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Does site-specific labelling and individual processing of sextant biopsies improve the accuracy of prostate biopsy in predicting pathological stage in patients with T1c prostate cancer?

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Objective To evaluate whether individual labelling and processing of the sextant of origin improves the accuracy of prostate biopsy in predicting the final pathological stage after radical prostatectomy in patients with T1c prostate cancer.

Patients and methods The charts of 386 patients treated for prostate cancer by radical prostatectomy between January 1996 and June 1999 were reviewed. In all, 124 patients fulfilled the following inclusion criteria: no abnormality on digital rectal examination (DRE) or transrectal ultrasonography, a prostate specific antigen (PSA) level before biopsy of $\leqslant 20$ ng/mL, and prostate cancer diagnosed after one set of random sextant biopsies, with the cores being submitted in six separate containers individually labelled for the sextant of origin.

Results Within this series of patients with a low tumour burden, the preoperative PSA, biopsy Gleason score and unilateral vs bilateral involvement were not significant predictors of disease extension. The percentage of positive cores and the number and topography of positive sextants were both statistically significant predictors of organ-confined disease. Although these two variables appeared to be statistically equivalent on a first analysis in the overall series, a subgroup of patients was identified who benefited from the complete topographical information, i.e. those 52 (42%) patients with a Gleason score of <7, 25–75% positive biopsies and $\leqslant 3$ positive sextants.

Conclusion These results support the individual labelling of biopsy cores in selected patients with a normal DRE and a moderately elevated PSA, as it helps to better predict the final pathological stage. This substantial benefit outweighs the additional effort by the pathologist.

Keywords prostate biopsy, neoplasm, staging, PSA, prostate cancer, tumour markers

Introduction

Counselling a patient with newly diagnosed prostate cancer on the optimal therapy he should undergo relies primarily on a correct estimate of tumour extension [1,2]. To date, prostate tumours are routinely staged by combining the PSA value and the findings on TRUS, DRE and pathology of the biopsy specimens. Unfortunately, these variables benefit patients whose values are within the extreme range, i.e. patients with a PSA of >20 ng/mL and a Gleason score of $\geqslant 8$ [3,4]. With the widespread application of screening and early-detection programmes, prostate cancer is currently often detected in men with a moderate elevation in PSA level (2.5–10 ng/mL) and no evidence of prostatic disease on DRE and TRUS (stage T1c). As most of the classical prognostic variables are useless for these patients, there is an urgent need for better indicators to distinguish between patients with innocuous and aggressive disease.

Several authors have tried to improve staging algorithms by increasing the amount of information gathered from the initial biopsy set [5–10]. There is controversy between urologists and pathologists on whether the biopsy cores should be submitted in one container or individually labelled and separately processed [11]. Urologists argue that it improves the accuracy of initial staging but pathologists counter that the increased technical effort required to process many samples outweighs the clinical benefit. In the present study we attempted to resolve this question by reviewing our series of prostate biopsies.

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Patients and methods

We retrospectively reviewed the charts of 368 patients who underwent radical retropubic prostatectomy (RRP) for prostate cancer in our institution between January 1996 and June 1999. Prostate cancer had been diagnosed after taking one set of random sextant TRUS-guided biopsies in 124 patients (median age 66.3 years, range 41–79) presenting for an isolated increase in PSA and a normal DRE and TRUS (stage T1c). In each patient the biopsy had been taken according to the following protocol: the left and right sides of the prostatic peripheral zone were divided into three zones (basal, median and apical), each representing about a third of the basal-apical distance. One to three cores (mean 1.24) were obtained from each sextant. Biopsy cores from a sextant were pooled in a unique container individually labelled for location. In 67 patients, a single core was obtained from each sextant. In 57 patients, several cores were sometimes obtained from the same sextant, the total number of biopsy cores being 7–13. A biopsy core was considered positive when it contained cancer. Cores containing only prostatic intraepithelial neoplasia lesions were considered negative. A sextant was considered positive when at least one of the biopsy cores obtained in that sextant contained cancer. The 'topography' of the positive sextant was then defined as their relative position (Fig. 1) within the prostate; two sextants were considered adjacent when contiguous (e.g. apex right and left) and distant when not contiguous (e.g. apex right and median left). Three sextants were defined to be contiguous if all the sextants were adjacent; all others combinations are considered distant.

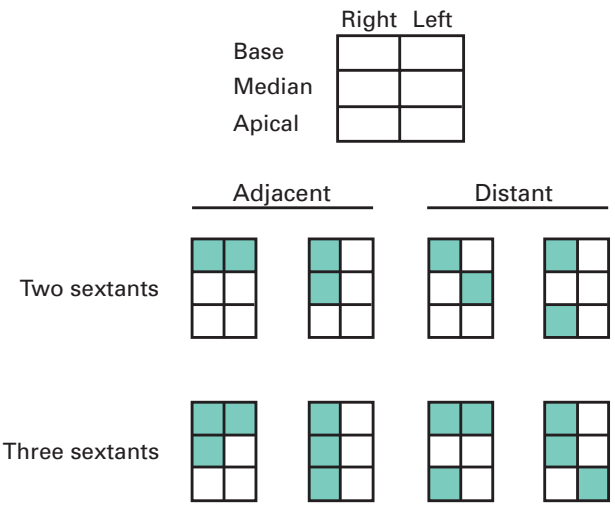

Fig. 1. Definition of the topographical relationship among the sextants.

PSA was measured using the Tandem® (Hybritech, San Diego, USA) assay. Biopsy specimens were analysed by the same pathologist and the cancer graded according to Gleason scoring system (the arithmetic sum of the two widely represented Gleason grades). Very small foci (5%) of Gleason grade 5 prostate cancer were not considered. RRP specimens were immediately fixed, inked and step-sectioned from base to apex. Sections were processed and analysed by the same pathologist and staged according to TNM 1992 and Gleason staging systems. For statistical evaluation of the predictive factors, the pathological results were classified into organ-confined disease (OCD) or extracapsular disease (ECD). ECD was diagnosed if there was capsular perforation, extracapsular positive margin, and positive seminal vesicles; OCD was diagnosed in every other case. Patients with capsular incision (intraprostatic positive margins) were staged as OCD.

Five variables were analysed as potential independent predictors of OCD; PSA, biopsy Gleason score, unilateral vs bilateral cancer invasion, percentage of positive biopsy cores, and number and topography of positive sextants. The percentage of positive biopsy cores is the number of cores containing cancer divided by the total number of cores $\times 100$. Unilateral (one lobe) vs bilateral (two lobes) involvement was extrapolated from the individual topography by pooling the results side by side. Numerical variables were stratified into categories to allow rank correlation tests as follows; PSA in three categories of <4, 4–10 and >10 ng/mL; percentage of positive biopsies into four categories of <25, 25–49, 50–74 and $\geqslant 75\%$ (positive predictive values, PPVs, were calculated for each of these variables to predict OCD); Gleason score into three categories of <5, 5–6 and $\geqslant 7$ (because there were very few patients with a Gleason score of $\geqslant 8$, all the patients with a Gleason score of $\geqslant 7$ were pooled in one category). An independent *t*-test procedure was used to compare variables between patients with OCD or ECD. Chi-squared analysis of contingency tables was used to compare the distribution of the data within the different categories. The Spearman correlation rank order test was used to compare the strength of association between each independent variable, the dependent variable being OCD.

Results

Pathological analysis of the RRP specimens showed OCD in 77 (62%) patients, capsular perforation in 47 (38%), positive margins in 28 (23%) and positive lymph nodes in four (3%)s (Table 1). All the patients selected for this retrospective study had a PSA of $\leqslant 20$ ng/mL (mean 9.4 ng/mL, 95% CI 8.5–10.3);

Table 1 The pathological characteristics of the 124 patients

Pathology	*n (%)*
pT2a	21 (17)
pT2b	7 (6)
pT2c	49 (40)
Positive margins (intracapsular)	25 (20)
pT3a	30 (24)
pT3b	5 (4)
pT3c	12 (10)
Positive margins (extracapsular)	28 (23)
Positive lymph nodes	4 (3)

79 (63%) had a PSA of $\leqslant 10$ ng/mL and there was no significant difference in PSA level between patients with OCD (mean 9.1 ng/mL) and ECD (mean 10 ng/mL; $P=0.41$). PSA was not predictive of OCD within this selected group of patients, neither as a categorical value ($\chi^2=1.31$ $P=0.519$) nor as a continuous variable ($P=0.359$).

In these patients only 13 (10.5%) of the tumours were graded Gleason score $\geqslant 7$; the Gleason score of the biopsy correlated with the Gleason grade of the RRP specimen in only 29 (24%) of the patients. The Gleason score of the biopsy overestimated the Gleason score of the RRP specimen in 41 (33%) and underestimated it in 54 (43%) patients. Within the series there were no significant differences in Gleason scores between patients with OCD and ECD ($P=0.156$). As shown in Table 2, the Gleason score did not statistically predict OCD ($P=0.339$). There was a lower proportion of OCD in patients with cancer detected in one prostatic lobe ($P=0.08$; Table 2) but the predictive value remained poor. There was a significant difference in the percentage of positive biopsy cores between patients with OCD (mean 24.6%) and ECD (mean 38.3%; $P<0.05$) and the percentage was significantly correlated with final pathological stage ($P<0.01$; Table 2), although it was mainly of use in predicting pathological stage in individuals with <25% (81% of pT2) or >75% of positive cores (none of pT2), but less useful for the 65 (49%) patients with 25–75% positive cores.

The biopsy cores were pooled into six different containers labelled for the sextant of origin, i.e. basal, median, and apical right or left. The biopsy procedure correctly identified the definitive location of the tumour within the prostatectomy specimen in 85% of the patients (data not shown). The number of positive sextants correlated significantly with final pathological stage (Table 2). In addition, in patients with two or three positive sextants, there was always a higher proportion of OCD when the positive sextants were topographically 'adjacent' (two sextants, 60% OCD; three, 43% OCD) than when the positive sextants were 'distant' (two sextants, 42% OCD; three sextants, 16% OCD). Notably, patients with three positive sextants distant from each other had a worse prognosis than those with >3 positive sextants. The conventional definition of a sextant biopsy is a single core obtained from each of the sextants. In the present study more than one core was obtained from some sextants in 57 patients, increasing the theoretical risk. This artefact might theoretically reduce sampling errors and alter the statistical value of the analysis. To exclude this hypothesis the subgroup of 67 patients in whom only one core was obtained from each sextant was analysed separately. The distribution and PPV of the number and topography of positive sextants in this subgroup did not differ significantly from the overall series and did not alter the PPV of the variable (chi-square 23.5 for the series vs 19.1 for patients with one core/sextant). This showed that multiple sampling in several patients did not influence the results of the analysis.

Table 2 The PPV for OCD with the biopsy Gleason score (in three categories), unilateral vs bilateral involvement, the percentage of positive biopsy cores (in four categories), and the number and topography of positive sextants (in six categories) both for all patients and for the subset with a Gleason score of <7, 25–75% positive cores and $\leqslant 3$ positive sextants

Variable	*No. of patients*	*PPV of OCD*	P*
Gleason range			
<5	48	0.65	0.339
5–6	62	0.48	
$\geqslant 7$	14	0.43	
Unilateral	95	0.66	0.08
Bilateral	29	0.48	
% positive biopsy			
<25	57	0.81	<0.01
25–50	43	0.51	
51–75	19	0.47	
>75	5	0	
No. of positive sextants			
1	64	0.80	<0.01
2 Adjacent	16	0.60	
Distant	12	0.42	
3 Adjacent	15	0.43	
Distant	7	0.14	
>3	10	0.40	
Subset			
1	9	0.66	
2 Adjacent	17	0.58	
Distant	9	0.44	
3 Adjacent	11	0.45	
Distant	6	0.17	

*Chi-squared test.

The Spearman rank order correlation coefficients for the univariate analysis are shown in Table 3, confirming that PSA and Gleason score are not predictors of OCD in these patients with stage T1c disease and a PSA of $\leqslant 20$ ng/mL. The number and topography of positive sextants and the percentage of positive cores were the best prognostic factors, although these two variables correlate almost linearly (Pearson correlation value 0.868, $P<0.005$), suggesting on first analysis that there is no benefit in identifying the exact position of the biopsy. These two variables are most useful at their extreme values, i.e. in patients with $<25\%$ and $>75\%$ positive cores or one and >3 positive sextants.

To identify a group of patients who would benefit from the complete topographical identification of the site of the biopsy, a subgroup of 52 patients (41%) were isolated with a Gleason score of <7, 25–75% positive cores and <4 positive sextants (Table 3). In this subgroup, none of the variables that did not require sextant-specific labelling predict OCD correctly (Table 3). This confirms that only extreme values of PSA, Gleason score and percentage of positive biopsy are helpful in individual patients. In contrast, assessing the number and topography of positive sextants helps to discriminate between patients with OCD and ECD (Table 2).

Discussion

The clinical behaviour of prostate cancer correlates directly with tumour extension (i.e. pathological stage) and the degree of histological differentiation (i.e. Gleason grade) [1,12,13]. As a complete evaluation of the prostate is only available after RRP, there is much enthusiasm in validating surrogate methods to enhance the prediction of pathological stage and grade at the time of diagnosis [2,5,11]. However, to date PSA and its derivatives, DRE, TRUS, age and a detailed analysis of biopsy cores remain the only practical and useful prognosticators for disease extension [3,8]. Unfortunately, these variables are helpful only for patients with extreme values, especially for PSA and Gleason score [1,3,14]. Meanwhile, screening strategies and early detection programmes have dramatically increased the number of men presenting with a low PSA and a low Gleason score [15,16]. In recent series the mean PSA is often <10 ng/mL and usually <25–30% of patients present with a Gleason score of >7 [1,2,11,13]. In the present patients undergoing RRP over the last 4 years, the mean PSA level was 9.4 ng/mL and only 11% of patients had a Gleason score of $\geqslant 7$. This might explain partly why PSA and Gleason score are not statistically significant predictors of disease extension in such a series of patient recruited through screening and an early detection programme.

In patients with a moderate increase in PSA but no palpable or visible lesions (stage T1c), the standard procedure is to take TRUS-guided random sextant biopsies of the prostate by dividing each side of the peripheral zone into three equidistant anteroposterior zones (i.e. apical, median and basal) and obtaining at least one sample from each [8,9,17]. Several authors previously focused on providing information about the final stage and grade from a detailed evaluation of this initial set of sextant biopsies [5,10,11,17]. The question of whether additional information can be retrieved from an extended topographical mapping of the biopsy location remains controversial, i.e. there is debate about whether the biopsy cores should be pooled in a unique container, in two containers labelled left and right, or into six or more containers identifying the site of the biopsy. Several authors previously suggested that topographical information about the site of the biopsy enhances the prediction of ECD and might help in selecting patients for a nerve-sparing procedure [11,18,19]. However, pathologists argue that individual processing of 6–8 separate containers increases the workload and cost of processing [11]. They also suggest that extended information can be obtained independently of the topographical data from variables such as the number of positive biopsies, the percentage of positive biopsy cores and the percentage of cancer per core [12,17,20,21]. In the present series, we confirmed that the percentage of positive cores was the best predictor of ECD not requiring individual labelling of the core (Table 2). Unfortunately, it provides a clear staging advantage only in patients with $<25\%$ or $>75\%$ positive biopsies.

Table 3 The Spearman rank order correlation and *P* value calculated for each variable, and for the subset of patients presenting with a PSA of <20 ng/mL, Gleason score $\leqslant 7$, 25–75% positive cores, and $\leqslant 3$ positive sextant biopsies

	Correlation coefficient	P
Variable		
Topography of +ve zones	0.41	<0.05
% of +ve biopsy cores	0.38	<0.05
Unilateral vs bilateral	0.157	0.08
Gleason grade	0.139	0.145
PSA	0.09	0.352
Subset		
No./topography of sextants	0.27	0.058
% of +ve biopsy cores	0.08	0.561
Unilateral vs bilateral	0	1
Gleason grade	0	0.783
PSA	0	1

Interestingly, previous detailed topographical analysis of prostate biopsy specimens was aimed almost exclusively at assessing the precise site of ECE, to provide anatomical information to the surgeons before nerve-sparing surgery [11,19,22]. Beyond intuitive anatomical considerations, it is now obvious that the information gained from prostate biopsies has little value in predicting the exact location of the extracapsular spread. Taneja *et al.* [11] suggested that site-specific labelling of an initial set of sextant biopsy cores was not justified based on the clinical information gained. In their series, the PPV of a single biopsy core in identifying the site of ECD was only 8.9%. Only 20% of patients were pT3, almost half of the mean proportion reported in selected series of radical prostatectomy [1,11,13]. In the present study we did not assess the ability of a complete topographical evaluation to precisely determine the site of the extracapsular lesion but rather evaluated its usefulness in predicting OCD. For the entire series the percentage of positive biopsy cores and the number/topography of positive sextants were statistically equivalent predictors of OCD, which would indicate that there is no advantage in individually labelling the cores. However, we identified a subgroup of patients who directly benefit from the topographical data, i.e. those with a mean value of all the other variables (a biopsy Gleason score of <7, 25–75% positive biopsy and $\leqslant 3$ positive sextants). In this series, 40% of the patients were in this so-called 'grey zone' where no variable provides useful information about their risk of ECD (Table 2). Assessing the number/topography of positive sextants was the only variable allowing effective discrimination between OCD and ECD.

In conclusion, the challenge of developing an accurate staging system for patients with prostate cancer has become critical since screening and early detection have dramatically increased the number of men presenting with earlier stages of the disease. The present data suggest that site-specific labelling of sextant prostate biopsy cores significantly improves the accuracy of preoperative staging, especially in the increasing cohort of patients with well-differentiated tumour and a low PSA level. A larger study with more patients is needed to validate these preliminary conclusions.

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Abbreviations: **RRP**, radical retropubic prostatectomy; **OCD**, organ-confined disease; **ECD**, extracapsular disease; **PPV**, positive predictive value.