

## ARTICLE

## Is Quadrant Biopsy Sufficient in Men Likely to Have Advanced Prostate Cancer? Comparison with Extended Biopsy

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We hypothesized that quadrant prostate biopsy (QPB) provides sufficient first-line pathological evaluation of patients with presumed advanced prostate cancer (PC). The aim of this study was to investigate whether the reduction of core number in first-line PB from 6-12 to 4 in patients with presumed advanced PC leads to loss of clinically relevant information. We retrospectively studied 113 men that underwent PB, classified in two groups: "H" (high) and "L" (low likelihood of having advanced PC), according to PSA, digital rectal and transrectal ultrasound findings. Pathological results of 6-12-core PB and QPB were retrospectively compared for the presence of malignancy, percentage of positive cores, Gleason score (GS), and the presence of high-grade prostatic intraepithelial

neoplasia (HGPIN). PC detection rate was not impaired in group H but dropped significantly in group L, and the percentage of positive cores was not significantly changed in group H ( $p=0.39$ ), but decreased in group L ( $p=0.04$ ), due to sampling scheme reduction. No HGPIN was missed with QPB in group H, while 2 HGPINs were missed in group L. No significant change in GS in either group was observed ( $p=0.12$ ,  $p=0.13$ ) due to reduction to QPB. We conclude that in patients with presumed advanced PC, reduction of the number of cores in PB may be an acceptable diagnostic strategy, but further studies are needed to analyze the impact of PB scheme reduction on other relevant pathological information obtained from PB. (Pathology Oncology Research Vol 11, No 1, 40-44)

*Key words:* prostatic neoplasms; needle biopsy

### Introduction

Recently, most urologists abandoned biopsy of hypoechoic focal lesions, and focused on multiple systematic sampling of the gland. Sextant prostate biopsy (PB) has proved to be of limited sensitivity in prostate cancer (PC) detection. Increase in the number of cores per PB session improves PC detection rate,<sup>2,3,5,13,15,22</sup> and contributes to the accuracy of preoperative staging.<sup>4,12,23</sup> Although extensive PB was proved to be relatively safe, discomfort and minor complications are present in many patients,<sup>8,14,16</sup> and it would be of benefit to avoid them. In patients with presumed high tumor burden, with regard to PSA, digital rectal examination

(DRE) or transrectal ultrasound (TRUS) and suspicion of metastases,<sup>9,10,17,25</sup> it is not reasonable to take a large number of cores in first-line PB, because PC is likely to be present in the entire gland volume, and assessment of intraprostatic tumor distribution is of minor importance. These men are at high risk to have non-organ-confined (NOC) PC, and they are rarely candidates for radical prostatectomy (RP). There is scant literature dealing with the possibility of reduction of PB protocols when extensive sampling is not necessary.<sup>16</sup> The aim of this study was to investigate whether the reduction of core number in first-line PB from 6-12 to 4 in patients with presumed advanced PC would lead to loss of clinically relevant information obtained by means of PB.

### Materials and methods

*Patients.* We retrospectively studied 113 consecutive patients (mean age 71.8 years, range 50-89), in which systematic PB was performed during a one-year period. The

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**Table 1. Selection criteria for classifying the patients into two categories, according to probability of the presence of advanced (NOC) PC**

Likelihood of the presence of advanced PC	PSA level	TRUS* and DRE** finding	Number of patients
Low	<4 ng/mL	TRUS suspect or DRE suspect	9
Low	4-10 ng/mL	TRUS non-suspect and DRE non-suspect	49
High	<4 ng/mL	TRUS suspect and DRE suspect	4
High	4-10 ng/mL	TRUS suspect and/or DRE suspect	12
High	>10 ng/mL	Irrespective of TRUS and DRE finding	39
Total			113

\*TRUS was considered suspicious of malignancy if hypoechoic sector or nodule in peripheral zone (PZ) was detectable, if the prostate was inhomogeneous without zonal discrimination, or if unsharp prostate margins or infiltration of extraprostatic tissues was seen

\*\*DRE was considered suspicious of malignancy if considerable irregularity of the prostate surface, "rocky hard" induration/nodule or considerable asymmetry was detected on palpation

men were previously untreated for PC, and PB was performed for the first time. The patients were classified into two study groups according to serum PSA, DRE and TRUS findings, the potential predicting factors for PC burden.<sup>9,10,17,23</sup> The group of men more likely to have NOC PC was assigned as "H" (high tumor burden), while "group L" contained the rest of patients (low tumor burden). The selection criteria for the study groups are given in *Table 1*. PSA test (Elecsys 1010, Roche Diagnostics GmbH, Mannheim, Germany) was done prior to any prostate manipulation, to avoid false positive findings; no patients in our series had acute prostatitis (possible cause of elevated PSA); mean prostate size was similar in groups H and L.

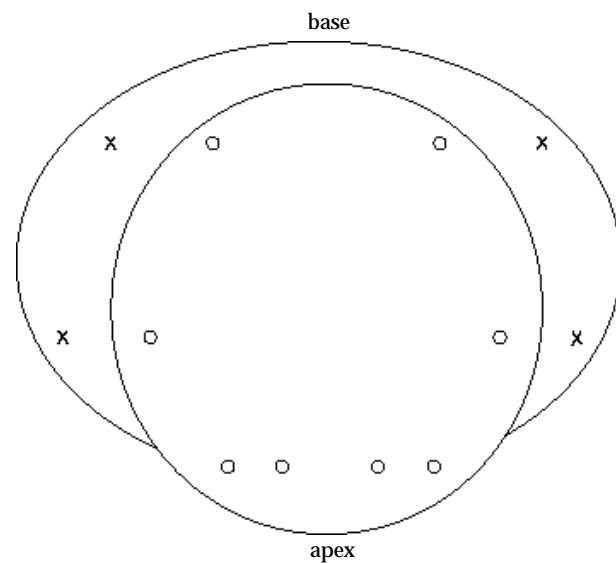
**Prostate biopsy protocol.** Transrectal US-guided PB was performed by sampling <50 cm<sup>3</sup> glands at 6-8 sites, and >50 cm<sup>3</sup> glands at 8-12 sites. Six cores were taken from the very lateral parts of peripheral zone (PZ) at the base, mid-gland and apex bilaterally,<sup>11,18</sup> as shown in *Figure 1*. Consequently, the material in the present study consisted of 6-12 cores per patient.

**Equipment and technique.** HP ImagePoint ultrasound system (Hewlett-Packard Company, Andover, MA, USA) with 5.0-7.5 MHz endorectal probe and biopsy needle guide was used to assist PB, performed with Bard Magnum biopsy device (Bard Urological Division, Covington, GA, USA), and disposable 18G needles. Biopsy cores from different sites were submitted to analysis in individually labeled separate containers.<sup>24</sup> The pathologist (S.G.) who analyzed the specimens was unaware of the aims of this study.

**Methods.** Pathological report for the complete set of PB samples (6-12 cores) was available for each patient. For each individual tissue core we considered whether it was positive for PC, and whether high-grade prostatic intraepithelial neoplasia (HGPIN) was present. Gleason score (GS) was determined on the basis of the complete 6-12 PB. Thereafter, for each patient we "reduced" 6-12 PB to quadrant prostate biopsy (QPB) scheme, in which apical and medial cores were eliminated, and then we compared the pathological results of 6-12 PB and QPB. The two sampling schemes are shown in *Figure 1*. In comparison of the two PB schemes the following pathologic parameters were considered: presence of prostate malignancy, evidence of HGPIN, and the percentage of positive cores. For the purpose of the study only, the same pathologist (S.G.), unaware of previously reported GS, determined GS for each patient from reduced biopsy material, i.e.

4 cores matching the sites of QPB, and this GS was then compared with the one determined from 6-12 PB. Student's t-test was used in statistical analysis.

Oral and written informed consent was obtained from each patient before PB, and information on possible complications of systematic PB was routinely given. This retrospective study did not influence patient management with 6-12 PB. The local ethics committee approved the investigation.



**Figure 1.** The two compared sampling schemes: o + x = 6-12 PB scheme, x = QPB scheme

**Table 2. General characteristics of patients in each study group**

	Group H	Group L	Total
Number of patients	55	58	113
Mean age (years)	71.2	72.9	71.8 (50-89)
Mean prostate volume (cm <sup>3</sup> )	63.2	63.7	63.4 (16-192)
Mean PSA level (ng/mL)	52.9	5.8	36.3
Median PSA level (ng/mL)	22 (1-346)	6 (0.03-9)	9
Number of patients positive for PC	44	16	60
Mean percentage of positive cores	69.3%	14.1%	54.5%
Mean Gleason score	6.8	4.5	6.5
HGPIN in negative patients	5/11 (45.5%)	8/42 (19.1%)	13/53 (24.5%)

**Table 3. Comparative results of different PB schemes in group H**

Parameter analyzed	6-12 PB	QPB	missed with QPB
Presence of malignancy	44	44	0
Presence of PIN in PC-negative patients			
HGPIN	5	5	0
LGPIN	3	2	1
Mean percentage of positive cores	69.3%	63.1%	6.2%, p=0.39 (NS)

NS = non-significant

**Table 4. Comparative results of different PB schemes in group L**

Parameter analyzed	6-12 PB	QPB	missed with QPB
Presence of malignancy	16	10	6
Presence of PIN in PC-negative patients			
HGPIN	4	2	2
LGPIN	7	5	2
Mean percentage of positive cores	14.1%	9.8%	4.3%, p=0.04

**Table 5. Gleason scores determined from 6-12 PB and QPB material**

Gleason score	6-12 PB	QPB	difference observed
Overall series			
median	6	6	0
mean	6.59	6.32	
range	3-9	3-9	p=0.13 (NS)
Group H			
median	7	6	-1 point
mean	6.79	6.36	p=0.13 (NS)
range	4-9	3-9	
Group L			
median	4	5	+1 point
mean	4.54	5.61	p=0.12 (NS)
range	3-5	4-6	

## Results

General characteristics of the patients in each study group are given in *Table 2*. There was no significant difference between groups H and L in patient age (p=0.86) and prostate volume (p=0.19). Comparative results of 6-12 PB and QPB for the two study groups are shown in *Tables 3* and *4*. Parameters that would have been missed with QPB are shown in the last columns. Median number of cores per one PB procedure was 8 (range 6-12). In 22/113 (19.5%) patients all cores were positive for malignancy on 6-12 PB (4 patients in group L, 18 patients in group H).

GS determined from 6-12 PB and QPB material are given in *Table 5*. GS determined from QPB did not differ significantly from GS determined from 6-12 PB, either for the whole series, or for particular groups (H: p=0.13, L: p=0.12), with maximum individual difference of 2 points. In 47.8% of patients, GS defined from 6-12 PB and QPB was identical, while in 43.5% it was undergraded by 1 point, and in 4.4% overgraded by 1 point with QPB.

## Discussion

The tendency to increase the number of cores in PB reflects the need of higher PC detection rate and staging accuracy,<sup>1,3-5,11,12,15,22-24</sup> but extensive PB can cause additional costs and patient discomfort. To balance both, PB should be individualized according to the patient's PSA, TRUS and DRE findings, prostate volume, age, and life expectancy. In the present study we focused on patients with laboratory and clinical suspicion of advanced PC. We hypothesized that extensive first-line PB is unnecessary in men that need only confirmation of prostate malignancy before androgen ablation treatment. If less extensive sampling protocols were applied in such patients, unnecessary discomfort, risks and costs might be avoided.

Cancer detection rate can decrease due to PB scheme reduction for two reasons: overall reduction of sampling den-

sity,<sup>1,3,5,11,13,15</sup> and lack of sampling the areas in which PC more frequently arises. Low sampling density can decrease sensitivity of PB, particularly in patients with negative DRE and TRUS, and lower PSA,<sup>3,15</sup> the population similar to our group L. Thus, reduced PB is not convenient for men with presumed low tumor burden, in which more extensive sampling is needed for early detection of PC.<sup>3</sup> In our series, a significant number (6/16, 37.5%) PCs would have been missed with QPB in group L. On the contrary, in men with presumed high tumor burden, there is lower risk of missing the tumor with reduced PB - all 44 PCs in our material could be detected either with 6-12 PB or QPB. Similarly, other authors showed that PC detection rate was less affected by an increase in the number of cores when PSA is >10 ng/mL, while significantly improved when PSA was <10 ng/mL.<sup>1,2,15</sup>

The question arises whether in larger series some PCs detected in group H patients with 6-12 PB would have remained undetected by QPB. In the very rare cases in which QPB may be negative in contrast to all clinical findings pointing to advanced PC, more extensive rebiopsy, which is obligatory in every negative group H patient because of persistent suspicion of PC,<sup>5</sup> could help to detect false negative patients. Thus, adhering to QPB as first-line PB in group H patients, we spare discomfort and save costs in the majority of patients correctly diagnosed as positive using QPB, with very little risk of missing malignancy in the prostate, which can be later detected by rebiopsy.

Non-sampling of different prostate areas can variably influence the decrease in sensitivity, because PC originates in some areas more frequently than in others. In our study, we decided to eliminate medial biopsies in the reduced PB scheme, because medial cores are less frequently positive for PC than lateral ones.<sup>2,3,5,11</sup>

The ability of pre-treatment variables to identify patients with organ-confined PC (OCPC) is a challenging issue. The presence of extraprostatic extension (EPE) is a feature that precludes radical treatment. Tumor volume is an important predictor of margin status and disease progression after RP, and underestimation of tumor volume may result in overindication of RP. The number and percentage of positive cores are valuable predictors of tumor volume, EPE and prognosis.<sup>4,12,13,22-24</sup> It was demonstrated that quantitative histological data are especially valuable in men with presumed low tumor burden (similar to our group L), predicting the final pathological stage more accurately.<sup>2,4</sup> Thus, the information on percentage of positive cores in PB must not be sacrificed in any reduced sampling scheme, particularly in group L in which RP can be a treatment option.

Grossklaus et al compared ≤6- vs. >6-core PB, and concluded that the reduction in core number could impair PC detection rate, but not other information, particularly the percentage of positive cores and bilaterality of PC.<sup>13</sup> In our

study, due to reduction to QPB the percentage of positive cores decreased significantly (14.1% to 9.8%,  $p=0.04$ ) in group L, but insignificantly in the whole series (54.5% to 45.1%,  $p=0.17$ ), and in group H (69.3% to 63.1%,  $p=0.39$ ). Maximum individual differences in the percentage were 20% and 25%, respectively, in two group H patients. Therefore, considering the parameter "percentage of positive cores", the use of QPB as first-line PB scheme is not appropriate in group L, while could be acceptable in group H. Although the conclusions of Grossklaus et al<sup>13</sup> and ours are similar for the overall series, the patient populations are not quite comparable, as these authors studied two different groups of men with different sampling schemes, while we compared two PB schemes on the same biopsy material.

Proper estimation of GS from PB specimens is essential in guiding treatment decision. GS determined from PB may be discordant to that determined from surgical specimens.<sup>7,19-21</sup> The magnitude of the discrepancy is directly related to the quantity of tissue in PB specimen; it is greater among specimens with  $GS<7$  than among those with higher GS.<sup>7,20</sup> Undergrading is particularly precarious, as it may lead the clinician to underestimate the true biological potential of PC, and proceed to RP in patients with NOC PC. Predisposing factors for error were limited core length and limited number of biopsy cores.<sup>19</sup> When low-grade PC is initially diagnosed on limited quantities of neoplastic tissue, PB should be repeated to reduce the risk of underestimation of GS. In our study, in group H GS was not significantly influenced by core number reduction, but the accuracy was decreased in group L. In group H, where fewer patients may be RP candidates, significant GS inaccuracy, even if it appeared, would not be critical.

Multiple core PB is an invasive procedure, and minor complications were reported in up to 78% of patients.<sup>8,16</sup> Although the rate of macrohematuria, pyrexia, and hospitalization after 10-core PB did not exceed significantly the one observed after sextant PB,<sup>14</sup> the rate of hematospermia and rectal bleeding was higher.<sup>14</sup> PB is associated with pain and discomfort in up to half the patients.<sup>8,16</sup> Although local anesthesia can help in acceptance of the procedure by patients,<sup>21</sup> we often faced the dilemma of whether the risk of complications and pain in extensive PB could be justified by real diagnostic needs, and whether extensive PB must be routinely and non-selectively applied to all patients. Reduction of extensive PB protocols may be especially favorable in elderly patients on chronic anticoagulation and those with severe co-morbidities. Some authors think, moreover, that PB is completely unnecessary in patients in which PSA levels >50 ng/mL indicate PC with positive prediction value of 98.5%.<sup>10</sup> Advantages of reduced PB include higher safety for performance on an outpatient basis, less patient anxiety for future PB, lower time consumption and workload for pathologists, lower costs, and lower risk of tumor cell seeding.

Our study may have limitations. Although PSA level and DRE findings may indicate statistical risk of PC in a defined population to some extent,<sup>9,10,17</sup> study groups H and L were defined arbitrarily, with an aim to categorize patients with significantly different tumor burden. None of these patients had formal step sectioning of the prostatectomy specimens, hence, H- vs. L- classification was only a provisional tool for rapid estimation of the patients who might benefit from PB scheme reduction, but not an attempt to stage the tumor or give prognosis.

### Conclusions

It seems that in patients with high likelihood to have advanced PC, reduction of the number of cores did not impair the overall sensitivity of PB, or the estimated percentage of positive cores. Further larger studies are needed to analyze the impact of PB scheme reduction on other relevant pathological information obtained from PB, to confirm whether QPB is adequate as a first-line sampling scheme in patients with advanced PC.

### References

1. *Aus G, Ahlgren G, Hugosson J, et al:* Diagnosis of prostate cancer: optimal number of prostate biopsies related to serum prostate-specific antigen and findings on digital rectal examination. *Scand J Urol Nephrol* 31: 541-544, 1997
2. *Aus G, Bergdahl S, Hugosson J, et al:* Outcome of laterally directed sextant biopsies of the prostate in screened males aged 50-66 years. Implications for sampling order. *Eur Urol* 39: 655-661, 2001
3. *Babaian RJ, Toi A, Kamoj K, et al:* A comparative analysis of sextant and an extended 11-core multisite directed biopsy strategy. *J Urol* 163: 152-157, 2000
4. *Borboroglu PG, Amling CL:* Correlation of positive sextant biopsy locations to site of positive surgical margins in radical prostatectomy specimens. *Eur Urol* 39: 648-653, 2001
5. *Chon CH, Lai FC, McNeal JE, Presti JC Jr:* Use of extended systematic sampling in patients with a prior negative prostate needle biopsy. *J Urol* 167: 2457-2460, 2002
6. *Damiano R, Autorino R, Perdoni S, et al:* Are extended biopsies really necessary to improve prostate cancer detection? *Prostate Cancer Prostatic Dis* 6: 250-255, 2003
7. *Djavan B, Kadeski K, Klopukh B, et al:* Gleason scores from prostate biopsies obtained with 18-gauge biopsy needles poorly predict Gleason scores of radical prostatectomy specimens. *Eur Radiol* 33: 261-270, 1998
8. *Djavan B, Waldert M, Zlotta AR, et al:* Safety and morbidity of first and repeat transrectal ultrasound-guided prostate needle biopsies: results of the prospective European Prostate Cancer Detection Study. *J Urol* 166: 856-860, 2001
9. *Eastham JA, May R, Robertson JL, et al:* Development of a nomogram that predicts the probability of positive prostate biopsy in men with an abnormal digital rectal examination and a prostate-specific antigen between 0 and 4 ng/mL. *Urology* 54: 709-713, 1999
10. *Gerstenbluth RE, Seftel AD, Hampel N, et al:* The accuracy of the increased prostate specific antigen level (greater than or equal to 20 ng/mL) in predicting prostate cancer: is biopsy always required? *J Urol* 168: 1990-1993, 2002
11. *Gore JL, Shariat SF, Miles BJ, et al:* Optimal combinations of systematic sextant and laterally directed biopsies for the detection of prostate cancer. *J Urol* 165:1554-1559, 2001
12. *Grossklaus DJ, Coffey CS, Shappell SB, et al:* Percent of cancer in the biopsy set predicts pathological finding after prostatectomy. *J Urol* 167: 2032-2035, 2002
13. *Grossklaus DJ, Coffey CS, Shappell SB, et al:* Prediction of tumor volume and pathological stage in radical prostatectomy specimens is not improved by taking more prostate needle-biopsy cores. *BJU Int* 88: 722-726, 2001
14. *Naughton CK, Ornstein DK, Smith DS, Catalona WJ:* Pain and morbidity of transrectal ultrasound guided prostate biopsy: a prospective randomized trial of 6 versus 12 cores. *J Urol* 163: 168-171, 2000
15. *Nava L, Montorsi F, Consonni P, et al:* Results of a prospective randomised study comparing 6, 12, 18 transrectal ultrasound guided sextant biopsies in patients with elevated PSA, normal DRE and normal prostatic ultrasound. *J Urol* 157(Suppl): 59A, 1997
16. *Peyromaure M, Ravery V, Messas A, et al:* Pain and morbidity of an extensive prostate 10-biopsy protocol: a prospective study of 289 patients. *J Urol* 167: 218-221, 2002
17. *Potter SR, Horniger W, Tinzl M, et al:* Age, prostate-specific antigen, and digital rectal examination as determinants of the probability of having prostate cancer. *Urology* 57: 1100-1104, 2001
18. *Ravery V, Goldblatt L, Royer B, et al:* Extensive biopsy protocol improves the detection rates of prostate cancer. *J Urol* 164: 393-396, 2000
19. *Ruijter E, van Leenders G, Miller G, et al:* Errors in histologic grading by prostatic needle biopsy specimens: frequency and predisposing factors. *J Pathol* 192: 229-233, 2000
20. *San Francisco IF, DeWolf WC, Rosen S, et al:* Extended prostate needle biopsy improves concordance of Gleason grading between prostate needle biopsy and radical prostatectomy. *J Urol* 169: 136-140, 2003
21. *Soloway MC, Obek C:* Periprostatic local anesthesia before ultrasound guided prostate biopsy. *J Urol* 163: 172-173, 2000
22. *Szabó J, Hegedüs G, Bartók K, et al:* Improving diagnostic accuracy of prostate carcinoma by systematic random map-biopsy. *Pathol Oncol Res* 6: 111-113, 2000
23. *Tigrani VS, Bhargava V, Shinohara K, Presti JC Jr:* Number of positive systematic sextant biopsies predicts surgical margin status at radical prostatectomy. *Urology* 54: 689-693, 1999
24. *Tombal B, Tajeddine N, Cosins JP, et al:* 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? *BJU Int* 89: 543-548, 2002
25. *Yamamoto T, Ito K, Ohi M, et al:* Diagnostic significance of digital rectal examination and transrectal ultrasonography in men with prostate-specific antigen levels of 4 ng/mL or less. *Urology* 58: 994-998, 2001