Prostate Cancer and Prostatic Diseases (2009) 12, 137–142
 1365-7852/09 $32.00
www.nature.com/pcan

ORIGINAL ARTICLE

Diagnostic accuracy of extended biopsies for the staging of microfocal prostate cancers in autopsy specimen

NB Delongchamps[1,2], G de la Roza[3], V Chandan[3], R Jones[1], G Threatte[3], M Jumbelic[4] and GP Haas[1]

[1]*Department of Urology, SUNY Upstate Medical University, Syracuse, NY, USA;* [2]*Department of Urology, Cochin Hospital, René Descartes University, Paris, France;* [3]*Department of Pathology, SUNY Upstate Medical University, Syracuse, NY, USA and* [4]*Onondaga County Medical Examiner, Syracuse, NY, USA*

Clinically insignificant prostate cancers may be predicted when biopsies show a microfocal cancer (MiFC). However, at least one-third of MiFC are underestimated by biopsies. The aim of this study was to evaluate the staging accuracy of different biopsy regimen showing a MiFC. We performed 18 biopsy cores on 164 autopsy prostates. Six cores were taken from the mid-peripheral zone (MPZ), 6 from the lateral PZ (LPZ) and 6 from the central zone (CZ). We tested seven different biopsy regimens by distinguishing the MPZ, LPZ or CZ biopsies either separately or associated with each other. Of the cancers detected by biopsies, we selected those showing a MiFC and compared our findings with whole mount analysis. The positive predictive value of a MiFC referred to how often, when needle biopsies showed a MiFC, there was a clinically insignificant cancer on whole mount prostate analysis. We found that the positive predictive value of a MiFC on 6 or 12 biopsy cores was similar irrespective of biopsy location ($P \approx 1$). On MPZ, MPZ plus LPZ and all 18 biopsies, it was 40, 70 and 87%, respectively ($P < 0.1$). Tumor volume of cancers showing a MiFC on MPZ biopsies was significantly higher than those showing a MiFC on MPZ plus LPZ, or all 18 biopsies ($P < 0.05$). These results show that performing additional cores in case of MiFC on sextant biopsies may help differentiating significant from insignificant cancers.
Prostate Cancer and Prostatic Diseases (2009) **12,** 137–142; doi:10.1038/pcan.2008.38; published online 15 July 2008

Keywords: adenocarcinoma; microfocal; autopsy; needle biopsy

Introduction

Major efforts have been carried out to enhance prostate cancer detection rate through prostate-specific antigen (PSA) screening and biopsy sampling, leading to an overall downward stage migration.[1–3] These efforts led to increased detection of small, well-differentiated cancers, which may not have an aggressive behavior.[4] These small ($\leqslant 0.5\,cm^3$) and well-differentiated cancers (Gleason score <7), designated as 'clinically insignificant',[5,6] may not be of immediate threat, and may not need radical and possibly morbid treatment. Clinically insignificant cancers represent up to 30% of all T1c stage cancers.[6,7]

To avoid overtreatment, staging tools are therefore needed to identify nonaggressive and clinically insignificant cancers. Some studies proposed models which based on clinical, biological and biopsy findings would predict the presence of clinically insignificant cancers on radical prostatectomy (RP) specimens.[6,8,9] The number of positive biopsy cores, the amount of cancer involvement and the Gleason score on biopsies were associated with clinical significance.[6,10] Small amounts of well-differentiated cancer on sextant biopsies, so called microfocal cancers (MiFCs), were reported to predict clinically insignificant cancer on RP specimen.[6] However, one to two-thirds of MiFC are clinically significant on RP.[11,12] The low number of cores taken at biopsy may explain these results. Indeed, prostate cancer is often multifocal[13] and 1 MiFC detected in 6–10 cores does not exclude other overlooked contiguous or distant tumors that could be detected by a more extensive biopsy protocol.

Unfortunately clinical studies are subject to verification bias because many small, insignificant cancers are treated by observation regimens or by radiation without ever obtaining histological verification of the true extend of the lesion. We identified 25 cases of MiFC from a cohort of 164 cases that were part of a larger prostate cancer detection study on autopsy prostates using an extended, *ex vivo* biopsy protocol and whole mount analysis of entire gland.[14] Of them, we selected those showing a MiFC in 1 of 6, 12 or 18 cores and compared our findings with whole mount analysis.

Materials and methods

Tissue collection

We prospectively collected 202 consecutive prostate glands from deceased men that were provided by the

Correspondence: Dr NB Delongchamps, 15 rue Ginoux, Department of Urology, Cochin Hospital, Paris 75015, France.
E-mail: nicolasbdl@hotmail.com
Received 9 May 2008; revised 16 June 2008; accepted 16 June 2008; published online 15 July 2008

University Hospital, Syracuse, NY, the Onondaga County Medical Examiner, Syracuse, NY, and by the National Disease Research Interchange, Philadelphia, PA. At autopsy, the entire prostate gland was excised and placed in 10% neutral buffered formalin. Prostatic tissue was not entirely removed in 38 (19%) of the prostates autopsied; these subjects were excluded, leaving 164 prostate glands available for analysis.

Ex vivo *prostate biopsy*

Biopsies were performed in a manner that mimicked clinical biopsy under the direction of an experienced urologist (GPH). Biopsies were taken with a standard 18F spring-loaded biopsy gun (Bard Maxcore, CR Bard, Covengton, GA, USA). The biopsy gun needle was inserted through the posterior surface of the gland with a 45° angle, and bilateral samples were taken from the apex, mid-gland and base. Six cores were taken from the mid-peripheral zone (MPZ) as in traditional sextant biopsy protocols. A total of 12 additional cores were taken, 6 cores from the central zone (CZ) and 6 from the lateral PZ (LPZ; Figure 1). For each biopsy with cancer, Gleason score, number of positive cores, percentage of cancer involvement in a core and tumor location were determined. A MiFC was defined as one positive core with less than 50% of cancer involvement and a Gleason score $\leqslant 6$. Comparatively, a macrofocal cancer (MaFC) was defined as more than one positive core and/or more than 50% of cancer involvement in 1 core and/or a Gleason score $\geqslant 7$.

Whole mount prostate processing and histological evaluation

After fixation for at least 72 h, the glands were separated from the surrounding tissue. The glands were cut into 4 mm sections perpendicular to the posterior plane. The blocks obtained were labeled and embedded in paraffin, and then sectioned to produce 5-μm whole mount sections that were stained with hematoxylin–eosin. A single pathologist (GdlR) microscopically analyzed all samples in a blinded fashion without any information on biopsy location. Examination of the biopsies was carried out prior to the examination of whole mount sections to avoid assessment biased of biopsies. Each tumor focus detected was outlined on whole mount sections. Immunohistochemical studies using a cocktail containing basal cell marker p63 and P504S/α-methylacyl-coenzyme A racemase were performed for cases that were not unequivocally considered cancerous on morphology alone. The total number of tumor foci and their location were recorded. An area of carcinoma was considered a separate focus if it was separated by a low-power field diameter (4.5 mm) from the nearest adjacent focus.[15] Each tumor focus was graded according to the modified Gleason grading system.[16]

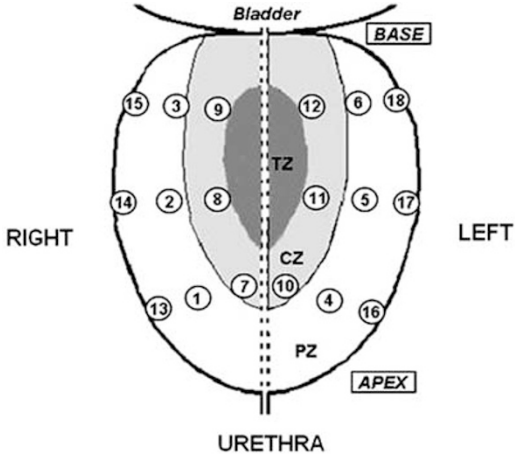

Figure 1 Schema of the biopsy cores location. The first six cores (1–6) were taken from the mid-peripheral zone (MPZ), the next six cores (7–12) from the central zone (CZ) and the last six cores (13–18) from the lateral PZ (LPZ).

Digital reconstruction and calculation of tumor volume

The surface of each tumor focus was determined by computerized planimetry, using an image analysis program (ImageJ).[17] Tumor volume was calculated by multiplying each tumor surface by the section thickness and by 1.5 to compensate for tissue shrinkage.[18] The index tumor volume was that of the largest focus of carcinoma. Total tumor volume was calculated as the sum of the volumes of individual foci. Tumors were considered clinically insignificant if they were organ confined with an index tumor volume $<0.5\,cm^3$ and a Gleason score 6 or less.[5,6]

Statistical analyses

Statistical analyses were performed using Stata 9.0 (Stata Corporation, College Station, TX, USA), with $P<0.05$ considered statistically significant. The positive predictive value referred to how often, when needle biopsies showed a MiFC, there was a clinically insignificant cancer on whole mount analysis. The negative predictive value referred to how often, when needle biopsies showed a MaFC, there was not clinically insignificant cancer but in fact a clinically significant cancer on whole mount analysis. The χ^2-test was used to compare predictive values and the Mann–Whitney test to compare tumor volumes between the groups.

Results

Table 1 shows the pathological characteristics of the 25 biopsy-detected prostate cancers. Median age at death was 70 years (range 49–92). Median gland volume was $45\,cm^3$ (range 22–95). Median index and total tumor volume was 0.4 and $0.83\,cm^3$, respectively. A total of 15 (60%) cancers were having Gleason score 6 or less, and 10 (40%) were having Gleason score 7 or higher. Six cancers were unifocal. The median number of tumor foci per cancer was 2 (range 1–6). On the basis of histological criteria, 16 cancers (64%) were clinically significant and 9 (36%) were clinically insignificant.

A total of 5 MiFC were detected with the MPZ biopsies alone, 13 with the LPZ biopsies alone and 5 with the CZ biopsies alone. Of them, two (40%), six (54%) and two (40%) were clinically insignificant, respectively. MPZ biopsies detected nine, LPZ biopsies detected six and CZ biopsies detected five MaFC. Of them, eight (89%), six

Table 1 Correlation between biopsy result and whole mount analysis in the 25 cases of biopsy-detected prostate cancers

Case	*Biopsy results*			*Whole mount analysis*		
	MPZ biopsies	*LPZ biopsies*	*CZ biopsies*	*Pathologic stage*	*Gleason score*	*Clinical significance*
1	Negative	MiFC	Negative	pT2a	3+3	Insignificant
2	Negative	MiFC	Negative	pT2a	3+3	Insignificant
3	MaFC	Negative	Negative	pT2c	3+3	Insignificant
4	MaFC	Negative	MaFC	pT3a	4+5	Significant
5	MiFC	MiFC	MiFC	pT2c	3+3	Insignificant
6	MaFC	MiFC	MaFC	pT2c	3+4	Significant
7	Negative	MiFC	MiFC	pT2c	3+3	Insignificant
8	Negative	MiFC	Negative	pT2c	3+3	Insignificant
9	MaFC	MiFC	Negative	pT3a	4+3	Significant
10	Negative	MiFC	Negative	pT2c	3+4	Significant
11	Negative	MiFC	Negative	pT2a	3+3	Insignificant
12	MaFC	MaFC	Negative	pT2b	3+3	Significant
13	Negative	MiFC	Negative	pT2c	3+3	Insignificant
14	MaFC	Negative	Negative	pT2a	3+4	Significant
15	Negative	MaFC	Negative	pT2a	3+3	Significant
16	Negative	MaFC	Negative	pT2a	3+4	Significant
17	MiFC	MiFC	MiFC	pT3a	3+3	Significant
18	MiFC	Negative	Negative	pT2c	3+3	Insignificant
19	Negative	MiFC	MiFC	pT2c	3+3	Significant
20	MiFC	Negative	MiFC	pT3a	4+3	Significant
21	MaFC	MaFC	Negative	pT2c	3+4	Significant
22	MaFC	Negative	MaFC	pT3a	3+4	Significant
23	MiFC	MiFC	Negative	pT2c	3+3	Significant
24	Negative	MaFC	MaFC	pT3a	3+3	Significant
25	MaFC	MaFC	MaFC	pT2a	4+4	Significant

Abbreviations: CZ, central zone; LPZ, lateral PZ; MaFC, macrofocal cancer; MiFC, microfocal cancer; MPZ, mid-peripheral zone.
Negative: no biopsy core positive for cancer.
MaFC: more than one positive core for cancer and/or more than 50% of cancer involvement in one core and/or Gleason grade patterns of 4 or 5.
MiFC: one single positive biopsy with less than 50% of cancer involvement and the absence of grade 4 or 5 patterns.

Table 2 Predictive values of a MiFC on 6, 12 and 18 cores

	PPV (%)	*NPV (%)*
6 cores		
MPZ	40	89
LPZ	54	100
CZ	40	100
12 cores		
MPZ plus LPZ	70	87
MPZ plus CZ	50	85
LPZ plus CZ	56	85
18 cores		
MPZ plus LPZ plus CZ	86	83

Abbreviations: CZ, central zone; LPZ, lateral PZ; MiFC, microfocal cancer; MPZ, mid-peripheral zone; NPV, negative predictive value; PPV, positive predictive value.

(100%) and five (100%) were clinically significant, respectively. The positive and negative predictive values of a MiFC on six cores were not statistically different between the three biopsy locations in the MPZ, LPZ or CZ ($P=1$).

MPZ and LPZ biopsies together detected 10 MiFC and 15 MaFC. A total of 7 (70%) of the MiFC were clinically insignificant and 13 (86.7%) of the MaFC were significant. MPZ and CZ biopsies together detected 4 MiFC and 13 MaFC. A total of 2 (50%) of the MiFC were clinically insignificant and 11 (85%) of the MaFC were significant. LPZ and CZ biopsies together detected 9 MiFC and 13 MaFC. A total of 5 (55%) of the MiFC were clinically insignificant and 11 (85%) of the MaFC were significant. The positive and negative predictive values of a MiFC on 12 biopsy cores were not statistically different between the 3 biopsy locations ($P=1$).

With 18 cores altogether (MPZ, CZ and LPZ), 7 MiFC and 18 MaFC were detected. A total of 6 (86%) of the MiFC were clinically insignificant and 15 (83%) of the MaFC were significant. The positive predictive value of a MiFC was increasing with the number of cores taken, but the difference was not significant ($P=0.1$).

Although three significant cancers detected on MPZ biopsies were MiFC (cases 17, 20 and 23), two of them showed additional foci of cancer when the six LPZ biopsies were added. The third showed additional foci of cancer when the six CZ biopsies were added (Table 1). Although three significant cancers detected on MPZ and LPZ biopsies together were MiFC (cases 10, 19 and 20), two of them showed additional foci of cancer when the six CZ biopsies were added (Tables 1 and 2).

The index and total tumor volumes of the MiFCs detected on either six MPZ, LPZ or CZ biopsies were not significantly different ($P>0.1$; Table 3). MiFCs detected on 18 biopsies had smaller tumor volumes than those detected on 6 biopsies targeted in the CZ or MPZ. MiFCs detected on 12 biopsies (in the MPZ plus LPZ) had smaller tumor volumes than those detected on six MPZ biopsies (Tables 3 and 4).

Discussion

With the widespread use of PSA screening, the incidence of T1c stage prostate cancer has increased. Many of the tumors are low-volume and low-grade cancer, which

Table 3 Index and total tumor volumes of prostate cancers detected with a MiFC on biopsies

	6 biopsies			*12 biopsies*			*18 biopsies*
	MPZ	*LPZ*	*CZ*	*MPZ plus LPZ*	*MPZ plus CZ*	*LPZ plus CZ*	*MPZ plus LPZ plus CZ*
Median TTV (cm^3)	0.96 (0.64–1.31)	0.51 (0.05–4.9)	0.95 (0.34–1.1)	0.32 (0.05–0.95)	0.76 (0.34–1.3)	0.29 (0.05–1.9)	0.29 (0.05–0.64)
Median ITV (cm^3)	0.59 (0.37–1.2)	0.32 (0.03–3.9)	0.59 (0.32–0.95)	0.24 (0.03–0.95)	0.59 (0.32–1.2)	0.18 (0.03–1.2)	0.17 (0.03–0.37)

Abbreviations: CZ, central zone; ITV, index tumor volume; LPZ, lateral PZ; MiFC, microfocal cancer; MPZ, mid-peripheral zone; TTV, total tumor volume.

Table 4 Tumor volume of cancers detected with a MiFC on 6 biopsies as compared to 12 or 18 biopsies: *P*-values, Mann–Whitney test

	12 biopsies			*18 biopsies*
	MPZ plus LPZ	*MPZ plus CZ*	*LPZ plus CZ*	*MPZ plus LPZ plus CZ*
6 biopsies				
MPZ				
ITV	0.03	0.6	0.2	0.006
TTV	0.007	0.4	0.1	0.006
LPZ				
ITV	0.4	0.4	0.6	0.1
TTV	0.2	0.6	0.5	0.1
CZ				
ITV	0.06	0.9	0.3	0.005
TTV	0.02	0.7	0.2	0.01

Abbreviations: CZ, central zone; ITV, index tumor volume; LPZ, lateral PZ; MiFC, microfocal cancer; MPZ, mid-peripheral zone; TTV, total tumor volume.

may not be clinically significant. Tumor volume is directly related to the risk of capsular penetration, seminal vesicle invasion and microscopic metastases to the pelvic lymph nodes.[5,19,20] Small and well-differentiated cancers are therefore not thought to be of immediate threat. Stamey *et al*.[5] and Epstein *et al*.[6] defined clinically insignificant cancers as organ confined with an index tumor volume $<0.5\,cm^3$ and absence of grade 4 or 5 patterns. Using these histological criteria in patients with T1c stage disease, the reported incidence of clinically insignificant cancers on RP specimen was reported to be up to 30%.[6,9,10,12] Increasing numbers of such patients are placed on active surveillance regimens.

The finding of adverse pathological features at biopsy is predictive of advanced disease on RP specimen.[21–23] However, predicting insignificant cancer at biopsy is more difficult. There has been several attempts to define criteria to predict insignificant cancer preoperatively, using biopsy results alone or combined with PSA density (PSAD) or f/t PSA. However, there are controversies on the amount of cancer on biopsies that should be considered as microfocal. Epstein *et al*.[6] first introduced the concept of MiFC on biopsies combined with PSAD to predict clinically insignificant disease. For patients with a PSAD less than $0.1\,ng\,ml^{-1}\,cm^{-3}$, a MiFC was defined by low-grade (Gleason score <7) cancer on less than three cores with no core showing more than 50% of cancer involvement. For patients with a PSAD between 0.1 and $0.15\,ng\,ml^{-1}\,cm^{-3}$, a MiFC was defined by no more than one positive core with less than 3 mm of cancer involvement. Using this model, they reported positive predictive values for insignificant cancer of 75–88.5% with negative predictive values of 75–95%.[6,8] In a subsequent study, they reported that patients with a f/t PSA >15% and no more than one positive core with low-grade cancer and less than 3 mm of cancer involvement had positive and negative predictive values of 94 and 77% for insignificant cancer on RP specimen.[7] In contrast, Noguchi *et al*.[9] did not find any advantage in using PSAD or f/t PSA in combination with biopsy findings. They reported that patients with one positive core with less than 3 mm of cancer involvement and low-grade cancer had positive and negative predictive values of 75 and 95%, irrespectively of their level of PSAD or f/t PSA. Other authors evaluated more restrictive biopsy criteria to predict clinical insignificance. Allan *et al*.[11] reported that less than 0.5 mm of cancer with no Gleason score >7 on a single core was predictive of insignificant cancer in only 67% of the cases. Others used the percentage of cancer involvement instead of the length of cancer, and reported that less than 10% of cancer involvement on a single core predicted clinically insignificant cancer in only 77% of the cases.[10]

Clearly, the multitude of proposed algorithms creates a challenge in proposing useful clinical recommendations. The studies have in common a low and heterogeneous number of cores taken at biopsy and differ in the biopsy schema used.[6,11] Moreover, there is no information currently available relative to the location of the MiFC at biopsy. Extended biopsies have been shown to increase the detection rate of prostate cancer,[24] suggesting that performing additional biopsies could be an interesting strategy to exclude any other contiguous or distant tumors in the prostate of patients presenting with a single MiFC on sextant biopsies. A recent report showed indeed that 70% of the patients presenting a MiFC on 10-core biopsies showed additional cancer patterns on saturation biopsies.[25] Epstein *et al*.[26] also reported that saturation biopsies showed additional tumor foci in patients with a MiFC on standard biopsies. They performed *ex vivo* saturation biopsies on RP specimen from patients harboring small amount of cancer on biopsies (no core with more than 50% involvement; Gleason score less than 7, and fewer than 3 cores involved). As in the present study, insignificant cancer at RP was considered organ confined, with no

Gleason score $\geqslant 7$, and a tumor volume $\leqslant 0.5\,cm^3$. Of the cancer specimens, 29% had been incorrectly classified before surgery using standard biopsy schemes. Using saturation biopsy, they decreased to 11.5% the amount of incorrectly classified cancers.[26]

We found that the predictive values of a MiFC on six biopsies were similar irrespectively of the cores location in the MPZ, LPZ or CZ. Increasing the number of cores increased the positive predictive value of a MiFC, although the difference was not significant ($P<0.1$). However, cancers showing a MiFC on MPZ biopsies had a significantly higher tumor volume than those showing a MiFC on MPZ plus LPZ biopsies together.

Contrary to LPZ biopsies, biopsies directed to the CZ did not demonstrate any advantage in enhancing cancer detection rate.[24] However, CZ biopsies could have an interest for cancer staging, by detecting additional tumors in this area. Recent reports suggested indeed that tumors located in the CZ were of higher volume than those located in the PZ.[27] With the additional LPZ and CZ biopsies, all three cases of significant cancers diagnosed with a MiFC on sextant biopsies were upgraded to cases with unfavorable biopsy features. With the additional CZ biopsies, two of the three cases of significant cancers diagnosed with a MiFC on extended 12-core biopsies (MPZ plus LPZ biopsies) were also upwarded to cases with unfavorable biopsy features.

Additional biopsies showed also additional cancer patterns in a small amount of prostate glands with insignificant cancers, therefore decreasing the negative predictive value of a MiFC. Nevertheless, the first objective is to detect aggressive cancers in patients that should not be included in active surveillance protocols.

The definition of MiFC we used differs from what has been proposed earlier in literature. However, there is currently no consensus on what amount of cancer on biopsies should be considered as microfocal, as well as how to measure it (percentage or length of cancer). The purpose of this study was not to identify the best criteria to define a MiFC, but to evaluate the ability of additional cores to increase its predictive value.

This study was limited by the small amount of cases diagnosed with a MiFC, and we failed to show any significant statistical difference between the positive predictive value of a MiFC on 6, 12 and 18 biopsies. However, even with this small sample size, the comparison of tumor volumes showed significant differences between MiFC detected with sextant and extended biopsies, suggesting that a MiFC on extended biopsies was more predictive of a small cancer. It is indeed likely that increasing the number of biopsies allows a better estimation of tumor volume. However, tumor volume is not the only criteria to characterize insignificant cancer, because small cancers can be poorly differentiated or have extracapsular extension. Another limitation of the study is related to the absence of a strict reproducibility of the *ex vivo* biopsy, that could have introduced detection bias. Some authors reported the use of biopsy templates to perform accurate pathological mapping of the prostate.[28] However, the aim of our biopsy technique was to mimic clinical biopsy, which is also known for its poor reproducibility, especially between prostates of very different sizes.

It should also be noted that the definition of 'clinical significance' is strictly based on histological criteria and does not include patients age, PSA, or comorbidities.[29] Furthermore, all the cancers detected in this study could be considered as 'clinically insignificant' as none of the deceased men were known to have prostate cancer. The purpose of this study was not to select the best candidates for prostate cancer screening or active treatment. Although autopsy data are of major value to investigate prostate cancer risk factors such as genetic polymorphism[30] or inflammatory changes,[31] we think that histological data alone are not sufficient to evaluate cancer significance. However, because of the absence of verification bias, we think that autopsied prostates are an accurate model for the evaluation of prostate biopsy.

In conclusion, the presence of a MiFC on sextant biopsies was not predictive of insignificant cancer. The MiFC detected with 12 and 18 biopsies were predictive of smaller cancers. All the significant cancers that were MiFC on sextant biopsies (MPZ cores) showed at least one additional positive biopsy with additional sampling. Performing additional laterally and centrally directed biopsies may therefore improve staging for patients showing a MiFC on sextant biopsies. In patients with 12 or more biopsy regimens MiFC predicts low-volume, low-grade disease and would not require additional biopsies in order to advise them of treatment strategies. The need for future biopsies would have to be based on clinical parameters.

Acknowledgements

This study was funded by National Institute on Aging (AG021389) and National Cancer Institute (CA097751).

References

1 Master VA, Chi T, Simko JP, Weinberg V, Carroll PR. The independent impact of extended pattern biopsy on prostate cancer stage migration. *J Urol* 2005; **174**: 1789–1793.
2 Ung JO, Richie JP, Chen MH, Renshaw AA, D'Amico AV. Evolution of the presentation and pathologic and biochemical outcomes after radical prostatectomy for patients with clinically localized prostate cancer diagnosed during the PSA era. *Urology* 2002; **60**: 458.
3 Galper SL, Chen MH, Catalona WJ, Roehl KA, Richie JP, D'Amico AV. Evidence to support a continued stage migration and decrease in prostate cancer specific mortality. *J Urol* 2006; **175**: 907–912.
4 Roemeling S, Roobol MJ, Postma R, Gosselaar C, van der Kwast TH, Bangma CH *et al*. Management and survival of screen-detected prostate cancer patients who might have been suitable for active surveillance. *Eur Urol* 2006; **50**: 475–482.
5 Stamey TA, Freiha FS, McNeal JE, Redwine EA, Whittemore AS, Schmid HP. Localized prostate cancer. Relationship of tumor volume to clinical significance for treatment of prostate cancer. *Cancer* 1993; **71**: 933–938.
6 Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (T1c) prostate cancer. *JAMA* 1994; **271**: 368–374.
7 Epstein JI, Chan DW, Sokoll LJ, Walsh PC, Cox JL, Rittenhouse H *et al*. Nonpalpable stage T1c prostate cancer: prediction of insignificant disease using free/total prostate specific antigen levels and needle biopsy findings. *J Urol* 1998; **160**: 2407–2411.
8 Carter HB, Sauvageot J, Walsh PC, Epstein JI. Prospective evaluation of men with T1c adenocarcinoma of the prostate. *J Urol* 1997; **157**: 2206–2209.

9 Noguchi M, Stamey TA, McNeal JE, Yemoto CM. Relationship between systematic biopsies and histological features of 222 radical prostatectomy specimens: lack of prediction of tumor significance for men with nonpalpable prostate cancer. *J Urol* 2001; **166**: 104–109.
10 Anast JW, Andriole GL, Bismar TA, Yan Y, Humphrey PA. Relating biopsy and clinical variables to radical prostatectomy findings: can insignificant and advanced prostate cancer be predicted in a screening population? *Urology* 2004; **64**: 544–550.
11 Allan RW, Sanderson H, Epstein JI. Correlation of minute (05 mm or less) focus of prostate adenocarcinoma on needle biopsy with radical prostatectomy specimen: role of prostate specific antigen density. *J Urol* 2003; **170**: 370–372.
12 Boccon-Gibod LM, Dumonceau O, Toublanc M, Ravery V, Boccon-Gibod LA. Micro-focal cancer: a comparison of biopsy and radical prostatectomy specimen features. *Eur Urol* 2005; **48**: 895–899.
13 Wise AM, Stamey TA, Mc Neal JE, Claytoin JL. Morphologic and clinical significance of multifocal prostate cancers in radical prostatectomy specimens. *Urology* 2002; **60**: 264.
14 Haas GP, Delongchamps NB, Jones RF, Chandan V, Serio AM, Vickers AJ *et al*. Needle biopsies on autopsy prostates: sensitivity of cancer detection based on true prevalence. *J Natl Cancer Inst* 2007; **99**: 1484–1489.
15 Troncoso P, Babaian RJ, Ro JY, Grignon DJ, von Eschenbach AC, Ayala AG. Prostatic intraepithelial neoplasia and invasive prostatic adenocarcinoma in cystoprostatectomy specimens. *Urology* 1989; **34**: 52–56.
16 Epstein JI, Allsbrook Jr WC, Amin MB, Egevad LL. The 2005 International Society of Urological Pathology (ISUP) concensus conference on Gleason grading of prostatic carcinoma. *Am J Surg Pathol* 2005; **29**: 1228–1242.
17 Noguchi M, Stamey TA, McNeal JE, Yemoto CE. Assessment of morphometric measurements of prostate carcinoma volume. *Cancer* 2000; **89**: 1056–1064.
18 Schned AR, Wheeler KJ, Hodorowski CA, Heaney JA, Ernstoff MS, Amdur RJ *et al*. Tissue-shrinkage correction factor in the calculation of prostate cancer volume. *Am J Surg Pathol* 1996; **20**: 1501–1506.
19 McNeal JE, Bostwick DG, Kindrachuck RA, Redwine EA, Freiha FS, Stamey TA. Patterns of progression in prostate cancer. *Lancet* 1986; **1**: 60–63.
20 Lowe BA, Listrom MB. Incidental carcinoma of the prostate: an analysis of the predictors of progression. *J Urol* 1988; **140**: 1340–1344.
21 Ravery V, Chastang C, Toublanc M, Boccon-Gibod L, Delmas V, Boccon-Gibod L. Percentage of cancer on biopsy cores accurately predicts extracapsular extension and biochemical relapse after radical prostatectomy for T1–T2 prostate cancer. *Eur Urol* 2000; **37**: 449–455.
22 Algaba F, Arce Y, Oliver A, Barandica C, Santaularia JM, Montanés R. Prognostic parameters other than Gleason score for the daily evaluation of prostate cancer in needle biopsy. *Eur Urol* 2005; **48**: 566–571.
23 Montironi R, Vela-Navarrete R, Lopez-Beltran A, Mazzucchelli R, Bono A. 2005 update on pathology of prostate biopsies with cancer. *Eur Urol* 2006; **49**: 441–447.
24 Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. *J Urol* 2006; **175**: 1605–1612.
25 Boccon-Gibod LM, Delongchamps NB, Toublanc M, Boccon-Gibod LA, Ravery V. Prostate saturation biopsy in the reevaluation of microfocal prostate cancer. *J Urol* 2006; **176**: 961–963.
26 Epstein JI, Sanderson H, Carter HB, Scharfstein DO. Utility of saturation biopsy to predict insignificant cancer at radical prostatectomy. *Urology* 2005; **66**: 356–360.
27 Koppie TM, Bianco Jr FJ, Kuroiwa K, Reuter VE, Guillonneau B, Eastham JA *et al*. The clinical features of anterior prostate cancers. *BJU Int* 2006; **98**: 1167–1171.
28 Barzell WE, Melamed MR. Appropriate patient selection in the focal treatment of prostate cancer: the role of transperitoneal 3-dimensional pathologic mapping of the prostate. A 4 year experience. *Urology* 2007; **70**: 27–35.
29 Dugan JA, Bostwick DG, Myers RP, Qian J, Bergstralh EJ, Oesterling JE. The definition and preoperative prediction of clinically insignificant prostate cancer. *JAMA* 1996; **275**: 288–294.
30 Iguchi T, Wang CY, Delongchamps NB, Sunheimer R, Nakatani T, de la Roza G *et al*. Association of prostate cancer and manganese superoxide dismutase AA genotype influenced by presence of occult cancer in control group. *Urology* 2008; [E-pub ahead of print].
31 Delongchamps NB, de la Roza G, Chandan V, Jones R, Sunheimer R, Threatte G *et al*. Evaluation of prostatitis in autopsied prostates: is chronic inflammation more associated with benign prostatic hyperplasia or cancer? *J Urol* 2008; **179**: 1736–1740.