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Do Clinically Insignificant Tumors of the Prostate Exist?

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Prostate cancer, clinical significance · Autopsy · Prostate-specific antigen

Abstract
Background: The discrepancy between minimal disease on biopsy and disease found in the subsequent prostatectomy specimen, in terms of the size and grade of tumor, extracapsular extension or positive margins, led several authors to dispute the existence of clinically insignificant impalpable tumors of the prostate. However, considering that prostate-specific antigen (PSA) is an indicator of prostate malignancy and since many impalpable prostatic carcinomas (PCs) are detected by a combination of PSA, transurethral ultrasound and needle biopsy (T1c), in the era of PSA screening, it is expected that most of the impalpable tumors found incidentally at transurethral resection of the prostate (stage T1a/b), could be clinically insignificant. ***Aim:*** The aim of this study was to identify the characteristics of latent, impalpable PCs and to analyze the incidence of clinically insignificant PCs among hypothetical stage T1 prostate cancers in tumors found incidentally at postmortem examination. ***Methods:*** We examined 40 cases of impalpable PCs found in 212 prostate autopsy specimens of men between 30 and 98 years of age who died of diseases other than carcinoma of the prostate and related conditions. ***Results:*** Most of T1 histological PCs (57.5%) had a Gleason score between 2 and 4, while 30% had Gleason score between 5 and 6. Only 5 (12.5%) had a Gleason score above 7. Twenty-nine of 40 stage T1 histological cancers (67.5%) had volume of <1 cm^3. The highest volume tumors were those of intermediate and high grade (Gleason sums 5–8). Among tumors with volumes of <1 cm^3, 96.55% were confined within the prostatic capsule. ***Conclusions:*** The majority of impalpable PCs were low-volume, well-differentiated tumors corresponding to clinically insignificant neoplasms. Similar characteristics could be attributed to most of the impalpable carcinomas detected after prostatectomy in clinical practice.

Introduction

The discrepancy between minimal disease on biopsy and disease found in the subsequent prostatectomy specimen, in terms of the size and grade of tumor, extracapsular extension or positive margins, has led several authors to dispute the existence of clinically insignificant impalpable tumors of the prostate [1]. Notably, prostate cancers (PCs) do not act predictably and vary between those that are aggressive and lethal and those that are

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slow-growing. Some of the slow-growing tumors are expected to be clinically insignificant indolent tumors that cause few changes in men's lives.

Considering that prostate-specific antigen (PSA) is an indicator of prostate malignancy and, in the era of PSA screening, it is always measured preoperatively in patients undergoing partial prostatectomy for benign prostatic hyperplasia (BPH), the possibility of finding clinically insignificant tumors among incidentally found impalpable tumors of the prostate (stage T1) in prostatectomy specimens has changed [2]. However, the exact rate of those well-differentiated, low-volume, indolent tumors among stage T1 cancers is unknown.

As autopsy constitutes an excellent opportunity for the epidemiologic study of PC, we have determined the rate of well-differentiated, low-volume, indolent tumors among hypothetical stage T1a PCs found incidentally on postmortem examination.

Methods

Study Population

The study was performed on 40 histological PCs found in 212 autopsy specimens from men (30 and 98 years of age) with normal PSA values, born and living in Greece, who died between August 2002 and August 2004 of diseases other than carcinoma of the prostate and related conditions. Coronary artery disease was the leading cause of death (acute myocardial infarction) and it occurred in 68 cases (32%). Stroke was the second leading cause of death (57 cases, 26.8%), while other causes of death were infections, chronic obstructive pulmonary disease and fatal injuries. Cases with macroscopic foci of neoplastic disease in any organ or tissue found during the autopsy examination were excluded from the study. None of the examined prostates was abnormal in the pre-necropsy digital rectal examination (DRE).

Sample Removal and Processing

The whole prostate and seminal vesicles were accurately removed. The specimens were weighed, numbered and registered. The surfaces of the two lobes were stained in different colors (red and blue ink for the right and left lobes, respectively) and fixed in acetic acid. A 10% formalin solution was injected uniformly into the gland and every single specimen was then immersed in formalin solution and allowed to rest for 3 days for fixation purposes. The seminal vesicles, base and apex were removed and sectioned through the base. The remainder of the two lobes was divided and step-sectioned at 4-mm intervals perpendicular to the long axis of the gland. The tissue was post-fixed, resectioned, dehydrated, cleared in xylene and embedded in paraffin. The microscope slides were numbered and registered in order to refer to the prostate specimen, the lobe and region from where they had been removed.

Histological Assessment

The diagnosis of PC was based to the WHO classification system histological criteria. PCs were classified according to the Gleason scoring system with a primary and secondary grade assigned to any positive specimen. Cases of multifocal tumors were classified according to the prevalent histological model of the larger focus (index tumor). Final tumor volume was determined by the grid method. Tumors with a volume of <1 cm^3 and Gleason grade 3 or less (Gleason score <7) were considered clinically insignificant [3].

Table 1. Correlation between age and number of carcinomas

Age, years	Specimens	Carcinomas	
		n	%
>89	16	9	56.2
80–89	30	12	40
70–79	36	11	30.5
60–69	36	5	13.8
50–59	38	2	5.2
40–49	38	1	2.6
30–39	18	0	–
Total	212	40	–

Results

Following the examination of the 212 DRE-negative prostatic specimens of the cadavers who fulfilled the inclusion criteria, 40 cases of impalpable histological PC were diagnosed (table 1).

Most of the T1 histological PCs (57.5%) had a Gleason score between 2 and 4 while 30% had a Gleason score of 5 or 6. Only 5 (12.5%) had a Gleason score of >7. Twenty-nine of 40 T1 stage histological cancers (67.5%), had volumes of <1 cm^3. The highest volume tumors were of intermediate and high grade (Gleason sums 5–8; table 2).

Among tumors with a volume of <1 cm^3, most (62%) had Gleason sums of 4 or less and the majority (96.55%) were confined within the prostatic capsule. Biologically aggressive behavior in terms of capsular neural and perivascular invasion was associated with both histological differentiation and tumor volume (tables 3, 4).

Twenty-four of 40 T1 (60%) tumors were multifocal and composed of two or more foci. Most of them were small neoplasms with volumes of <0.5 cm^3. The relation between tumor volume and histological differentiation per single focus was examined. Small foci with a volume of <0.5 cm^3 showed histological characteristics of a favorable type: 64% of them corresponded to Gleason scores of 3 and 4. Most tumor foci with a volume of >0.5 cm^3 had intermediate differentiation (table 5).

Table 2. Correlation between Gleason score and overall tumor volume

Overall volume	Gleason score		
	2–4	5–6	7–8
<1 cm^3	18	8	1
>1 cm^3	5	4	4

Table 3. Correlation between overall tumour volume and invasiveness

Overall volume	Capsular invasion	Neural invasion	Vascular invasion
<1 cm^3	1 (3.57%)	1 (3.57%)	1 (3.57%)
>1 cm^3	3 (27.2%)	5 (45.45%)	2 (18.18%)

Table 4. Correlation 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

Table 5. Correlation between Gleason patterns and focus volume

Focus volume	Gleason pattern		
	1–2	3	4–5
<0.5 cm^3	22	12	0
>0.5 cm^3	9	8	5

Discussion

Adenocarcinoma of the prostate exhibits a wide range of biological behaviors. Epidemiological evidence from autopsy studies [4–7] shows 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 it is commonly stated that many more men die with PC than of it.

Although the natural history of the disease is poorly understood, progression appears to be related to the stage, grade of tumor and serum PSA levels [8]. Therefore, the clinical and pathological features associated with clinically important PC include a palpable tumor, diffuse involvement and moderately or poorly differentiated histology. In contrast, microfocal, well-differentiated PCs have a relatively good biological behavior [9]. Indeed, microscopic foci of highly differentiated tumors, have been demonstrated to have a constant (log-linear) growth rate that is very slow [10]. Literature reviews indicate that such a disease progresses in only about 2–8% of patients and that virtually none of them succumb to the disease [11, 12]. For these reasons, well-differentiated and focal microcarcinomas are probably clinically not important and insufficient to threaten survival [9]. Based on the current autopsy study, the majority of impalpable prostate carcinomas are low volume, well-differentiated tumors corresponding to clinically insignificant neoplasms, and similar characteristics could be attributed to most of the impalpable carcinomas detected after prostatectomy for BPH in clinical practice (stage T1A).

In the era before the widespread use of PSA screening, impalpable (histological) PCs were exclusively found incidentally among prostatectomy specimens. Low-volume, well-differentiated tumors (such as those described in the Results section) corresponded in a relatively small percentage of T1 (formerly stage A) PCs [13, 14].

Since the introduction of PSA testing, the most effective and widely adopted screening test, there has been a substantial increase in PC detection. Subsequently, in the era of PSA screening, many impalpable PCs have been detected by a combination of PSA, transurethral ultrasound and needle biopsy (T1c) [15]. Considering that PSA has been shown to be proportional to PC volume [16], it is expected that most of the tumors found incidentally at transurethral resection of the prostate should be of low volume (stage T1a) [17]. Several studies, based mainly on the analysis of PCs found accidentally in cystoprostatectomy specimens, demonstrated that the higher proportion of stage T1a could actually be potentially insignificant carcinomas [18–20], similar to those found in our autopsy study.

Although the prevalence of PCs found on autopsy has increased over the last 15 years, when compared to the findings of the only available autopsy study ever performed in Greece [21], our findings show that there has been a dramatic decrease in the prevalence of latent PC in men younger than 70 years (table 1). With the widespread use of screening in our country, it seems that the

prevalence of latent PC has decreased 3-fold in the age groups eligible for PSA screening, a finding which is in accordance with other autopsy studies [2]. However, it is uncertain to what extent clinically insignificant tumors are being diagnosed and over-treated [22].

Recently several authors reported that most PCs found to be insignificant on biopsy were found to be significant in the subsequent prostatectomy specimen [1, 23].

The most probable explanation for the discrepancy between minimal disease on biopsy and disease found in the subsequent prostatectomy specimen, is that such cases had been incorrectly classified before surgery using standard biopsy schemes [24].

In conclusion, we feel that clinically insignificant tumors of the prostate exist. With a high number of clinically insignificant PCs found among T1 prostatectomy specimens and an extraordinarily slow tumor doubling time, there appear to be substantial consequences for therapeutic decisions. It seems that only saturation biopsy provides accurate predictability of prostate tumor volume and grade to select suitable candidates for watchful-waiting therapy.

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