopsy vs radical prostatectomy.

Materials and methods:

This study was conducted in the Clinical Hospital of Urology "Prof. Dr. Theodor Burghele" and 341 prostate cancer patients were admitted to the clinic between 2010 and 2016, out of which 51 (2010-2011) had conventional biopsies performed and 291 (2012-2016) underwent biopsies with BxChip™. Contact anesthetic (lidocaine gel 2g) was used, and the biopsy was conducted with a 18G biopsy needle (Bard Medical, Covington, GA, USA). In 2010 and 2011 the sextant biopsy method was largely used but since 2012 it was largely replaced by the 12-fragment biopsy scheme, resulting in a better correlation between the Gleason PNB score and the Gleason RP score. The prostatic biopsies were collected, processed, sectioned, stained and examined individually for the patients analyzed in 2010 and 2011, and starting from 2012 the fragments collected from the patients were immediately placed in the LUMEA BxChip™, a sectionable matrix system created for multiplexing core biopsies (Fig.1).

Themis BxChip™ is a biomimetic sectionable matrix with 1 mm wide channels that can accommodate 6 prostate biopsy cores in a single chip. The biomimetic properties of the chip allow it to be processed, sectioned, and stained similarly to human tissue. The separators and markers (dots or numbers) between each channel allow the unambiguous identification of each individual core.



Fig. 1 BxChip™ for prostatic cancer



Fig.2 BxChip™ in paraffin block

All cases had a radical open retropubic extraperitoneal prostatectomy.

The microscopical examination of the fragments obtained from the prostate needle biopsy was performed in the hospital's pathology laboratory, and each histopathological result was interpreted by the consensus of 3 trained uropathologists.

Patients whose Gleason score could not be pre-operatively documented and those whose pathology examination was performed in another clinic were excluded. Also excluded were patients who have already started neoadjuvant therapy, which could interfere with the postoperative Gleason score [9,10]. For each patient, preoperative staging was performed by analyzing samples obtained by prostate needle biopsy and by calculating the Gleason score [11]. The prostatectomy sample was fixed in 10%

formaldehyde, marked with India ink, grossed, processed and sectioned in the pathology laboratory according to current guidelines [12-14].

Results:

The patients' ages ranged from 47 to 80 years with an average of $\cong 65$ years (64.74 ± 5.86). The BxChip™ group has an average age ($m_{65} \cong$; $sd=5.75$), higher than for the Classic group ($m_{63.5} \cong$; $sd=6.42$), but following the application of the *t* test comparison for independent samples, the age distribution for the two groups was similar ($t(338)=1.68$ and $p>.05$). The two samples are part of a population aged between 45 and 80 years, with an average age that can vary between 64 and 65.5 years (C.I. 95% 64 ÷ 65.5). We will consider the two age distributions approximately equal.

Descriptive indicators of the age distribution of patients

Group	N	min	Max	m	sd	sk	k	t (df)	p
BxChip™	290	47	80	64.97	5.75	-.21	-.10	1.68 (338)	NA
Classic	50	50	75	63.46	6.42	-.20	-.57		
Total	340	47	80	64.74	5.86	-.23	-.17	C.I. 95% (64.18 – 65.42)	

Note: N – number of subjects, m – arithmetic mean, sd – standard deviation, sk – asymmetry coefficient, k – vault coefficient, t – t test value for independent samples, df – degree of freedom, p – level of statistical

The two groups were compared based on the Gleason score obtained from the initial biopsy. Description table of the distributions of the Gleason score, Major pattern, Minor pattern, ISUP Score categories measured after biopsy for the two groups of patients.

Category	BxChip™		Classic		Total		χ ²	p	
	N	%	N	%	N	%			
Gleason score	5	0	0.0	2	3.9	2	0.6	11.26	.010
	6	32	11.0	14	27.5	46	13.5		
	7	191	65.6	27	52.9	218	63.7		
	8	61	21.0	7	13.7	68	19.9		
	9	7	2.4	1	2.0	8	2.3		
Major pattern Gleason	2	0	0.0	1	2.0	1	0.3	.47	NA
	3	162	55.7	30	58.8	192	56.1		
	4	128	44.0	20	39.2	148	43.3		
	5	1	0.3	0	0.0	1	0.3		
Minor pattern Gleason	2	0	0.0	1	2.0	1	0.3	9.18	.010
	3	93	32.0	27	52.9	120	35.1		
	4	192	66.0	22	43.1	214	62.6		
	5	6	2.1	1	2.0	7	2.0		
ISUP Score	1	32	11.0	16	31.4	48	14.0	16.54	.002
	2	130	44.7	15	29.4	145	42.4		
	3	61	21.0	12	23.5	73	21.3		
	4	61	21.0	7	13.7	68	19.9		
	5	7	2.3	1	2.0	8	2.3		

Note: χ² – value of the Chi-square test, p – level of significance of the test value.

The following statistically significant results were obtained from the ordinal logistic regression analyzes: For the Gleason score categories the median level (7) reached $\cong 67\%$ in the case of the BxChip™ group and $\cong 84\%$ in the case of the Classic method. The regression analysis identified a chance of 1.38 (C.I. 95% 1.14 – 1.68) times higher in the case of the BxChip™ group to show a higher level than in the Classic group, with a statistically significant chance difference for a Wald Chi-square value=10.68 df=1 and p.<01; For the Minor Gleason pattern categories, the median level for BxChip™ is 4 and comprises a proportion of 98% of patients, while for Classic the median level is 3. The regression analysis identified a 1.28 (95% 1.10 – 1.50) chance of BxChip™ being at a higher level than in the Classic group, with a statistically significant chance

difference for a Wald Chi-square=10.35 df=1 and p.<01. In the case of ISUP Scor categories, the median category (2) for BxChip™ is $\cong 56\%$ of patients, and the proportion for the Classic group is $\cong 61\%$. Regression analysis showed a 1.40 (95% 1.03 – 1.90) chance of the BxChip™ showing a higher level than in the Classic group, with a statistically significant chance difference for a Wald Chi-square value=4.66 df=1 and p.<05.

Following prostatectomy, the distribution of the Gleason scores for the patients of the two groups showed the following differences:

Description table of the distributions of the categories: Gleason score, Major and Minor patterns, ISUP Score measured after prostatectomy for the two groups.

	Category	BxChip™		Classic		Total		X ²	p
		N	%	N	%	N	%		
Gleason score	6	7	2.4	3	5.9	10	2.9	4.76	NA
	7	259	89.0	40	78.4	299	87.4		
	8	11	3.8	3	5.9	14	4.1		
	9	14	4.8	5	9.8	19	5.6		
Major pattern	3	141	48.5	29	56.9	170	49.7	1.36	NA
	4	149	51.2	22	43.1	171	50.0		
	Gleason	5	1	0.3	0	0.0	1		
Minor pattern	3	132	45.4	17	33.3	149	43.6	4.17	NA
	4	146	50.2	29	56.9	175	51.2		
	Gleason	5	13	4.4	5	9.8	18		
ISUP Score	1	9	3.1	3	5.9	12	3.5	5.73	NA
	2	134	46.0	26	51.0	160	46.8		
	3	122	41.9	14	27.5	136	39.8		
	4	12	4.1	3	5.9	15	4.4		
	5	14	4.8	5	9.8	19	5.6		

Note: χ^2 – value of the Chi-square test, p – level of significance of the test value.

- There are major proportions of grade 7 Score Gleason for both groups, 89% in the case of BxChip™ and 78.4% in the case of the Classic group, the difference between the two trends is not statistically significant for a test value $\chi^2=4.76$, df=3 and p>.05. Major pattern grades 3 and 4 have roughly equal percentages in the BxChip™ group, 48.5% grade 3 and 51.2% grade 4, while in the Classic group the Major pattern percentage was observed in grade 3 (56.9%), and grade 4 showed a proportion of 43.1%. According to the comparison test of the two distributions, the trend difference is not statistically significant for a test value $\chi^2=1.36$, df=2, and p>.05. For the BxChip™ group, the Minor

pattern has a greater percentage for grade 4 (50.2%), while grade 3 has 45.4%. This also occurs in the Classic group, where the higher percentage was observed in the grade 4 (56.9%), while grade 3 showed a percentage of 33.3%. According to the comparison test of the two distributions, the trend difference is not statistically significant with a test value $\chi^2=4.17$, df=2, and p>.05. Following the non-differentiation of the two distributions, the analysis of ordinal logistic regression was no longer applied. The difference between the score obtained from the prostatectomy and the score obtained from the biopsy was coded as follows:

- Up (1, 2, >2) – biopsy Gleason score > prostatectomy Gleason score, overvaluation.

Description table of Score Gleason difference distributions on the two lots.

		Difference Gleason score (total)					Total	χ^2	P
		up 2	up 1	same	down 1	down 2			
BxChip™	Count	5	45	201	36	4	291	27.64	.001
	%	1.7%	15.5%	69.1%	12.4%	1.4%	100.0%		
Classic	Count	0	7	22	18	4	51		
	%	0.0%	13.7%	43.1%	35.3%	7.8%	100.0%		
Total	Count	5	52	223	54	8	342		
	%	1.5%	15.2%	65.2%	15.8%	2.3%	100.0%		

Note: χ^2 – value of the Chi-square test, p – level of significance of the test value.

A symmetrical approximation of the score differences is observed for the BxChip™ group with a marked trend for the lack of difference ($\cong 69\%$), while for the Classic group the median trend is also for the lack of differentiation, but with a significantly lower weight ($\cong 43\%$) and a high weight for under valuations (down 1 and 2) of $\cong 43\%$. Following the analysis of the ordinal logistic regression, a 1.5 (C.I. 95% 1.24 ÷ 1.84) times higher chance of obtaining under valuations in the Classic biopsy group than in the BxChip™ group was identified. The trend is statistically significant for a Wald test value $\chi^2=16.60$, $df=1$, and $p<001$. In both groups, major trends are observed for the lack of difference between the two Gleason scores (prostatectomy – biopsy), about 71% for patients in the BxChip group and about 67% for those in the Classic group. The difference between the two distributions is not statistically significant. For Minor Gleason pattern scores, a major trend in the equality of biopsy and prostatectomy scores (54%) and a slight increase in overvaluation (28.2%) was identified in patients in the BxChip™ group, while the major trend in Classic biopsy was undervaluation (down 1 and 2) ($\cong 49\%$), and the equality of scores was observed in only 31.4% of cases. The trend difference is statistically significant for a test value $\chi^2=26.72$ $df=$ p.<001. Following the analysis of the ordinary logistic regression, a 1.53 (C.I. 95% 1.23 ÷

1.90) higher chance of obtaining under valuations was identified for the Class group when compared to the BxChip™ group.

The trend is statistically significant for a Wald test value $\chi^2=14.68$, $df=1$, and $p.<001$. For ISUP Scores, a major trend in the equality of biopsy and prostatectomy scores (46.7%) and a slight accentuation of undervaluation (26.5%) was identified in the BxChip™ group, while the major trend in classical biopsy is undervaluation (down 1 and 2) ($\cong 49\%$), while the equality of scores was observed in only 23.5% of the cases. The trend difference is statistically significant for a test value $\chi^2=20.31$ $df=$ p.<01. Following the analysis of the ordinary logistic regression, a 1.42 (C.I. 95% 1.07 ÷ 1.90) times greater chance of obtaining under valuations for the Classic biopsy group was identified, comparing to the BxChip™. The trend is statistically significant for a Wald χ test value $2=14.68$, $df=1$, and $p.<001$.

The concordance analysis was carried out using the web application VassarStat (Kappa (vassarstats.net) and the value of the Kappa coefficient was determined using three weighting variants: without weighting (considering only absolute concordances), with linear weighting (considering also the relative concordances according to the distance from the position of the absolute concordance), and square weighting through the squares of the linear weights.

Gleason biopsy/prostatectomy score association table for the BxChip™ group

	Gleason score prostatectomy				Total	
	6	7	8	9		
Gleason	6	5	27	0	0	32
Score	7	0	184	3	4	191
	8	2	45	8	6	61
	9	0	3	0	4	7
Biopsy						
Total		7	259	11	14	291

Table of the frequencies and weights of concordances
 The confidence interval (C.I. 95%) for proportions was calculated with Wilson continuity correction.

Kappa coefficient values

Method of calculation	Kappa	Standard error	C.I. 95%	
			Inf. Lim.	Sup. Lim.
Non-weighted	.235	.067	.103	.366
Linear weighted	.288	.054	.182	.394
Square weighted	.369	.041	.290	.449

All 3 values obtained for the Kappa concordance coefficient belong to the range .20 - .40, thus indicating a satisfactory concordance (according to Cohen interpretation). Considering the relative concordances, the value of the Kappa coefficient increased significantly, from a value at the lower end of the range (.235) to a value toward the upper end of the range (.369). The observed concordance was about 69%.

It was not possible to calculate the concordance coefficient for Gleason scores biopsy vs prostatectomy for the Classic group, because the observed concordance weight (44.9%) is lower than the randomly obtained concordance weight (45.6%)

Major Gleason biopsy/prostatectomy pattern association table for the BxChip group

	Major pattern Gleason prostatectomy			Total	
	6	7	9		
Major pattern	3	110	52	0	162
Gleason Biopsy	4	31	96	1	128
	5	0	1	0	1
Total	141	149	1	1	291

Table of the frequencies and weights of concordances

Gleason score	Frequency of concordance			The proportion of concordances %			C.I. 95%	
	Maximum possible	Expected	Observed	Maximum possible	Expected	Observed	Inf. Lim.	Sup. Lim.
3	141	78.5	110	87.0	35.0	57.0	49.7	64.0
4	128	65.5	96	85.9	31.0	53.0	45.5	60.4
5	1	.0	0	100	0.2	.0	.0	80.2
Total	270	144.0	206	92.8	49.5	70.8	65.1	75.9

The confidence interval (C.I. 95%) for proportions was calculated with Wilson continuity correction.

Kappa coefficient values

Method of calculation	Kappa	Standard error	C.I. 95%	
			Inf. Lim.	Sup. Lim.
Non-weighted	.422	.053	.318	.525
Linear weighted	.426	.052	.325	.527
Square weighted	.434	.081	.275	.593

All 3 values obtained for the Kappa concordance coefficient belong to the range .41 - .60, thus indicating a moderate concordance (according to Cohen interpretation). Considering relative concordances, the value of the Kappa coefficient increased slightly between 0,422 and 0,434. The observed concordance was about 71%.

Major pattern Gleason biopsy-prostatectomy association table for the Classic group

	Major Gleason prostatectomy		Total
	3	4	
Major Gleason biopsy	3	21	9
	4	7	13
Total		28	22
			50

Table of the frequencies and weights of concordances

Score	Frequency of concordance			The proportion of concordances %			C.I. 95%	
	Maximum possible	Expected frequencies	Observed	Maximum possible	Expected	Observed	Inf. Lim.	Sup. Lim.
3	28	16.8	21	93.3	40.8	56.8	39.6	72.5
4	20	8.8	13	90.9	26.5	44.8	27.0	64.0
Total	48	25.6	34	96.0	51.2	68.0	53.2	80.1

The confidence interval (C.I. 95%) for proportions was calculated with Wilson continuity correction.

Kappa coefficient values

Method	Kappa	Standard error	C.I. 95%	
			Inf. Lim.	Sup. Lim.
Non-weighted	.344	.14	.079	.609
Linear weighted	.344	.13	.082	.606
Square weighted	.344	.11	.127	.562

All 3 values obtained for the Kappa concordance coefficient belong to the range .20 - .40, thus indicating a satisfactory concordance (according to Cohen interpretation). The observed concordance was about 68%.

Minor Gleason biopsy/prostatectomy pattern association table for the BxChip group

	Minor pattern Gleason prostatectomy			Total	
	6	7	9		
	Minor pattern	3	49		40
Gleason Biopsy	4	81	105	6	192
	5	2	1	3	6
Total	132	146	13	291	

Table of the frequencies and weights of concordances

Minor pattern Gleason	Frequency of concordance			The proportion of concordances %			C.I. 95%	
	Maximum possible	Expected	Observed	Maximum possible	Expected	Observed	Inf. Lim.	Sup. Lim.
3	93	42.2	49	70.5	23.1	27.8	21.5	35.2
4	146	96.3	105	76.0	39.9	45.1	38.6	51.7
5	6	.3	3	46.2	1.4	18.8	5.0	46.3
Total	245	138.8	157	84.2	47.7	54.0	48.0	59.8

The confidence interval (C.I. 95%) for proportions was calculated with Wilson continuity correction.

Kappa coefficient values

Method of calculation	Kappa	Standard error	C.I. 95%	
			Inf. Lim.	Sup. Lim.
Non-weighted	.120	.056	.010	.229
Linear weighted	.120	.054	.014	.226
Square weighted	.121	Nc	Nc	Nc

The value of the coefficient of concordance (.120) belongs to the range .0 – 0.20, which indicates a poor concordance.

The concordance coefficient could not be calculated for the Minor Gleason biopsy/prostatectomy pattern for the Classic group because the weight of observed concordances (32%) is lower than the weight of randomly obtained concordances (43%).

ISUP Score biopsy-prostatectomy score association table for the BxChip group

	ISUP Score prostatectomy					Total	
	1	2	3	4	5		
ISUP Score	1	5	24	3	0	0	32
Biopsy	2	0	81	46	3	0	130
	3	2	16	38	1	4	61
	4	2	12	33	8	6	61
	5	0	1	2	0	4	7
Total	9	134	122	12	14		291

Table of the frequencies and weights of concordances

Score Gleason	Frequency of concordance			The proportion of concordances %			C.I. 95%	
	Maximum possible	Expected frequencies	Observed	Maximum possible	Expected	Observed	Inf. Lim.	Sup. Lim.
1	9	1.0	5	28.1	2.5	13.9	5.2	30.3
2	130	59.9	81	97.0	29.3	44.3	37.0	51.8
3	61	25.6	38	50.0	16.3	26.2	19.4	34.3
4	12	2.5	8	19.7	3.6	12.3	5.8	22.4
5	7	.3	4	50	1.6	23.5	8.8	50.2
Total	219	89.3	136	75.3	30.7	46.7	40.9	52.6

The confidence interval (C.I. 95%) for proportions was calculated with Wilson continuity correction.

Kappa coefficient values

Method of calculation	Kappa	Standard error	C.I. 95%	
			Inf. Lim.	Sup. Lim.
Non-weighted	.232	.042	.150	.314
Linear weighted	.348	.040	.271	.426
Square weighted	.479	.078	.327	.632

The unweighted Kappa concordance value starts from a value close to (.232) obtained for the Gleason Scores, which indicates a satisfactory concordance (according to Cohen interpretation) but increases strongly when square weighting to a value (.479), belonging to the range .40 to .60 of moderate concordance. The observed concordance was about 47%, but with a higher chance of showing less evolution differences than those displayed.

It was not possible to calculate the concordance coefficient for ISUP Score biopsy-prostatectomy scores for the Classic group because the weight of observed concordances (23.5%) is lower than the weight of randomly obtained concordances (24.3%).

Conclusions: Gleason biopsy scores were compared and the logistic regression analyzes showed greater consistency in the BxChip™ group compared to the conventional biopsy group, the difference being statistically significant in all categories (total Gleason score, Major pattern, Minor pattern, ISUP Score). Thus, we can conclude that the use BxChip™ in routine medical practice is a real innovation in the correct classification of prostate cancer.

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