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Insignificant Prostate Cancer in Radical Prostatectomy Specimen: Time Trends and Preoperative Prediction

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Abstract

Objectives: We analysed systematically a consecutive series of radical prostatectomy specimens performed between January 1992 and June 2002 with emphasis to time trends, tumour characteristics and preoperative prediction of insignificant prostate cancers (cancer volume $\leq$0.5 cm^3 and Gleason pattern $\leq$6).

Methods: In a total of 1254 patients, prostate cancers (PC) were divided by a cancer volume of 0.5 cm^3. The two groups were compared in their clinical and pathological tumour characteristics. Correlation was determined between yearly incidence rates of T1c and insignificant PC. Furthermore, a logistic regression analysis was performed to calculate the ability to predict insignificant PC and a statistical model was established.

Results: Overall, 73 (5.8%) of 1254 men presented with insignificant PC. The incidence of insignificant PC showed no significant linear correlation with that of T1c PC ($p < 0.61$). PSA density and percentage of cancer per biopsy set were assessed as independent prognosticators predicting insignificant PC. Using a threshold of 1% of cancer per biopsy set and a PSA density $\leq$0.10, positive and negative predictive values were 45.0% and 93.3%, respectively.

Conclusion: In our series, only few men undergoing radical prostatectomy were affected by insignificant PC. Their incidence showed no statistically significant correlation with that of T1c tumours. Furthermore, insignificant PC was predictable by PSA density and percentage of cancer per biopsy set. Mainly elderly patients facing different treatment options for localized PC may benefit from this information.

Keywords: Insignificant cancer; Prostate cancer; Radical prostatectomy; PSA density

1. Introduction

About one third of men older than 50 years of age will harbour prostate cancer (PC) at autopsy, whereas men's lifetime probability of developing invasive cancer is estimated to be 16.7% and to die from it is approximately 2.5%, respectively [1,2]. Thus, many men decease rather with than because of PC. Unlike most other types of malignancies, not every PC poses a serious threat to life and consequently does necessarily require therapy. In this case, expectant management (watchful waiting) might be a reasonable treatment option [3,4]. However, the challenge is to distinguish accurately those potentially dangerous lesions from non-threatening cancers. In particular, small-volume cancers ($\leq$0.5 cm^3) especially when well differentiated, are unlikely to progress clinically within an individual's lifespan [5,6].

The ability to detect PC earlier with serum prostate-specific antigen (PSA) testing and multiple prostate biopsies has led to a distinct increase of localized

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disease [7]. For obvious reasons, this tendency might go together with a higher incidence of small-volume cancers, too. Meaning that the widespread use of PSA may also pander to a probable overtreatment of localized PC. However, with regard to small-volume cancers nearly all data are derived from US institutions which may differ from European centers due to a probably other management of PSA testing (e.g. extensive screening and definition of cut-off).

Therefore, we analysed systematically a large consecutive series of radical prostatectomies, performed in the last 10.5 years, for time trends concerning the incidence of well differentiated small-volume tumours (insignificant cancers). Additionally, clinical and pathological differences were assessed between small-volume cancers and those with a total cancer volume of more than 0.5 cm^3 with a view to the development of a useful model to predict insignificant tumours.

2. Patients and methods

2.1. Study population

Between January 1992 and June 2002 a consecutive series of 2392 patients underwent radical retropubic prostatectomy (RP) for localized PC at our department. Men with complete data about clinical and pathological stage, preoperative serum PSA level, total cancer volume, Gleason score on biopsy and prostatectomy specimen were enrolled. Patients were excluded due to neoadjuvant hormonal treatment ($n = 341$), prior transurethral resection ($n = 14$) as well as incomplete data on clinical stage ($n = 33$), preoperative PSA value ($n = 34$), biopsy Gleason score ($n = 84$) and cancer volume ($n = 632$). Finally, a total of 1254 (52.4%) were enrolled.

2.2. Assessment of tumour characteristics

Clinical and pathological staging were assessed according to the 5th edition of TNM Classification of Malignant Tumors [8]. No imaging information was used to determine clinical stage. Staging work-up included serum PSA determination, digital rectal examination and transrectal ultrasound of the prostate. Serum PSA determinations were performed with the Abbott Axym assay. All prostatectomy specimens were inked entirely on their surfaces and processed according to the Stanford protocol using serial transverse sections at 3 mm [9]. Total cancer volume was calculated by a computerized planimetric method [10]. Histological grading was performed according to the Gleason classification [11]. Insignificant cancers were defined as organ-confined tumours with a cancer volume ≤ 0.5 cm^3 and without any Gleason pattern 4 or 5 [12].

In patients, who had undergone needle biopsy at our outpatient clinic, the percentage of prostate cancer was assessed in all biopsy cores using the formula: mm cancer/mm total tissue $\times$ 100. We analysed sextant transrectal biopsies, which were obtained via an 18 gauge spring-loaded biopsy gun. From these patients we selected a subset ($n = 480$) with a biopsy Gleason score ≤ 6 for the calculation of the predictive model.

2.3. Statistical analysis

For statistical calculations we used a commercially available software package (SPSS®). The significance level was determined at 0.05. Spearman rank order correlation was calculated between the yearly incidence rates of T1c and those of insignificant PC. Small-volume cancers (≤ 0.5 cm^3) were compared with cancers of more than 0.5 cm^3 in their clinical and pathological characteristics by using t-test and χ^2-test. A logistic regression analysis with insignificant cancer as dependent variable and clinical stage, preoperative serum PSA level, PSA density, biopsy Gleason score and percentage of cancer per biopsy set as predictor variables, was done. Deviation contrast coefficients with the first level as reference were used for the variables "clinical stage" and "biopsy Gleason score". The relative importance of prognostic variables was measured by the χ^2 values, based on the Wald test. By using different levels of the assessed independent predictors, predictive values were calculated for the presence of insignificant cancers in a subset of 480 patients.

3. Results

3.1. Clinical and pathological characteristics

Tables 1 and 2 summarise clinical and pathological characteristics of prostate cancers stratified by a threshold of 0.5 cm^3 of total cancer volume. Overall, 79 (6.3%) of 1254 enrolled patients showed a small-volume tumour (≤ 0.5 cm^3) and the tumour of 73 (5.8%) men met the criteria of insignificant cancer. Insignificant PC was detected in 59 (80.8%) of 73 patients exclusively because of an elevated PSA value and only 14 (19.2%) men presented with a suspicious finding on digital rectal examination.

3.2. Time trends

After a peak in the first two years of observation, the incidence of insignificant cancers was stable by about 5% until 1999. Afterwards this rate increased to 7.8% in the years 2000 and 2001. In the first six months of the year 2002 it culminated in 9.5% (Fig. 1). Since 1992 until the first half-year of 2002, T1c PC showed a steady increase to 67.5% and organ-confined PC to 65%, respectively (Fig. 1). However, over the period of 10.5 years the incidence of insignificant cancer presented no significant linear correlation with those of T1c PC ($r = 0.17$, $p < 0.61$).

3.3. Prediction of small-volume cancers

In the logistic regression analysis, PSA density and percentage of cancer per biopsy set were independent predictors for the presence of insignificant cancer (Table 3). Hereby, percentage of cancer volume per biopsy set showed the highest χ^2 value presenting the strongest predictor in this analysis.

In the subset of 480 patients with biopsy Gleason score ≤ 6, 40 men (8.3%) presented with insignificant cancer. For this subset, Table 4 shows the positive and

Table 1
Comparison of clinical tumour characteristics in 1254 patients stratified by a total cancer volume of 0.5 cm^3

Tumour characteristic	≤0.5 cm^3 cancer volume ($n = 79$)	>0.5 cm^3 cancer volume ($n = 1175$)	*p*-value
Mean patient age ± S.D.	63.1 ± 5.8	62.5 ± 6.3	0.348
Mean PSA ± S.D. (ng/ml)	6.0 ± 3.9	11.3 ± 11.5	<0.001
Mean PSA density ± S.D. (ng/(ml cm^3))[a]	0.11 ± 0.07	0.27 ± 0.26	<0.001
Mean ratio of free PSA (%)[b]	19.02 ± 7.6	13.3 ± 7.5	0.277
Mean prostate volume ± S.D. (cm^3)[a]	53.5 ± 21.2	46.3 ± 19.5	0.198
No. of clinical stage (%)			<0.001
T1c	65 (82.3)	620 (52.8)	
T2a/b	14 (17.7)	525 (44.7)	
T3	0 (0)	30 (2.6)	
No. of biopsy Gleason score (%)			<0.001
≤6	77 (97.5)	720 (61.3)	
7	2 (2.5)	410 (34.9)	
≥8	0 (0)	45 (3.8)	
Percentage of cancer per biopsy set (%)[c]	3.8 ± 4.8	18.8 ± 16.3	<0.001

[a] Not available in 9 and 109 patients.
[b] Not available in 19 and 550 patients.
[c] Not available in 36 and 379 patients.

negative predictive values (PPV, NPV) for different percentages of cancer per biopsy set and different PSA densities. Briefly, the lower the percentage of cancer per biopsy set and the PSA density, the higher was the PPV for the presence of insignificant PC. PPV was highest (45.0%) with 1% of cancer in needle biopsies and PSA density lower than 0.10 ng/(ml cm^3). Patients not meeting these clinical requirements would present with significant PC in 93.3%. Sensitivity was low with 22.5%, but specificity was high with 97.5%. Using the aforementioned clinical criteria, nine of 40 men with insignificant cancers would have been identified correctly. Vice versa, we would have misinterpreted 11 of 440 patients with a cancer volume of more than 0.5 cm^3 as insignificant cancers.

Table 2
Comparison of pathological tumour characteristics in 1254 patients stratified by a total cancer volume of 0.5 cm^3

Tumour characteristic	≤0.5 cm^3 cancer volume ($n = 79$)	>0.5 cm^3 cancer volume ($n = 1175$)	*p*-value
Mean cancer volume ± S.D. (cm^3)	0.26 ± 0.15	6.30 ± 6.64	<0.001
No. of stage (%)			<0.001
T2a/b	79 (100)	671 (57.1)	
T3a	0 (0)	309 (26.3)	
T3b	0 (0)	171 (14.6)	
T4	0 (0)	24 (2.0)	
No. of Gleason score (%)			<0.001
≤6	73 (92.4)	461 (39.2)	
7	6 (7.6)	691 (58.8)	
≥8	0 (0)	23 (2.0)	

On the other hand, when using a threshold of 0.15 ng/(ml cm^3) of PSA density and 5% of cancer extent in the biopsies, we found a PPV of 27.2% and a NPV of 96.8%. Under these conditions, sensitivity was 70% and specificity 83.0%, respectively. With other words, 28 of 40 men with insignificant cancers would be diagnosed correctly, whereas 75 of 440 patients with a cancer volume of more than 0.5 cm^3 would be regarded as insignificant cancers.

4. Discussion

Facing the diagnosis of clinically localized prostate cancer, patients and their counselling clinicians may choose from different options. In the majority of cases, some kind of interventional treatment such as radical prostatectomy or external beam radiation will be considered appropriate for an individual's situation. Nevertheless, at present there are two groups of

Table 3
Logistic regression analysis of preoperative parameters in predicting insignificant prostate cancer in 1254 men

Preoperative parameter	DF	*p*-value	χ^2 (Wald)
Clinical stage	2	0.921	0.165
PSA	1	0.739	0.111
PSA density	1	0.025	5.027
biopsy Gleason score	2	0.367	2.006
Percentage of cancer per biopsy set	1	<0.001	17.468

Abbreviations: DF: degrees of freedom.

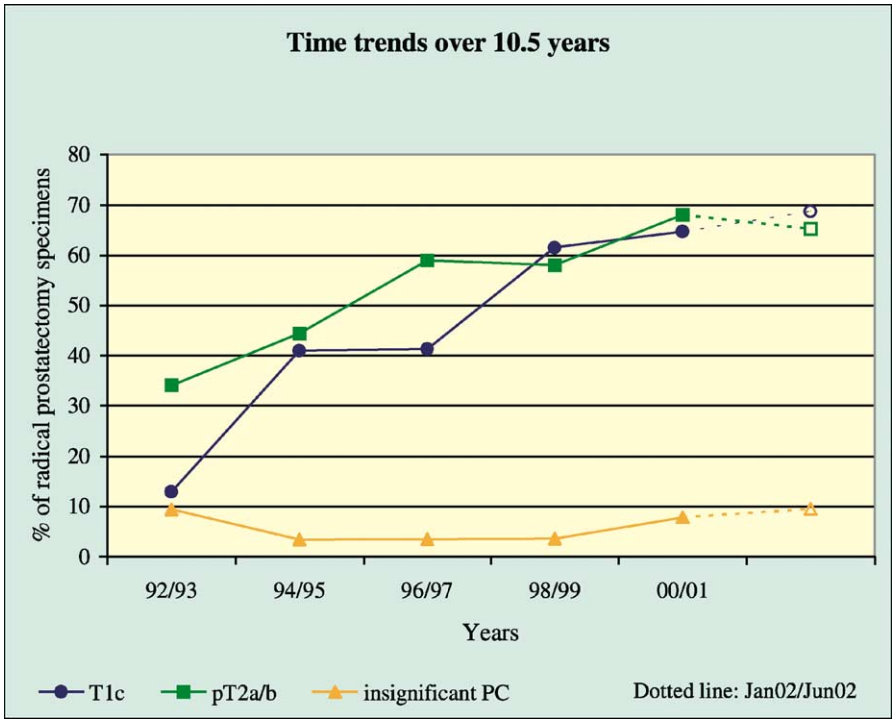

Fig. 1. Analysis of time trends in 1254 eligible patients for insignificant cancer, T1c and organ-confined disease from January 1992 until June 2002.

patients who might be best managed expectantly. The first are patients with life expectancy less than 10 years due to co-morbidity or advanced age [3,4]. The second group concerns men with insignificant PC, who might also be candidates for watchful waiting [3,4]. The latter is of growing importance as the widespread application of PSA testing may lead to overdetection and probable overtreatment of some prostate cancers without the propensity of causing patient morbidity or mortality [13].

Insignificant PC was reported to be found in 6.4–26% of contemporary prostatectomy specimens [5,14–16]. In the present series their overall incidence was 5.8%. Interestingly, in the last two years this rate was increasing to 9.5% in the first six months of the year 2002. Over a time period of 10.5 years, however, we found no statistically significant linear correlation between the incidence of insignificant cancer and T1c PC ($r = 0.17$; $p = 0.61$). Meaning, that the increasing and widespread use of PSA testing in the last years might not imply inevitably a higher rate of insignificant cancer. However, it is noteworthy that the detection rate of insignificant PC may also depend on the number of prostate biopsies [17]. Comparable to our series, Stamey et al. [14] and Soh et al. [15] did not assess a time trend in their series performed between 1988 and 1996 as well as between 1983 and 1995, too.

The results of our analysis demonstrated that only PSA density and percentage of cancer per biopsy set were independent predictors of insignificant cancer. Thereupon, we analysed multiple combinations of

Table 4
Positive and negative predictive values predicting insignificant PC by different percentages of cancer per biopsy set and PSA densities in a subset of 480 patients with biopsy Gleason score ≤6

Percentage of cancer per biopsy set (%)	PSA density					
	0.10		0.125		0.15	
	PPV (%)	NPV (%)	PPV (%)	NPV(%)	PPV (%)	NPV (%)
1	45.0	93.3	39.3	93.6	37.5	93.8
2	42.4	94.2	39.6	95.1	37.5	95.5
3	35.0	94.1	33.3	95.2	31.4	95.6
4	29.8	94.0	26.7	95.1	25.9	95.4
5	30.4	94.6	28.9	96.4	27.2	96.8

Abbreviations: PPV: positive predictive value; NPV: negative predictive value.

these prognosticators to develop a model that would discriminate insignificant from significant cancers. This model was restricted to patients with a biopsy Gleason score ≤6, as it is very unlikely to meet the criteria of insignificant cancer with a higher score. Unfortunately, our model did not show a good sensitivity and specificity combination. Moreover, even when fulfilling the strictest clinical criteria of our model (PSA density ≤0.1 ng/(ml cm^3) and 1% of cancer per biopsy set) about half of these patients would present significant PC. The difficulty in accurately predicting insignificant PC from needle biopsy findings and PSA density is highlighted in Table 4.

Goto et al. [12] assessed PSA density and maximum length of cancer in any core as significant predictors. Additionally, by analysing 170 patients they identified correctly 9 of 12 men (PPV = 75%) with unimportant PC (≤0.5 cm^3, biopsy Gleason score <7) when maximum cancer length was ≤2 mm and PSA density ≤0.1 ng/(ml cm^3), respectively. In another study, Epstein et al. [6] were able to predict accurately 73% of PC, clinically insignificant (as defined as <0.2 cm^3) as well as "minimal" (0.2–0.5 cm^3) by a biopsy Gleason score <7, a PSA density was <0.1 ng/(ml cm^3) and cancer extent smaller than 3 mm in one needle core only. Notably, as the positive predictive value depends on incidence, their distinct higher positive predictive value may be explained by a higher incidence of insignificant cancers in their series compared to our analysed subset (26% versus 8.3%). It seems important to note that the model from Epstein et al. [6] performed well in a validation analysis from the same institution by Carter et al. [18], but not when validated by Goto et al. [12]. The latter authors showed a considerable decrease of PPV to 29% applying the model of Epstein et al. [6] to their own patients. Moreover, Carter et al. [19] recently reported that 25 of 81 men (31%) with probable small-volume disease (cancer volume <0.5 cm^3 and no Gleason pattern 4 or 5) according to their statistical model [6,18], showed progression of disease after a median follow-up of 23 months.

Whether a PC is really insignificant can only be proved when a patient will die from it. Interestingly, Dungan et al. [20], using a statistical model with life tables and different cancer volume doubling times, found that the overwhelming majority of men undergoing radical prostatectomy would suffer from clinically significant PC. Considering this, preferably elderly men may fit for expectant management but young men might do better with curative therapy in case of insignificant PC predicted by preoperative tumour characteristics.

Limitations exist to the present study, as only about half of the study population was eligible for evaluation and data were based on the classical sextant biopsy scheme only.

With the contemporary available algorithms it seems to be difficult to identify insignificant cancers accurately [16,21]. The reasons are certainly multiple. One main point may be due to obvious shortcomings of tissue sampling by transrectal needle biopsy [21]. In spite of the above mentioned limitations, our detailed analysis presents the largest European series on this topic so far and may allow a more differentiated consideration.

5. Conclusion

Over a time period of 10.5 years, the present study revealed an overall incidence of 5.8% of insignificant cancers. This rate showed no significant linear correlation with the increasing rate of PC detected exclusively due to an elevated PSA level. PSA density and percentage of cancer per biopsy set were assessed as independent predictors of insignificant cancer. However, by using the lowest threshold of these prognosticators, the accuracy of our predicting model was 45% only. Nevertheless, the knowledge about the inaccurate prediction of insignificant cancer is useful for elderly patients, who are in between the treatment options of some kind of curative therapy and watchful waiting. These men might better balance the potential risk of disease progression under watchful waiting policy against the possibility of cure also by a less aggressive therapy (e.g. brachytherapy).

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