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TITTLE PAGE

Title:

Histological characteristics of the index lesion in whole-mount radical prostatectomy specimens: implications for focal therapy

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Running tittle:

Role of prostate cancer focality in focal therapy

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ABSTRACT

Background. It has been suggested that in multifocal prostate cancer, focal therapy to the largest (index) lesion is sufficient, because secondary non-index lesions are unlikely to contribute to disease progression. In this study the role of PCa focality in selecting men for focal therapy was evaluated.

Methods. A histopathological analysis of the index and non-index lesions of 100 consecutive radical prostatectomy specimens was carried out. Cases that would have been suitable for focal ablation were also evaluated.

Results. Tumours were more often multifocal (78%) and bilateral (86%). In total 270 tumour foci were identified. In multifocal disease, tumor volume, Gleason score and pathological stage were almost invariably defined by the index lesion of the specimen; among the 170 satellite foci, 148 (87%) were <0.5cc and 169 (99.4%) had Gleason score <6. Using the defined criteria, 51% of men in this series would have been considered suitable for focal ablation of the index lesion.

Conclusions. Histological features of poor prognosis in the prostate are associated with the index lesion. There is a high proportion of patients who may be suitable for focal therapy and clinical trials of index lesion ablation should be considered as part of this therapeutic strategy.

Keywords:

Prostatic neoplasm; Ultrasound; High Intensity focused; Transrectal

INTRODUCTION

Focal therapy has recently gained interest as a new method to control clinically localized prostate cancer (1,2) and has been defined as “individualized treatment that selectively ablates known disease and preserves existing function, with the overall objective of minimizing morbidity without compromising life expectancy” (3). The principal theoretical objection to focal prostate therapy includes the multifocal nature of prostate cancer. However, recent histological studies within the PSA-screening era from the USA have demonstrated that in men undergoing radical prostatectomy, 10-40% have unilateral disease (4-8) and 10-44% have unifocal tumors (9-12). These data raise the possibility that half-gland treatment (hemiblation) or focal ablation of tumor foci alone might be possible for between 10% and up to 50% of patients who would currently receive whole-gland treatment; on average about one third of men would be suitable. Furthermore, it has been suggested that in multifocal disease, the largest cancer focus (index lesion) determines disease progression and secondary lesions do not contribute to clinical outcome (13-15). Therefore, targeting the index lesion alone may be sufficient (1,16,17).

Our objective was to examine the pathologic features of clinically localized prostate cancer in a UK series in order to 1) evaluate cancer focality and 2) determine the relationship between the index lesion and histological features of prognosis. These data may be useful for informing the design of clinical protocols assessing hemiblation, focal ablation or focal index lesion ablation.

MATERIALS AND METHODS

Patient population

A total of 100 consecutive cases of whole mount radical prostatectomy specimens were selected for analysis from a single centre between the dates 01/07/2001 to 30/10/2003. Exclusion criteria included radiation or hormonal treatment prior to surgery.

Histopathologic evaluation

Each prostatectomy specimen was totally embedded and processed by the whole-mount method. That is, after surgical resection each prostate was fixed in 10% buffered neutral formalin for 24-48 hours. Following fixation, the apex and the base were amputated and serially sectioned parallel to the urethra. Seminal vesicles were sectioned parallel to the junction with the prostate. The remainder of the prostate gland was serially sectioned perpendicular to the longitudinal plane of the gland at 5mm intervals and refixed for a further 24 hours. From each 5mm tissue block, a single 5µm thick section was generated and stained with hematoxylin-eosin.

In each prostate, the areas of adenocarcinoma were identified and outlined with an ink tracing placed on each slide. Tumor grade for each prostate was determined according to the Gleason system. Pathologic staging was based on the 1997 TNM system. For each tumor focus volume was calculated using the cubic volume method i.e the raw product of tumour length, width and height of each focus (L x W x H) (18,19). Length was the longest linear dimension of the largest cross sectional profile for that focus

and width was the second linear dimension in the maximum cross sectional profile, approximately at the right angles to the length. Height was defined as the number of cross sections occupied by each focus multiplied by 0.5 cm which was the thickness of each tissue block.

Three-dimensional reconstruction was performed by manually placing all slices in serial order and using the urethra as a reference point. When tumor areas were separated by more than 4mm within the same slide (20-22) or 5mm in adjacent slides, the areas were regarded as separate foci. When multifocal disease was observed, the index lesion was considered the largest focus as measured by volume, without considering its Gleason score (15). Secondary foci were defined as all other smaller lesions. Laterality was determined using the urethra as the dividing line in the sagittal plane. Tumors were classified as unilateral if all the foci were completely confined to either the right or left side of the prostate.

Suitability for focal therapy

Patients that would appear to have been suitable for focal ablation (ablation of tumor focus alone with small margin of normal tissue) were defined as:

- a) Unifocal cases: organ confined, Gleason score ≤ 7 (1)
- b) Multifocal cases: organ confined, Gleason score ≤ 7 with clinically insignificant secondary foci defined as tumor foci with total TFV $< 0.5\text{cc}$ and Gleason score ≤ 6 (1)

Patients suitable for hemi-ablation (ablation of entire one half of prostate) were defined as:

a) Unilateral cases (unifocal or multifocal): organ confined with Gleason score ≤ 7

b) Bilateral cases: organ confined, Gleason score ≤ 7 , with the index lesion confined to one side of the gland and the contralateral side harbouring clinically insignificant secondary foci (1).

Patients with multifocal bilateral disease where the index lesion occupied both sides of the gland were not considered suitable for focal therapy.

Database and statistical analysis

The following features were recorded for each case: 1) age; 2) prostatic specific antigen (PSA) 3) pathological stage of the specimen; 4) focality and number of tumour foci; 5) tumour laterality; 6) volume of each tumour focus (TFV), total tumour volume (TTV) in the specimen, and the total volume of the satellite foci of each specimen; 7) Gleason score of the specimen and Gleason score of each tumour focus; 8) extracapsular extension of each focus; 9) seminal vesicle invasion of each focus.

Pearson's Chi square test was used to compare characteristics of different groups based on non-continuous variables (e.g Gleason score, pathological stage). Comparison of characteristics based on continuous variables such as tumour volume was performed by two-tail Mann-Whitney U test. Pearson product moment correlation was used to describe the relationship between two continuous variables. All statistical analyses were performed using Minitab 15 statistical software and a 2-sided $p \leq 0.05$, indicated statistical significance.

RESULTS

Characteristics of prostate cancers

The median age was 62 years (range 48-74). PSA data were available for 81 patients (mean: 9.48 ng/ml; range: 1.14-28 ng/ml). Baseline characteristics of the 100 radical prostatectomies are presented in Table 1 and individual tumor characteristics in Table 2. The mean total tumor volume was 3.5cc (range 0.03-24). The majority of the cases were multifocal (78%), well to moderately differentiated (Gleason score 6, 69%) and organ-confined (pT2, 66%).

Comparison between unifocal and multifocal tumours

Comparative analysis of patient and tumor characteristics of unifocal versus multifocal disease is presented in Table 3. No significant difference in age, PSA, proportion of tumors with Gleason score ≥ 7 , non-organ confined disease and total tumor volume was observed between unifocal and multifocal cases.

Characteristics of tumour foci

In total, 270 tumor foci ranging from 0.002 to 24 cc in volume were identified among the 100 whole-mount specimens (Table 4). Figure 1 illustrates the distribution of number of foci per prostate. In multifocal disease, among the 170 satellite foci, 148 (87%) were <0.5cc and 169 (99.4%) had Gleason score ≤ 6 . There were 25 (32.1%) specimens that had at least 2 tumour foci within the gland with different Gleason score. There was no case however in which a satellite focus had a higher Gleason score than the index lesion of the specimen. Two satellite foci were found to extend extracapsularly. In one case, there were 2 foci in the specimen and both the index (1.24cc) and the secondary focus (1.15cc) extended beyond the capsule. In the other case, it was a secondary focus with volume 0.84cc that extended beyond the capsule whilst the index lesion was organ-confined. No satellite foci were found to invade the seminal vesicles. A strong relationship was observed between total tumor volume in the specimen and volume of the index lesion of each multifocal case ($p < 0.01$) (Figure 2). The R^2 value shows that the value of the index lesion explains 90.5% of the variance in total tumor volume in the specimen.

Suitability for focal therapy

Focal ablation

Among the 22 unifocal cases, there were 14 patients suitable for focal ablation i.e organ confined, Gleason score ≤ 7 tumors. Figure 3 illustrates the proportion of patients with multifocal disease suitable for focal index

lesion ablation. Among the 78 multifocal cases, there were 37 patients with organ-confined, Gleason score ≤ 7 cancer in which the total volume of the secondary foci was less than 0.5cc, with Gleason score 6 or less.

Therefore, in toto there were 51 (14 unifocal and 37 multifocal) patients in this series that could be considered suitable for focal ablation.

Hemiablation

Another manner of delivering focal therapy is hemiablation. The same cohort of cases was analysed to determine the proportion that would be suitable for hemiablation as opposed to focal ablation.

Among the 14 unilateral cases, there were 10 patients suitable for hemiablation i.e organ confined, Gleason score ≤ 7 tumor, disease limited to one side of the urethra. Among the 86 bilateral cases, there were 35 patients with organ confined, Gleason score ≤ 7 , bilateral and multifocal disease where the index lesion was confined to one lobe and secondary foci in the contralateral side had total volume $<0.5\text{cc}$ and Gleason score ≤ 6 .

Therefore, in toto there were 45 (10 unilateral and 35 bilateral) patients in this series that could be considered suitable for hemiablation if index lesion ablation was considered an appropriate focal therapy strategy.

DISCUSSION

The concept of focal therapy in prostate cancer, in which only areas of cancer are treated, offers an opportunity for effective therapy with minimal morbidity. As prostate cancer is multifocal in the majority of cases, the concept of ablating only the index lesion with the remaining clinically insignificant foci undergoing surveillance has evolved. Recent studies have suggested that only a very small minority of men undergoing radical prostatectomy have pathologically unilateral disease with low risk features that may be amenable to hemiablation of the prostate (8,23). Neither of these groups however evaluated the proportion of patients with bilateral disease with clinically insignificant tumour foci (<0.5cc tumour volume, Gleason score \leq 6) on the side contralateral to the index lesion.

To the best of our knowledge, our study is the first to address the issue of tumor focality and index lesion from a focal therapy strategy. In our series, most prostate cancer was multifocal (78%) and bilateral (86%), similar to that recorded in other countries. Contrary to other studies (4,24), our analysis revealed no apparent association between tumor focality and pathological features of poor prognosis. Further, our data highlight the significance of the index lesion as an important pathologic feature in prostate cancer. In fact, Gleason score, tumour volume, extracapsular extension and seminal vesicle invasion were almost invariably determined by the largest tumour focus within the gland. Satellite lesions tended to be small and well differentiated.

As yet no definitive conclusions can be reached from our analysis about the biological significance of tumor focality due to the lack of sufficient follow-up data but Noguchi et al (25) examined the prognostic significance of secondary tumors in the prostate and showed multifocal tumours were not associated with adverse features of prostatectomy specimens. By contrast they found multifocal disease had fewer cases of disease progression. In other words, when men were stratified by tumor focality, PSA-failure free survival rates were consistently higher in the multifocal compared to the unifocal groups. This suggests that multifocality *per se* seems not be a risk factor for disease progression in the prostate and as such patients harboring multifocal tumours should not be excluded *a priori* for focal prostate therapy. Most importantly the Stanford group elegantly demonstrated that progression was related to the index lesion and not secondary foci (13).

Our analysis of the histopathological characteristics of the index lesion demonstrates that index lesion ablation may be a possible therapeutic strategy under the umbrella of focal therapy. Indeed, two groups have already commenced prospective trials evaluating the role of ablating the dominant lesion in clinically localised prostate cancer. The MD Anderson Group (Protocol ID: 2008-0244NCT00877682) are using cryotherapy and the UK London Group (Protocol ID: 09/H0714/7) are using high intensity focused ultrasound. It is important to recognize that such data point only to a possible relationship between size and cancer progression, but do not prove it. There were 2 foci in our series in which a secondary focus and not the index lesion demonstrated extracapsular extension. Interestingly, in both of these specimens the secondary focus in question actually measured >0.5cc and

could be regarded as a significant lesion in its own right on volume criteria. A prostate need not necessarily have just one index lesion. Ruijter et al (22) examined a series of 61 radical prostatectomy specimens from patients with palpable disease and found that a quarter of the tumors with extracapsular extension in multifocal disease were not the index lesion. Importantly, two of these secondary tumours extended beyond the prostatic capsule, influencing the pathological stage whilst the largest tumour in the same specimen remained organ confined. Thus, they hypothesized that the index tumor may not always be representative of the pathological stage. Similarly, other investigators observed that even small foci, down to 0.2cc in size, may show a significant release of tumor cells into the bloodstream (26) and can give rise to lymph node metastasis (27). As Miller and Cygan (10) pointed out, tumors need not acquire a large volume before they become locally invasive.

Nonetheless, we have shown that among a cohort of UK patients undergoing radical prostatectomy for clinically localized prostate cancer there is a high proportion of men with cancer that appear suitable for focal ablation. Nearly half of our studied group had unifocal or multifocal organ confined disease suitable for focal ablation, if that included an index lesion protocol.

We acknowledge certain limitations to this study inherent in its design. First, our investigation focused exclusively on the histopathological analysis of the prostatectomy specimens and clinical outcome was not included in the study protocol. Therefore, no definitive conclusion can yet be drawn as to the prognostic effect of tumor focality and laterality on disease progression. However, it has been demonstrated by the Duke group that laterality does

not impact on disease progression (20). Second, no preoperative data were included which could illustrate the reliability of the current diagnostic methods to detect multifocal disease. We hope that future studies can be based on this report in order to better delineate the significance of prostate cancer focality and prediction of the presence and location of the index lesion.

CONCLUSIONS

Multifocality is a common feature on radical prostatectomy specimens, but is not associated with pathological features of poor outcome. Tumor volume, Gleason grade, extracapsular extension and seminal vesicle invasion is almost invariably determined by the index lesion. Secondary foci are typically small volume, well differentiated lesions, rarely associated with aggressive features. Such findings provide evidence in support of the proposition within focal therapy enthusiasts for targeting only the index lesion within the gland. However, prudence is required in deciding appropriate surveillance of the satellite lesions. Further studies are needed to evaluate the clinical and biological implications of prostate cancer focality and molecular genetic, epigenetic and proteomic work needs to be carried out to determine if these foci differ in their molecular and behavioural profiles.

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Hashim Uddin Ahmed receives funding from the Medical Research Council, Pelican Cancer Foundation, Prostate UK, Prostate Cancer Research Centre and St Peters Trust for work on focal therapy.

Conflicts of interest

Hashim Uddin Ahmed receives funding from USHIFU/Misonix/UKHIFU/Focus Surgery (manufacturers and distributors of the Sonablate 500 HIFU device) for proctoring HIFU cases and travel grants to conferences.

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ABBREVIATIONS

ECE	Extracapsular Extension
PCa	Prostate Cancer
PSA	Prostatic Specific Antigen
SGs	Specimen Gleason score
SVI	Seminal Vesicle Invasion
TFV	Tumor Focus Volume
TTV	Total Tumor Volume

TABLES

TABLE 1. Baseline characteristics of 100 radical prostatectomy specimens in a UK cohort

PSA, ng/ml	
Mean	9.48
Range	1.14 - 28
Total number of foci	270
Focus Volume (cc)	
Mean	1.293
Median	0.3
Range	0.002 - 24
Unifocal	22
Multifocal	78
Unilateral Unifocal	8
Unilateral Multifocal	6
Bilateral Unifocal	14
Bilateral Multifocal	72
Gleason	
6	69
7	27
8	2
9	2
Pathologic Stage	
PT2a	11
PT2b	65
PT3a	10
PT3b	2
PT3c	12

TABLE 2. Individual Tumor Histological Characteristics from 100 Radical Whole-mount prostatectomy samples

Individual Tumor Gleason score	5	6	2.2%
	6	232	85.9%
	7	28	10.4%
	8	2	0.7%
	9	2	0.7%
Individual Tumor Extracapsular Extension	Positive	20	7.4%
	Negative	250	92.6%
Focus Seminal Vesicle Invasion	Positive	12	4.4%
	Negative	258	95.6%

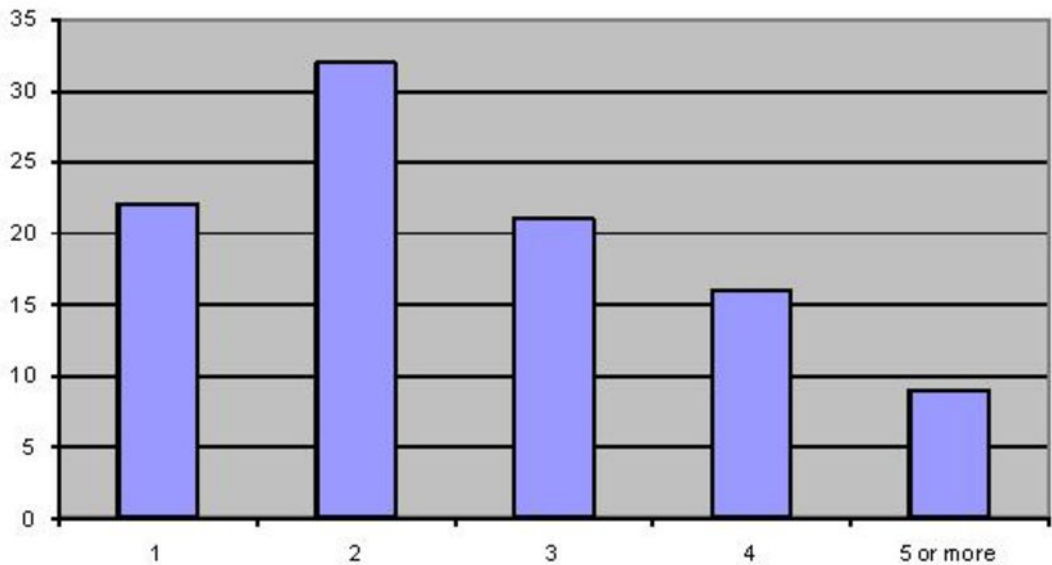
TABLE 3. Comparison between unifocal and multifocal tumors

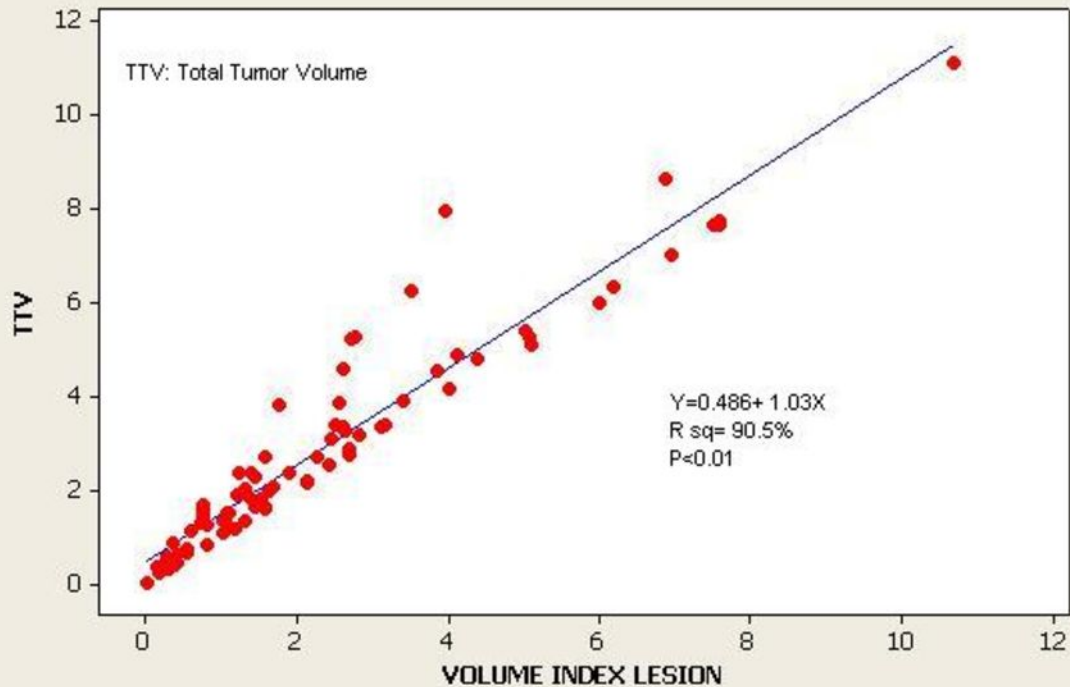
	UNIFOCAL	MULTIFOCAL	p value
N	22	78	
Age (years)			
median	61	63	0.22
range	51-69	48-74	
PSA, ng/ml			
mean	8.96	9.6	0.5
range	2.49-28	1.14-28	
Total Tumor Volume, cc			
Mean	5.42	2.94	
Median	3.45	2.24	0.3
Range	0.22-24	0.03-11.14	
Gleason score ≥ 7	7 (31.8)	24 (30.7)	0.9
Non organ confined tumors	7 (31.8)	17 (21.8)	0.33

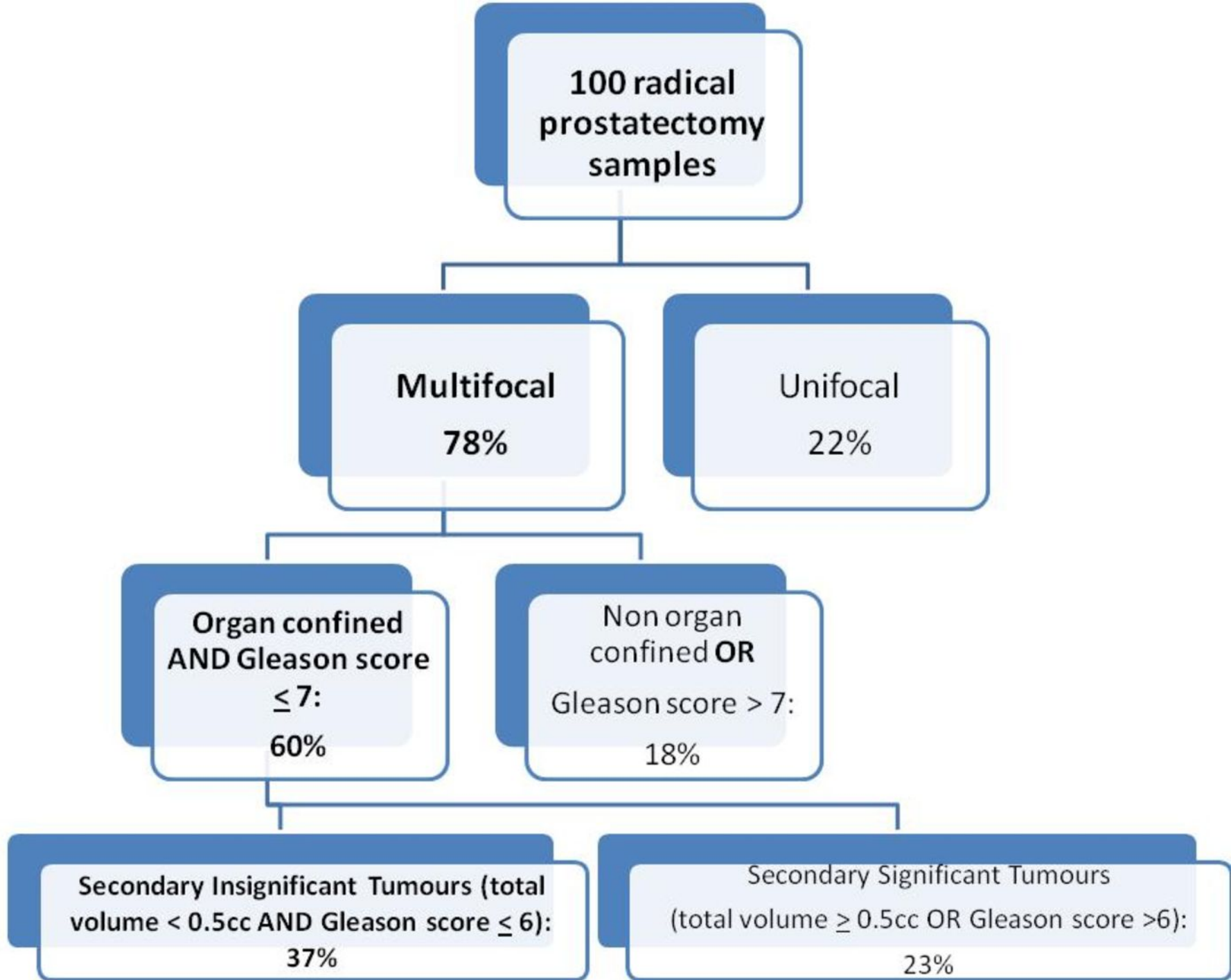
TABLE 4. Histological characteristics of the individual tumor foci

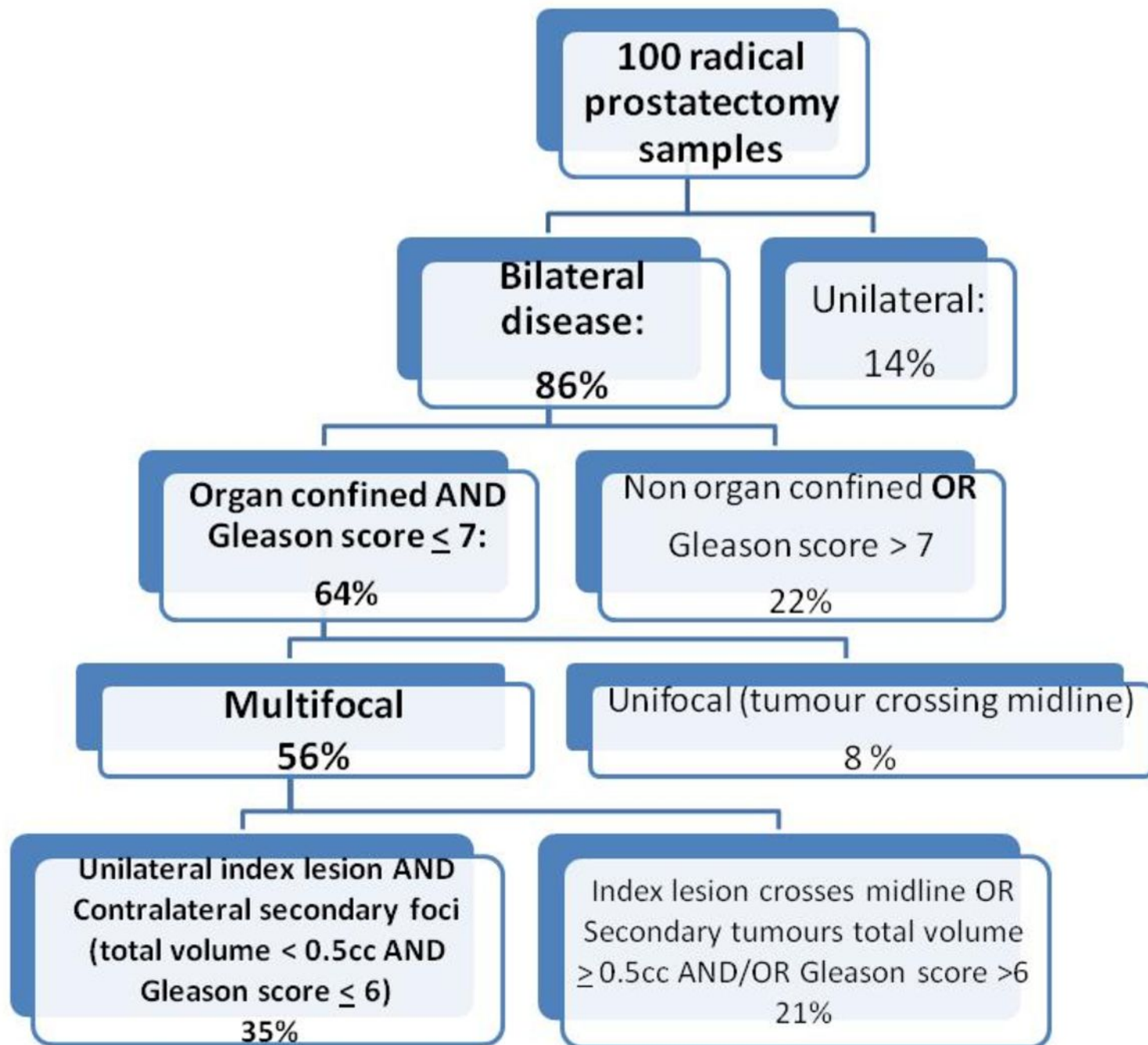
Tumor type	Total	Gleason ≥ 7		Gleason ≤ 6		Volume ≥ 0.5 cc		ECE		SVI	
		n	%	N	%	n	%	n	%	n	%
Unifocal	22	7	31.8	15	68.2	18	81.8	5	22.7	7	31.9
Index lesions	78	24	30.7	54	69.3	66	84.6	13	16.6	5	6.4
Secondary lesions	170	1	0.6	169	99.4	22	12.9	2	1.1	0	0
Total	270	32		238		106		20		12	

ECE: Extracapsular Extension
SV: Seminal Vesicle Invasion









anterior

right

left

posterior



Index lesion
Gleason score: 3+3=6.



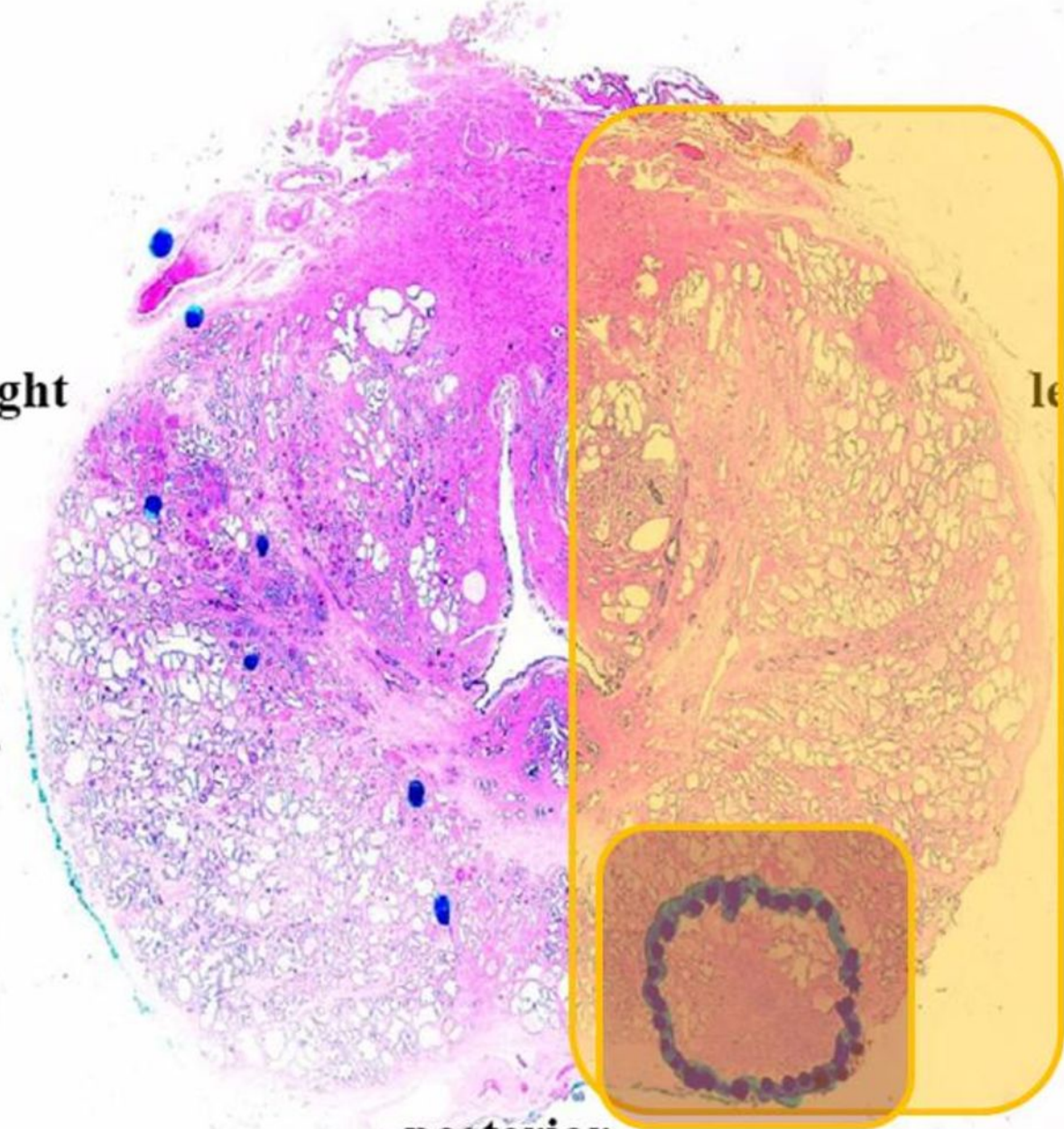
Satellite focus
Gleason score: 3+3=6

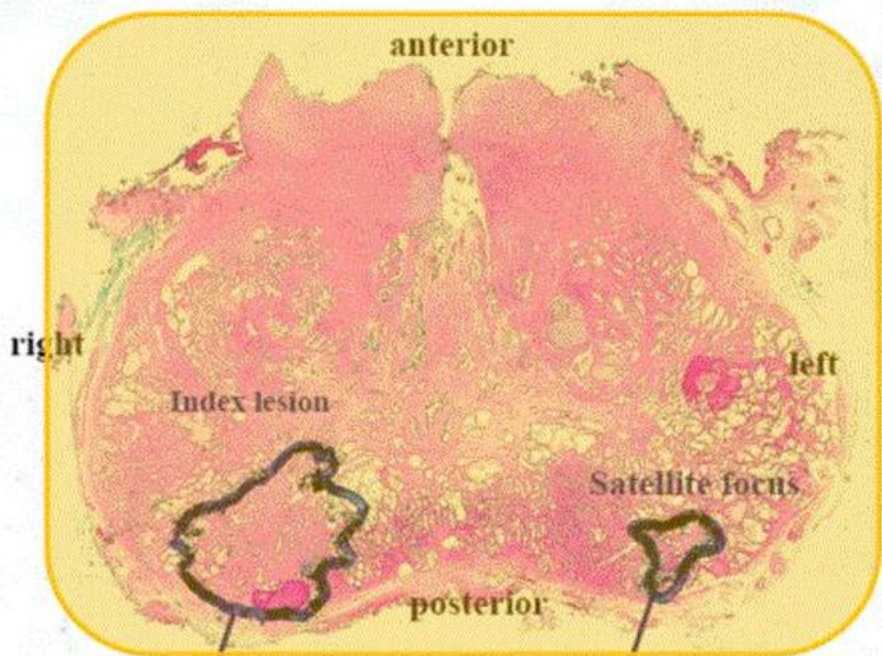
anterior

right

left

posterior





Volume: 0.81cc
Gleason score: 3+4=7

Volume: 0.24cc
Gleason score: 3+4=7