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### Identification of Insignificant Prostate Cancers

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**Abstract:** The aim of this study was to identify the characteristics of clinically insignificant prostate cancer in autopsy material. It was examined that the histological characteristics (tumor volume and Gleason score) of stage T1a carcinomas found in autopsy among 40 impalpable (hypothetical stage T1) carcinomas of the prostate of 212 men between 30 and 98 years who died of diseases other than carcinoma of the prostate and related conditions. Other pathological features (capsular penetration, perineural and perivascular invasion) were also examined and cross-correlated with histological differentiation and tumor volume of the 40 cancers, 36 occupied less than the 5% of the total volume of the prostate gland and would be classified as of stage T1a if diagnosed during lifetime. Twenty seven (75%) out of 36 hypothetical T1a cases had favourable histological features (relatively low volume, Gleason score between 2 and 6 and absence of invasiveness). The lowest volume tumours were those of low and intermediate grade (Gleason sums 2 through 6). Among tumours with volumes of less than 1 cc, 96.55% were confined within the prostatic capsule. According to present findings as insignificant T1a tumours could be considered those of volumes of less than 1 cc and Gleason sums 2 through 6.

**Key words:** Prostate cancer, clinical significance, autopsy

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### INTRODUCTION

Prostate Cancer (PC) exhibits a wide range of biologic behaviour. Epidemiological evidence from autopsy studies show that while a very high proportion of elderly men has histological evidence of the disease, a much smaller proportion actually develop clinically apparent PC and is commonly quoted that many more men die with PC than of it. Traditional clinical and pathological features associated with clinically important PC include a palpable tumour, diffuse involvement and moderately or poorly differentiated histology. In contrast, microfocal, well differentiated PCS show a relatively good biologic behaviour while some are considered to be possibly clinically not important (Miyake *et al.*, 2005). With the term clinically not important or insignificant PC is defined a disease of virulence insufficient to threaten survival. Various models of clinically not important PC have been proposed, based mainly on a constellation of histological findings of biopsy and radical prostatectomy specimens. Since minimal disease on biopsy does not reliably predict minimal disease in the subsequent prostatectomy specimen, in terms of the size and grade of tumor, extracapsular extension or positive margins (Johnstone *et al.*, 2007), the existence of clinically not important or insignificant prostate cancer remains controversial. On the other hand, Prostate-Specific Antigen (PSA) remains an important diagnostic tool and as preoperative PSA is always measured in patients who undergo prostatectomy

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for BPH, a large number of tumours found incidentally (stage T1) in prostatectomy specimens (TUR-P or open prostatectomy) from patients with normal PSA levels, are expected to be clinically insignificant (Merrill and Wiggins, 2002). Some of those patients are potential candidates for watchful waiting. In the sequent study authors' investigated the clinically not important adenocarcinoma of the prostate in autopsy material clear in order to provide a decision-making tool for patients with incidentally found prostate cancer (stage T1).

## **MATERIALS AND METHODS**

### **Study Population**

The study was performed in the Athens morgue between August 2002 and August 2004 on 212 prostatic specimens of men above 30 and 98 years of age, born and living in Greece, who died, of diseases other than carcinoma of the prostate and related conditions. Coronary artery disease was the leading cause of death (acute myocardial infarction) and occurred in 68 cases (32%). Stroke was the second leading cause of death (57 cases-26.8%), while other causes of death were various infections, chronic obstructive pulmonary disease, fatal injuries. Cases with macroscopic foci of neoplastic disease in any organ or tissue, found in the autopsy examination, were excluded from the study. None of the examined prostates was abnormal in the preneecropsy Digital Rectal Examination (DRE).

### **Sample Removal and Processing**

The whole prostate and seminal vesicles were removed with accuracy. The specimens were weighted, numbered and registered. The surface of the two lobes was coloured in different colours (red and blue ink for right and left lobe, respectively) and fixed in acetic acid. A 10% solution of formalin was injected uniformly into the gland and every single specimen was then immersed in formalin solution allowed to rest for 3 days for fixation purposes. Seminal vesicles, base and apex were removed and sectioned through the base. The rest of the two lobes were divided and step sectioned at 4 mm intervals perpendicular to the long axis of the gland. Pieces were post fixed, resectioned, dehydrated, cleared in xylene and embedded in paraffin (Henson *et al.*, 1994). Microscope slides were numbered and registered in order to refer to the prostate specimen, the lobe and region from where they removed. Histological assessment: The diagnosis of PC was based to the WHO classification system histological criteria (Sesterhenn, 2003). PCS were classified according to the Gleason scoring system. A primary and a secondary Gleason grade were to any positive specimen. Cases of multifocal tumours were classified according to the prevalent histological model of the index tumour (Montironi *et al.*, 2003). Final tumour volume was determined by the grid method (Montironi *et al.*, 2003).

### **Analyses**

Correlations among histologic characteristics were assessed with parametric and non-parametric statistical methods.

## **RESULTS**

After accurate removal and examination of the 212 DRE negative prostatic specimens of the cadavers who fulfilled the inclusion criteria, 40 cases of impalpable histologic prostate carcinoma were diagnosed. Most of T1 histological PCS (57.5%) had Gleason score between 2 and 4, while 30% had Gleason score 5 or 6. Only five (12.5%) had Gleason score above 7. Twenty nine out of 40 T1 stage histological PSs (67.5%), had volume less than 1 cc. There was a clear correlation ( $p < 0.001$ ) between tumor volume and histological differentiation: Among tumours with overall volume less than 1 cc, most (62%) had Gleason sums of 4 or less. On the contrary, the highest volume tumours were those of intermediate and high grade (Gleason sums 5 through 8) (Table 1).

**Table 1: Associations between Gleason score and overall tumour volume**

Overall volume	Gleason 2-4	Gleason 5-6	Gleason 7-8
< 1 cc	18	8	1
> 1 cc	5	4	4

**Table 2: Associations between Gleason patterns and focus volume**

Focus	Gleason pattern 1-2	Gleason pattern 3	Gleason pattern 4-5
< 0.5 cc	22	12	0
> 0.5 cc	9	8	5

**Table 3: Associations between overall tumour volume and invasiveness**

Overall volume tumour volume	Capsular invasion	Neural invasion	Vascular invasion
< 1 cc	1 (3.57)	1 (3.57)	1 (3.57)
> 1 cc	3 (27.2)	5 (45.45)	2 (18.18)

Values in parentheses show percentage

**Table 4: Associations between Gleason score and invasiveness**

Gleason score	Capsular invasion	Neural invasion	Vascular invasion
3-4	0	0	0
5-6	1	1	1
7-10	3	5	2

Twenty four out of 40 T1 (60%) PCS were multifocal and composed by two or more foci. Most of them were comprised by small neoplasms of volume less than 0.5 cc. The relation between tumor volume and histological differentiation per single focus was examined. Small foci of volume less than 0.5 cc showed histological characteristics of favorable type: 64% of them corresponded to Gleason score 3 and 4. Most tumor foci of volume greater than 0.5 cc had intermediate differentiation (Table 2).

Among PCS with volumes of less than 1 cc, 96.55% were confined within the prostatic capsule. More precisely, capsular penetration was observed in four cases: Three of them corresponded to tumours of volume greater than 1 cc. Perineural invasion was observed in six cases: Five of them corresponded to tumours of volume greater than 1 cc. Finally, perivascular invasion was observed in three cancer cases two of them corresponded to tumours of volume greater than 1 cc. There was a positive correlation between tumor volume and the pathological features suggesting clinical significance ( $p < 0.001$  in both parametric and nonparametric tests for the capsular invasion,  $p < 0.001$  (t-Test) and  $p < 0.001$  (Mann-Whitney Test) for perineural invasion and  $p < 0.002$  (t-Test) for perivascular invasion) (Table 3).

Biologic aggressive behaviour in terms of capsular neural and perivascular invasion was associated with histological differentiation. A positive correlation has been found between Gleason score and the pathological features suggesting clinical significance in both parametric and nonparametric tests for the capsular perineural and perivascular invasion ( $p < 0.001$  (t-Test) and  $p < 0.001$  (Mann-Whitney Test)) (Table 4).

According to present findings, as clinically insignificant cancers would determined, those with volume less than 1 cc, Gleason grade 3 or less (Gleason score  $< 7$ ) with absence of capsular perineural and perivascular invasion. On the contrary clinically important cancers, would determined those composed from up to three foci, with volume larger than 1 cc and Gleason grade 4 or 5 and level of invasiveness.

## DISCUSSION

PC has been the most commonly diagnosed cancer in men in the United States, as well as the second leading cause of male cancer deaths since the early 90s and is becoming an increasingly important health problem in many countries worldwide (Pienta and Esper, 1993). However, PC exhibits a wide range of biologic behaviour. Epidemiological evidence from autopsy studies show that

while a very high proportion of elderly men has histological evidence of the disease, a much smaller proportion actually develop clinically apparent PC and is commonly quoted that many more men die with PC than of it (Billis, 1986; Guileyardo *et al.*, 1980; Nicolo *et al.*, 1986; Schutze, 1984). It has been proposed since the early 80s, that microcarcinomas and focal carcinomas could be of minimal clinical significance (Hradec *et al.*, 1980; Kliucharev and Vorob'ev, 1979), therefore the discrepancy in terms of biologic behaviour between the incidentally (histologically identifiable) and clinically diagnosed carcinomas led to the introduction of the term latent PC (Schmid, 1994). Indeed, some stage-T1, well-differentiated tumour could be described as a latent process which rarely progresses. These clinically not important or insignificant microscopic foci of high differentiated tumours have a constant (log-linear) growth rate that is very slow 5-7 years (Whittemore *et al.*, 1991). Literature reviews indicate that such disease progresses in only about 2 to 8% of patients and that virtually none of them succumb to the disease (Baron *et al.*, 1989; Farkas *et al.*, 1998; Brawn *et al.*, 1995).

Several authors suggested models of clinically not important adenocarcinoma of the prostate, based mainly on a constellation of histological findings of biopsy and radical prostatectomy specimens. All proposed models of 'Insignificant' prostate cancer include well differentiated carcinomas (Gleason grade 1 through 3) however they vary in the determination of minimal tumor volume in biopsy material (Epstein *et al.*, 1994; Irwin and Trapasso, 1994; Goto *et al.*, 1996; Anast *et al.*, 2004). Despite the relatively high sensitivity and specificity of those models (up to 72 and 96%, respectively) (Epstein *et al.*, 1994; Irwin and Trapasso, 1994; Goto *et al.*, 1996; Anast *et al.*, 2004) it has been proved that minimal disease on biopsy does not reliably predict minimal disease in the prostatectomy specimens (Johnstone *et al.*, 2007), therefore the existence of clinically not important or insignificant prostate cancer has been subsequently contested (Winkler *et al.*, 2007).

From present perspective, since many impalpable PCS are detected by a combination of PSA, TRUS and needle biopsy (T1c) (Stamey *et al.*, 1998) and considering that PSA has been shown to be proportional to PC volume (Schmid *et al.*, 1993), in the era of PSA screening, it is expected that most of the tumors found incidentally at transurethral resection of the prostate (stage T1a), should be of low volume and of high or moderate histological differentiation, similar to the small tumours found at postmortem examination.

## CONCLUSIONS

In conclusion it is felt that based on the current autopsy study, the majority of impalpable prostate carcinomas are low volume, well differentiated tumours corresponding to clinically insignificant neoplasms and that similar characteristics could be attributed to most of the impalpable carcinomas detected after prostatectomy for BPH in clinical practice. With such a high number of clinically insignificant PCS among T1 prostatectomy specimens and with an extraordinarily slow tumour doubling time, there appear to be substantial consequences for therapeutic decisions. Although further studies are needed in order to determine the exact significance of incidentally detected T1a tumours of the prostate, urologists should be more prudent in making their decision on whether to adopt early invasive treatment options for their patients or not.

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