ASSESSMENT OF GLEASON SYSTEM USE ON DIFFERENT TYPES OF PROSTATIC TISSUE SAMPLES

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Summary. One of the well-known and accepted methods of prostatic adenocarcinoma grading is Gleason system. The authors made a retrospective analysis of 221 prostatic adenocarcinomas divided into three groups (transvesical prostatectomies, transurethral resections and needle biopsies) following the type of surgical procedure used for drawing the tissue. Gleason scores and comparison between odd and even Gleason scores were assessed in the entire group and in each subgroup. High scores prevailed, meaning a tendency towards a low grade of differentiation. Even scores also prevailed meaning, on one hand, that, often, the examined specimen reveals only one pattern and, on the other hand, that surgical procedures as transurethral resections and unique needle biopsies cannot offer a sufficient material for examination, the multicentricity of prostatic carcinoma being well known.

Key words: prostate, carcinoma, Gleason score.

INTRODUCTION

The Gleason system is one of the most internationally accepted and used methods for grading prostate cancer, due mainly to its marked prognostic value, being well correlated with the stage and metastatic potential (Mora *et al.*, 2001; De la Taille *et al.*, 2003; Shen et al 2003; Xiao *et al.*, 2004; Humphrey, 2004). Prostatic adenocarcinoma often is multifocal, and different Gleason grades may be present in different foci. The Gleason grading system uniquely combines data from different areas of carcinoma in the same prostate specimen (Arora *et al.*, 2004).

This grading system, proposed by Gleason in 1977, is based only on architectural criteria, i.e. the type of tumor glandular appearance as identified on a relatively small magnification. In contrast to other systems used for histological grading of prostate carcinoma, this one does not use the cytological aspect as grading criterion. Grading criteria are very precisely defined (Gleason, 1977). The variety of histopathologic features on the same sample is surpassed by:

– establishing a "primary grade", assigned to the histological aspect that represents the greatest area of the fragment.

– establishing a "secondary grade" for the histological aspect that represents the second area in terms of extention.

Both the primary architectural pattern (dominant pattern) and the secondary one (second in terms of spreading) are identified and are assigned a grade from 1 to 5, which means: (1) – **very well differentiated**; (2) – **well differentiated**; (3) – **moderately differentiated**; (4) – **poorly differentiated** and (5) – **very poorly differentiated** (Gleason, 1977). Clarifying the histologic criteria for distinguishing each grade, especially between Gleason grades 2 and 3, is important for accurate grading (Fukagai *et al.*, 2001).

The primary and secondary patterns are combined to give a tumor score, referred to as Gleason score or sum (Rubin *et al.*, 2000). Gleason combined scores are between 2 (1+1=2), which represents a tumor, composed of uniformly disposed Gleason 1 pattern and 10 (5+5=10), which represents an entirely undifferentiated tumor. If the tumor presents only one histological pattern or if only a minute focus of tumor is present on biopsy, in order to obtain uniformity, both primary and secondary scores are assigned the same rang respectively the Gleason score is assigned by doubling the Gleason pattern (Rubin *et al.*, 2000). When more patterns are present, identifying the two dominant patterns may prove to be difficult.

The main advantage of Gleason system is that it is based only on morphological criteria. Gleason score is well correlated with other prognostic factors such as the size of the tumor, the presence of metastases in the pelvic lymph nodes and PSA level (Mora *et al.*, 2001; De la Taille *et al.*, 2003; Shen *et al.*, 2003; Xiao *et al.*, 2004; Humphrey, 2004).

A frequent problem in using Gleason system is distinguishing Gleason score 6 from 7 especially among biopsy specimens with lower tumor volumes, particularly among those with less than 30% involvement (Coard and Freeman, 2004). The major deficiency of the Gleason system is that, even if both low grades (2–4 combined) and high grades (8–10 combined) have a pretty accurate predictive capacity, in most patients with medium degree tumors the prognostic is uncertain.

In our laboratory, the pathologist could examine three kinds of prostatic tissue samples: specimens proceeding from transvesical prostatectomy, performed for benign nodular hyperplasia (BNH); specimens proceeding from transurethral resection, performed mainly also for BNH; ultrasound guided biopsies performed mainly for suspicion of prostatic carcinoma. Therefore we intended to make an assessment of the way that Gleason system is applied to each of these three categories of specimens and to the entire group of diagnosed prostatic carcinomas.

MATERIAL AND METHODS

A retrospective review of 221 prostate specimens from patients hospitalised in the Urology Department of Craiova Emergency County Hospital between 1992

and 1999 in which a diagnosis of adenocarcinoma was made in the Pathology Department of the same hospital was conducted.

Using the type of surgical procedure performed for each patient as a distribution criterion, the selected cases were divided into three groups as follows: group 1: transvesical prostatectomies (TVP) for BNH – 33 cases; group 2: transurethral resections (TUR) – 82 cases; group 3: prostatic needle biopsies (B) – 106 cases.

Histopathological slides and paraffin blocks of each case represented the materials from the Pathology Department archives. The stain technique used in all cases was haematoxylin-eosin. The algorithm of study was the following: assessment of Gleason scores in the entire group and in each subgroup and comparison between odd and even Gleason scores in the entire group and in each subgroup.

RESULTS AND COMMENTS

ASSESMENT OF GLEASON SCORES IN THE ENTIRE GROUP

Gleason score analysis showed that tumoral proliferations were mostly labelled as score "6" This score was followed, in a decreasing occurring scale by scores "8", "9" and "10" (Figure 1).

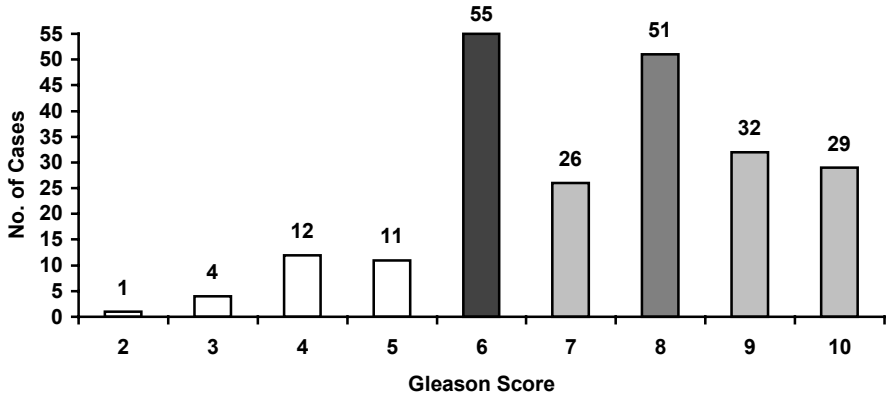

Figure 1 – Gleason scores distribution in the entire group

Score 2

Gleason score "2" was established only in one case in which, one of the transurethral resection specimens showed a small nodule composed of glands

resembling normal ones but with compact disposition and slightly delimited from the rest of the hyperplastic prostatic tissue (Figure 2).

Score 3

This score was established in 4 cases in which pattern "1" and pattern "2" were also present on the samples that were examined. In two of these cases the dominant pattern was pattern "1" and in the remaining two cases the dominant pattern was pattern "2".

Score 4

This score was established in 12 cases after multiplying by 2 the index of the single pattern observed on the examined samples (Figure 3).

Score 5

In the 11 cases with Gleason score "5" there could be seen only combinations of patterns "2" and "3". In 7 cases the dominant pattern was pattern "2" while in the other 4 cases the dominant pattern was pattern "3". Pattern "3" was usually a type "a" pattern (7 cases).

Score 6

Score "6" was established in 55 cases. All 55 cases were combinations of the different subtypes of pattern "3" alone (Figure 4, a and b). In 5 cases the subtype of pattern "3" was not mentioned.

In 32 cases only one subtype was identified: in 4 cases there was only subtype "a"; in 17 cases only subtype "b" and in 11 cases only subtype "c". 18 cases were combinations of pattern "3" subtypes as follows: 2 cases with subtypes "a"+"b"; 3 cases with subtypes "a"+"c"; 10 cases with subtypes "b"+"c" and 3 cases in which the combination was "c"+"b".

Score 7

This score was established in 26 cases. There were 25 cases with combinations between patterns "3" and "4" (Figure 5) as follows: 18 cases with pattern "3" as the dominant pattern and 7 cases with pattern "4" as the dominant pattern. Pattern "3" was usually of type "b" and pattern "4" was mostly of type "a".

Score 8

Score "8" was established in 51 cases. 35 of them were combinations only between different subtypes of pattern "4" (Figure 6, a and b).

Score 9

32 cases were assigned a score "9" as a combination between patterns "4" and "5". Pattern "4" was the dominant one in 19 cases and mostly of "a" type while pattern "5" was the dominant one in the other 13 cases, and mostly of "b" type.

Score 10

A score "10" was established in 29 cases and only as a combination between different subtypes of pattern "5". In 26 cases, there was only one subtype, as follows: 6 cases with subtype "a" (Figure 7a) and the other 19 cases with subtype "b" (Figure 7b). The remaining 4 cases were combinations of subtypes "a"+"b".

DIFFERENCE BETWEEN DOMINANT AND SECONDARY PATTERNS

There were only 17 out of all the 221 studied cases with a somewhat more unusual situation consisting of a difference between the dominant pattern and the secondary one >1. In one case from the score "7" group, the grade was determined by the association of patterns "5" and "2", the dominant one being pattern "5". The others 16 cases were assigned a score "8", being combinations between patterns "3" and "5". In 9 cases the dominant pattern was "3" and, in the other 7 cases, "5" respectively. Pattern "3" was mostly of type "b", followed by type "c". In most cases pattern "5" was of type "b". In his study on 2911 cases of prostate carcinoma, Gleason found that in 505 cases the difference between the dominant pattern and the secondary one was 2 and only 3 cases with a difference of at least 3 (Gleason, 1977) (Table 1). The difference between the two studies was confirmed by the value of "13.78"of (2×2) "χ^2" test, considered as significant.

Table 1
The rate of cases with difference between dominant and secondary pattern >1

Study	**No. of cases**		**%**
	Difference >1	*The whole group*	
Craiova	17	221	7.7
Gleason	508	2911	17.5

Difference between dominant and secondary patterns may be significant if the Gleason score is converted to 1–2–3 system. When, after conversion, the tumor is placed in the moderately differentiated category but the dominant pattern was one equivalent with poor differentiation, the risk of undergrading the tumor aggressiveness using the Gleason score is present. In our study group this situation was seen in only one case, with Gleason score "7" and pattern "5" as the dominant one. On the contrary, in all the other 16 cases we could say that the score (i.e., "8") placed the tumor in a group that was closer to its aspect and behaviour although the dominant pattern ("3") was one characterising better differentiated tumors.

ASSESMENT OF GLEASON SCORES IN INDIVIDUAL GROUPS

Group 1 (TVP)

In the group with transvesical prostatectomy, the most frequent cases were those with score "6", followed by score "9" and "8" (Table 2).

Group 2 (TUR)

In the group with transurethral resection, the different scores were more heterogenously distributed. Thus, the most frequent score was "8", followed by scores "6", "10" and "7" (Table 2).

Group 3 (B)

In the group III (with ultrasound guided single biopsy), score "6" was again the most frequent one and was followed by those indicating a poorly differentiated cancer such as "8", "10" and "9" (Table 2).

Table 2
Gleason scores distribution in the three study groups

Subtype	Gleason Score (No. of cases)									
	Total	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
I (TVP)	33	0	3	1	3	8	5	6	7	0
II (TUR)	82	1	1	6	6	16	11	20	9	12
III (B)	106	0	0	5	2	31	10	25	16	17

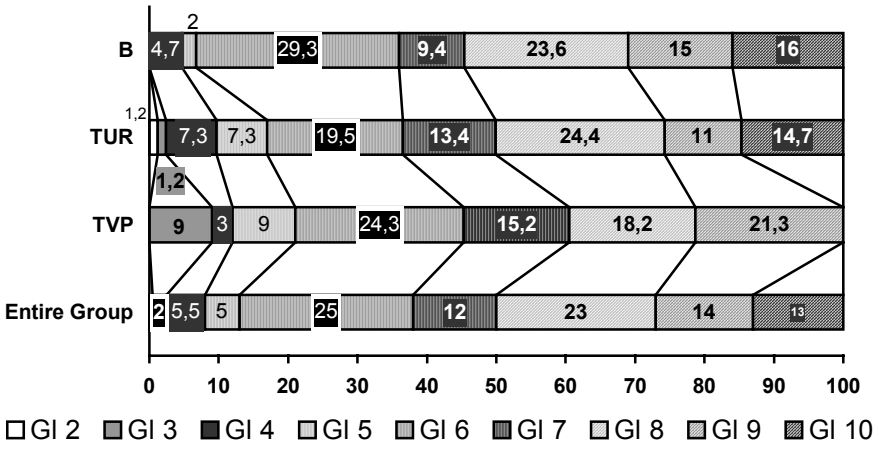

Figure 8 – Gleason scores rates in the three studied groups

Comparing the score distribution in the three groups we could observe a relatively homogenous distribution (excepting the lack of score "10") in TVP group, with large specimens and, therefore, large amounts of tumoral tissue. The rates of low scores ("2"–"4") are decreasing parallel with the amount of drawn tissue from group 1 (TVP) to group 3 (B) whereas high scores ("8"–"10") rates are conversely increasing. This different score distribution in the three groups was confirmed by the statistic analysis using (3×9) "χ^2" test, which revealed, for the given data, a value of "28.58", considered as significant (Figure 8).

COMPARISON BETWEEN ODD AND EVEN SCORES

We also calculated the sum of odd and even scores for each group and for the entire group and then compared the results (Table 3, Figure 9).

Table 3
Odd and Even scores distribution in studied groups

Score	I (TVP)		II (TUR)		III (B)		Entire Group	
	Cases	%	Cases	%	Cases	%	Cases	%
G3+G5+G7+G9	18	54.5	27	32.9	28	26.4	73	33
G2+G4+G6+G8+G10	15	45.5	55	67.1	78	73.6	148	67
Cases (No. / %)	33	100	82	100	106	100	221	100

Group I (TVP)

The sums of odd and even scores showed that, in this group, there is a prevalence of odd scores (Table 3). Another important observation is that, of the 6 cases assigned as score "8", three showed a difference between the dominant score and the secondary one >1.

The amount of prostatic tissue, offered by these large samples, allowed a better evaluation of a greater area of the tumor, which led to a more frequent finding of both a dominant and secondary different patterns. Thus, the score could be established on more than one pattern (Figure 5).

Group II (TUR)

In this group, the same sums show a clear prevalence of the even scores (Table 2). It should also be mentioned that, of the 20 cases that were assigned a score "8", five showed a difference between the dominant score and the secondary one >1, with pattern "3" as the dominant one. In the remaining cases, the even scores were obtained by doubling the index of the only pattern seen on the studied samples.

Group III

In this group, the sums of odd and even scores show a clear prevalence of the even ones (Table 2). This is a consequence of the fact that on biopsy materials different patterns of the intraprostatic proliferation are very rarely observed, especially if the proliferation is also multicentric.

We saw also that only 3 out of the 25 cases that were assigned a pattern "8" showed a difference between the dominant pattern and the secondary one >1, with pattern "3" as the dominant one.

Figure 9 clearly reveals the prominent decrease of odd scores from group 1 (TVP) to group 3 (B). This trend was outlined also by the statistic analysis using (2×3) "χ^2" test whose obtained value of "9" was considered as significant.

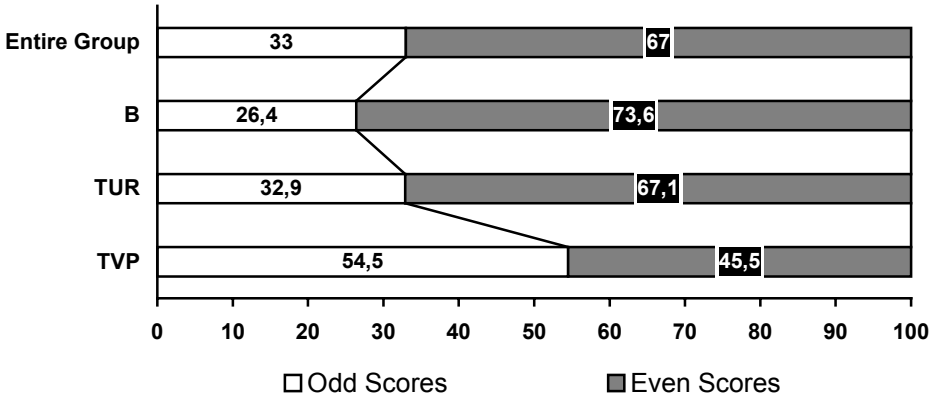

Figure 9 – Odd and Even scores rates in studied groups

FINAL COMMENTS

The analysis of Gleason scores showed that, through the overall most frequent score was "6", meaning a moderately differentiated malignant proliferation, high scores (from "8" to "10"), together, were seen in half of the all cases, meaning an increased prevalence of low differentiated and aggressive cancers. Moreover, the important group of carcinomas discovered on TUR specimens (82 cases), from which 63.4%, i.e. 52 cases, had a score ≥7 is another argument sustaining the aggressiveness of these tumors which widely invaded the prostatic parenchyma, till the anterior periurethral areas.

Even scores are, usually the result of a sum between the same types of patterns. The high prevalence of these scores in our study (more than two thirds of cases) meant, on one hand, the discovery, in most of the cases, of a single pattern on the tissue sample, the score being obtained by doubling the pattern index.

This was, without any doubt, the consequence of the great number of cases in the groups 2 (TUR) and 3 (B), with small amounts of prostatic tissue where it is most likely to find the same type of architectural arrangement of tumoral glands or cells.

On the other hand, the high prevalence of even scores could be the result of an insufficient interception of tumoral tissue by drawing procedures such us transurethral resection, which could intercept the peripheral areas of the malignant proliferation, or the unique needle biopsies.

Our data are concordant with those from other studies and support the idea of a more aggressive investigation for detecting the prostatic cancer in its intraprostatic stage, emphasizing the usefulness of a multiple-core needle biopsy.

Thus, recent studies concluded that, when only a minute focus of tumor is present on biopsy, the Gleason score is assigned by doubling the Gleason pattern and, consequently, the assigned Gleason score could not predict tumor stage, Gleason grading remaining, in these cases a poor predictor of pathological outcome (Lattouf and Saad, 2002; Rubin *et al.*, 2000).

Therefore, an extended (18 or 12-gauge rather than six-core) prostate needle biopsy strategy for TRUS-guided biopsy of the prostate gland improves detection and histologic grading and provides better guidance to determine the appropriate treatment in patients with prostate carcinoma (Shen *et al.*, 2003; San Francisco *et al.*, 2003; O'Connell *et al.*, 2004).

The prominent frequency of high grade carcinomas among the studied cases could be an argument for sustaining the introduction, in our country, of PSA serum level determination as a screening test, in order to trace out the early stages of prostatic cancer and guide further the ultrasound examination and multicore needle biopsies, being well known that the Gleason histological grading of prostate carcinoma is positively related to the serum PSA level (Xiao *et al.*, 2004).

CONCLUSIONS

In conclusion, we can say that, in the studied groups, high scores prevailed, showing tumors with a marked tendency towards a low grade of differentiation and high grade of aggressiveness.

Prevalence of even scores meant that, with only few exceptions, there was only one architectural pattern on the studied samples, due to the large number of cases with transurethral resection and unique needle biopsies, which could offer no sufficient information about the real status of the prostatic malignant proliferation.

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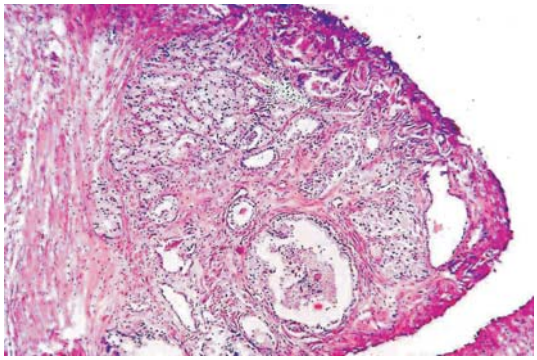

Figure 2 – Gleason Score 2, TUR specimen

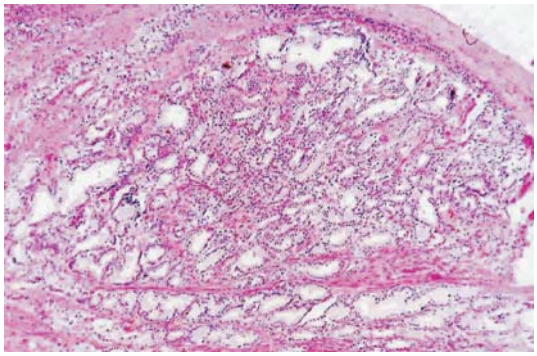

Figure 3 – Gleason Score 4, TUR specimen

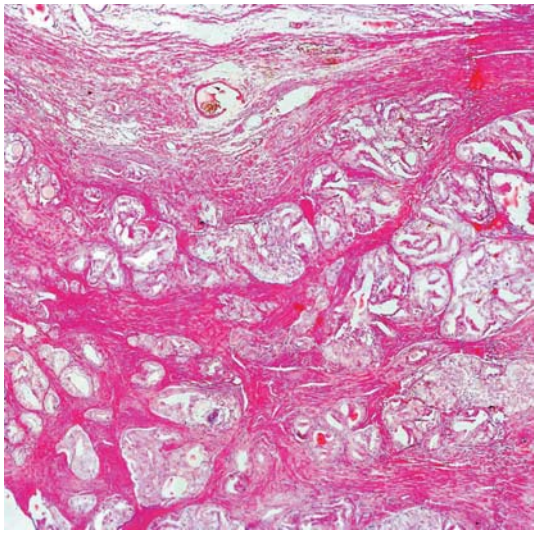

Figure 5 – Gleason Score 7 (3c + 4a), TVP specimen

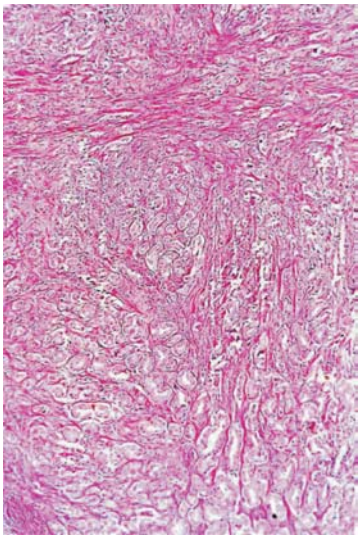

Figure 4 – a) Gleason Score 6
3a (up) + 3b (down), TVP specimen

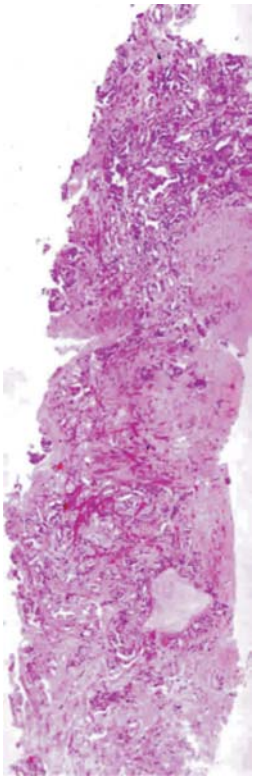

Figure 4 – b)
Gleason Score 6
3a + 3a,
B specimen

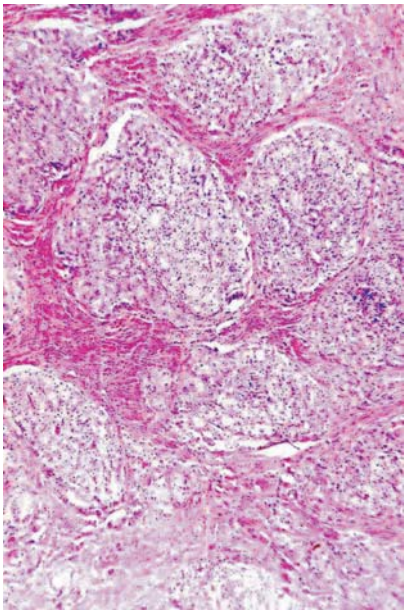

Figure 6 – a) Gleason Score 8 (4a + 4a),
TVP specimen

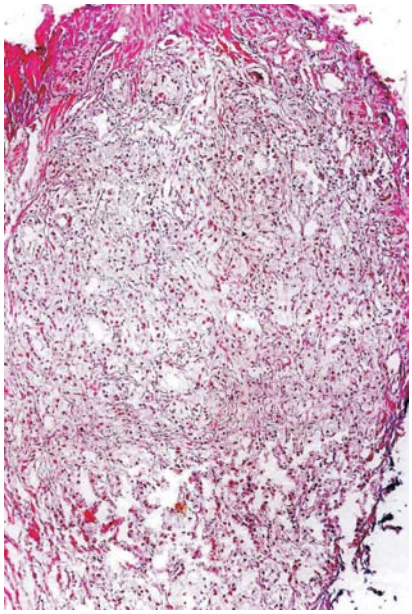

Figure 6 – b) Gleason Score 8 (4b + 4b),
TUR specimen

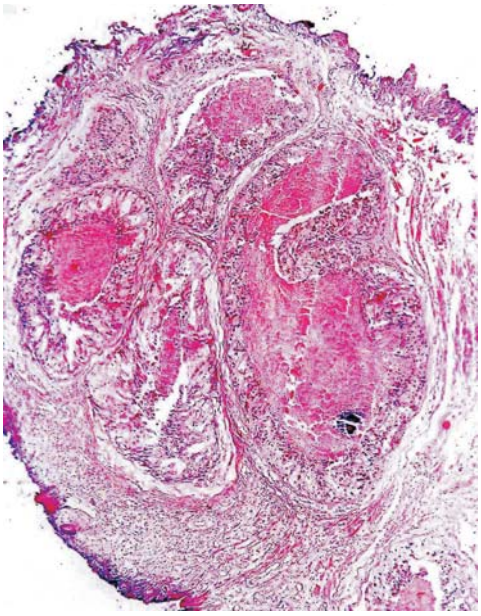

Figure 7 – a) Gleason 10 (5a + 5a),
TUR specimen

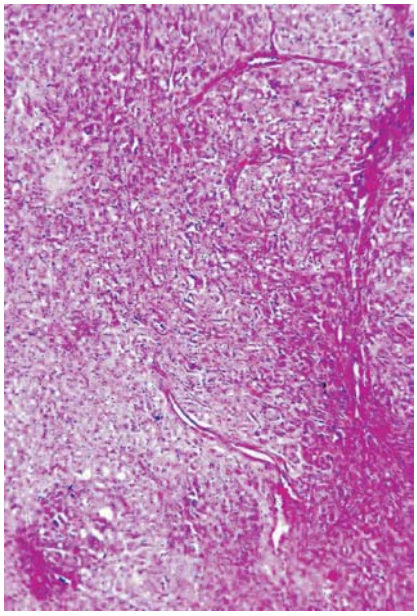

Figure 7 – b) Gleason Score 10 (5b + 5b),
TVP specimen