Clinically Insignificant T1 Stage Tumors Of The Prostate

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Citation

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Abstract

Aim: To determine the rate of clinically insignificant histological prostate carcinomas among stage T1 cancers in autopsy material and discuss the possible implications in clinical practice.

Methods: We examined 40 cases of impalpable prostate carcinomas found between 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 cancers (57.5%) had Gleason score between 2 and 4 while 30% had Gleason score between 5 and 6. Only five (12.5%) had Gleason score above 7. Twenty nine out of 40 T1 stage histological cancers (67.5%), had volume less than 1cc. The highest volume tumours were those of intermediate and high grade (Gleason sums 5 through 8). Among tumours with volumes of less than 1 cc, 96.55% were confined within the prostatic capsule.

Conclusions: The majority of impalpable prostate carcinomas were low volume, well differentiated tumours corresponding to clinically insignificant neoplasms. Similar characteristics could be attributed to most of the impalpable carcinomas detected after prostatectomy in clinical practice.

INTRODUCTION

Traditional clinical and pathological features associated with clinically important PC (PC) include a palpable tumour, multifocal or diffuse involvement and moderately or poorly differentiated histology. In contrast, microfocal, well differentiated tumours show a relatively good biologic behaviour while some are considered to be possibly clinically not important ([1]). As preoperative serum marker prostate-specific antigen (PSA) is always measured in patients who undergo partial prostatectomy for BPH, a large number of tumours found incidentally in prostatectomy specimens (stage T1) from patients with normal PSA levels, are expected to be clinically insignificant tumours ([2]). Several studies suggested that after the widespread use of PSA screening, rates of impalpable (histological) PCs found incidentally among prostatectomy specimens have diminished ([3]). However, the exact rate of those well differentiated, low volume, indolent tumours among stage T1 cancers is unknown. As necropsy constitutes an excellent material for the epidemiologic study of PC, we have determined the rate of well differentiated, low volume, indolent tumours among stage T1 PCs and discuss their clinical importance.

METHODS

Study population: The study was performed in 40 histological cancers found between 212 autopsy specimens of men above 30 and 98 years of age, 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 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 prenecropsy 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 4mm intervals perpendicular to the long axis of the gland. Pieces were post fixed, resectioned, dehydrated, cleared in xylene and embedded in paraffin. 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. Cancers 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 larger focus (index tumour). Final tumour volume was determined by the grid method. As clinically insignificant cancers were determined, those with volume less than 1cc, Gleason grade 3 or less (Gleason score <7). As for clinically important cancers, those were determined if composed from up to three foci, with volume larger than 1cc and Gleason grade 4 or 5, and level of invasiveness.

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. (Table 1)

Figure 1

Table 1: Correlation between Age and number of Carcinomas.

Age group		Specimens	Carcinomas	
			n	%
1	>90	16	9	56.2%
2	80 -89	30	12	40%
3	70-79	36	11	30.5%
4	60-69	36	5	13.8%
5	50-59	38	2	5.2%
6	40-49	38	1	2.6%
7	30-39	18	0	-
Total		212	40	-

Most of T1 histological cancers (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 cancers (67.5%), had volume less than 1cc. The highest volume tumours were those of intermediate and high grade (Gleason sums 5 through 8). (Table 2)

Figure 2

Table 2: Correlation between Gleason score and overall tumour volume.

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

Among tumours with volume less than 1 cc, most (62%) had Gleason sums of 4 or less, while among tumours with volumes of less than 1 cc, 96.55% were confined within the prostatic capsule. Biologic aggressive behaviour in terms of capsular neural and perivascular invasion was associated with both histological differentiation and tumour volume. (Tables 3 and 4)

Figure 3

Table 3: Correlation between overall tumour volume and invasiveness

	Capsular invasion	Neural Invasion	Vascular Invasion
Overall volume < 1cc	1	1	1
%	3,57%	3,57%	3,57%
Overall volume > 1cc	3	5	2
%	27,2%	45,45%	18,18%

Figure 4

Table 4: Correlation between Gleason score and invasiveness

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

Twenty four out of 40 T1 (60%) tumors were multifocal, and composed by two or more foci. Most of them were comprised by small neoplasms of volume less than 0,5cc. The relation between tumor volume and histological differentiation per single focus was examined. Small foci of volume less than 0.5cc showed histological characteristics of favorable type: 64% of them corresponded to Gleason score 3 and 4. Most tumor foci of volume greater than 0.5cc had intermediate differentiation.

Figure 5

Table 5: Correlation between Gleason patterns and focus volume.

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

DISCUSSION

Adenocarcinoma of the prostate 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 ([4] ,[5] ,[6] ,[7]). On the other hand, 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 ([8]). With no proven primary prevention strategies for PC and no definitive treatments for metastatic disease available up to date ([9] ,[10]), cancer control efforts have focused on detecting and treating early-stage PC with screening tests. Currently, the most effective and widely adopted screening test is the prostate-specific antigen (PSA) assay, which substantially enhances cancer detection rate. Moreover, the quantification of serum prostate-specific antigen (PSA) levels is used for detecting PC along with digital rectal examination (DRE) and transrectal ultrasonography (TRUS) ([11]). Although the natural history of the disease is poorly understood, progression appears to be related to stage, grade of tumor and serum prostate-specific antigen (PSA) levels ([12]). In the era before the widespread use of PSA screening, impalpable (histological) PCs were exclusively found as an incidental finding among prostatectomy specimens. Low volume, well differentiated tumors - as those described in the results section- corresponded in a relatively small percentage of T1 (formerly stage A) PCs ([13] ,[14]). On the contrary, since many impalpable PCs are detected by a combination of PSA, TRUS and needle biopsy (T1c) ([15]), and considering that PSA has been shown to be proportional to PC volume ([16]), 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. It has been proposed since the early 80s, that microcarcinomas and focal carcinomas could be of minimal clinical significance ([17] , [18]), 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 ([19]). Indeed, a stage-T1 (A), well-differentiated tumour could be described as a “latent” process which rarely progresses. Microscopic foci of high differentiated tumours, are supposed to have a constant (log-linear) growth rate that is very slow 5-7 years([20]). 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 ([21] ,[22] ,[23]). According to our findings, although autopsy rate of PC prevalence has increased in the last 15 years, when compared to the findings of the only available autopsy study ever performed in Greece ([24]), there is a dramatic decrease in the prevalence of latent PC in men younger than 70 years (Table 1). With the more widespread use of screening in our country, it seems that the prevalence of latent PC has decreased 3-fold in age groups which are eligible for PSA screening, a finding which is in accordance with other autopsy studies ([3]). Such findings could indicate that even in European countries the reality of overtreatment for prostate cancer caused by the use of PSA screening could have reached the levels recently reported for the U.S. ([25]).

In conclusion we feel 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. The diagnosis and treatment of such tumors remains controversial. There are currently four major classic treatment options for PC such as observation, hormonal therapy, radiation therapy, and radical prostatectomy. According to our findings, there is possibly a high overtreatment rate in many patients with clinically insignificant PC, which could be avoided in patients older than 70 y.o, and that such patients would mostly benefit from watchful waiting rather than early aggressive treatment. 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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