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# Optimization of Prostatic Biopsy: A Prospective Randomized Trial Comparing the Sextant Biopsy with a 10-Core Biopsy

## Impact of Prostatic Region of Sampling

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**Key Words**
Prostatic biopsy · Prostate cancer detection rate · Prostate cancer, morbidity

**Abstract**
***Objective:*** New prostatic biopsy protocols suggest to increase the core numbers to enhance detection. Additional cores are usually sampled from the lateral part of the p-zone. We direct the sextant biopsy to the most lateral part of the p-zone, therefore we investigated if there is a gain by adding 4 median biopsy cores. ***Material and Methods:*** The prospective randomized trial (n = 200) compared our modified sextant biopsy to a 10-core strategy with 2 additional median cores on both sides. Directed biopsies to suspicious areas were allowed in both groups. Morbidity was assessed by a self-administered questionnaire. ***Results:*** PC detection was 32% for 6 cores and 40% for 10 cores. Four patients were detected only by median biopsies. Using the binomial distribution table the gain of 4% is statistically significant. There was no statistical difference in morbidity, but a trend towards a higher rate of side effects in the 10-core group. ***Conclusions:*** The gain in prostate cancer detection rate by additional median biopsies is low, but statistically significant. There is no difference in morbidity and patient acceptance is high, therefore we favor the 10-core biopsy in our patients.



## Introduction

Prostatic biopsy is the only possible procedure to confirm the diagnosis of prostate cancer. Transrectal ultrasound (TRUS)-guided biopsy has become standard [1], but the details of prostatic biopsies are discussed controversially and no 'standard' has been defined regarding lesion directed or random biopsies, the number of biopsy cores and the regions of the prostate which should be biopsied. Systematic sextant biopsy of the prostate was used as a standard procedure since first reports demonstrated that the detection rate was improved [2]. The perfect prostatic biopsy should offer a sensitivity of 100% with low morbidity. But the systematic sextant biopsy demonstrates a sensitivity of only 60 or 83.3% if clinical insignificant cancers (<0.5 $cm^3$) will be eliminated [3]. Newer strategies for prostatic biopsies emphasize the increase in number of cores [4, 5] and/or biopsy sampling of the lateral aspect of the peripheral zone (p-zone) or so-called

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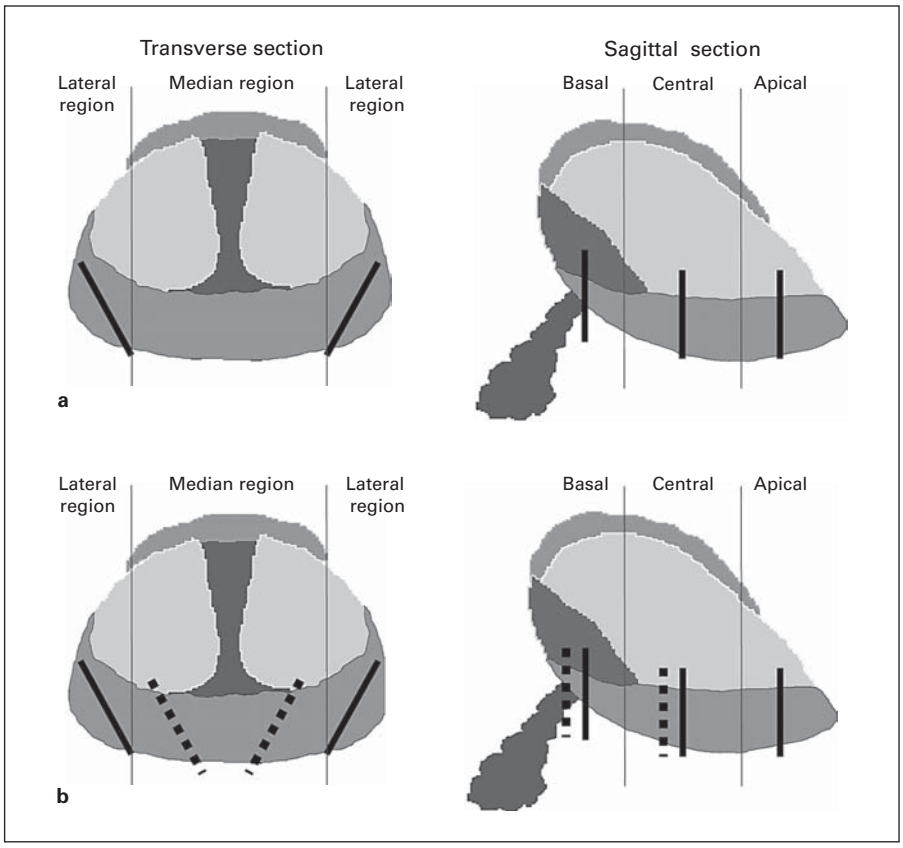


**Fig. 1.** Schematic drawing of sampling region of (**a**) modified systematic sextant biopsy and (**b**) 10-core biopsy including median prostatic region.

anterior horn [6, 7]. More biopsy cores do not necessarily result in a higher detection rate. In this respect, Naughton et al. [8] reported of no increase in the detection rate for 12 cores compared to sextant biopsy, and Horninger et al. [9] presented no differences comparing 10- vs. 14-core biopsy strategies. In our institution we are using a modified sextant biopsy because we direct the biopsies to the most lateral aspect of the peripheral zone and not as described by Hodge et al. [2] to the middle of the lateral lobe.

The aim of our study is to evaluate the gain in prostate cancer detection rate and associated morbidity by increasing the number of cores to 10 by adding 4 median biopsies of the p-zone (fig. 1). Our hypothesis is that sampling in the most lateral aspects will demonstrate the highest yield of prostate cancer and adding biopsy cores more medially located, the region where the systematic sextant biopsy by Hodge et al. [2] is located, will add only a minor gain of prostate cancer.

## Materials and Methods

Between May 2000 and April 2001, 200 patients scheduled for first time prostatic biopsy were randomized to either a TRUS-guided modified sextant biopsy (6+X) or a 10-core biopsy strategy (10+X). The modified sextant biopsy is composed of 3 biopsies of the peripheral zone of each lateral prostatic lobe from the basal, the central and the apical area (fig. 1). Biopsies are directed towards the most lateral aspect of the p-zone. Additional biopsies were allowed to suspicious areas on digital rectal examination (DRE) and/or sonographic hypoechoic areas outside the sextant area. For the 10-core biopsy we performed a modified sextant biopsy as described and additionally 2 cores were sampled on each lateral lobe medially from the sextant series (median biopsies) from the p-zone (fig. 1). Again, additional directed biopsies to suspicious areas were allowed.

All patients received local anesthesia (lidocaine gel) and a perioperative antibiotic prophylaxis with ciprofloxacin. We used an ATL HDI 1000 multiplanar 5–9 MHz probe and the Topnotch automatic 18 Ga core biopsy system (Microvasive, Boston Scientific). Morbidity was assessed by a self-administered questionnaire 1 week and 1 month after biopsy. We evaluated pain during and after biopsy, gross hematuria, blood in stool, hematospermia, fever and chills. The length and intensity of side effects were noted. Patients were asked if they would agree to repeat prostatic biopsy if necessary as well. IBR approval was obtained.

*Statistical Analysis*

Statistical analysis was performed using SPSS V10 software. Binominal distribution was used to evaluate the gain in prostate cancer detection rate with a confidence interval of 95%. To assess differences in morbidity, we used the Mann-Whitney U-test and Kruskal-Wallis test for continuous variables and the Pearson $\chi^2$ test or Fisher exact test for nominal variables. Statistical power to detect differences in morbidity for a calculated 10% difference was 80%. Statistical significance was accepted at 5% ($p < 0.05$).

## Results

*Patient Cohort*

200 patients were recruited and 100 patients were randomized to either group (6+X or 10+X cores). Mean age was 64.3 years. For the modified sextant biopsy group (6+X) mean age was 64.4 years and for the 10-core biopsy group (10+X) 64.2 years. Equal distribution is shown for PSA (median 5.9 vs. 5.6 ng/ml, p = 0.13), % free PSA (median 12.9 vs. 13.6, p = 0.46), prostatic size (median 50 vs. 50 ml, p = 0.53), transitional zone size (median adenoma size 30.0 vs. 27.5 ml, p = 0.24), suspicious DRE (41.1 vs. 35.7%, p = 0.3) and suspicious TRUS (53.8 vs. 45.9%, p = 0.3). The mean number of core biopsies was 6.4 (range 6–8) for the 6+X group and 10.3 (range 10–13) for the 10+X group.

*Prostate Cancer Detection Rate*

Overall prostate cancer detection rate was 36% (72/200 patients). 32% of the standard sextant biopsy group and 40% of the 10-core biopsy group revealed prostatic carcinoma. Looking at the different regions with prostatic carcinoma we found that 96.9% were positive in the sextant region and 46.9% in the directed biopsy of the 6+X group (table 1). In the 6+X group, only 3.1% were missed in the sextant series and found only by directed biopsies to suspicious areas. In the 10+X group, 85% were positive in the sextant area, 67.5% were positive in the additional 4 median biopsies and 20.0% were positive in the directed biopsies (table 1). In the 10+X group, 15.0% (6/40 patients) were missed with the standard sextant biopsy, 10.0% (4/40 patients) were found only positive in the median biopsies, 2.5% (1/40 patients) were detected only by additional directed biopsies to suspicious areas, and 2.5% (1/40 patients) were detected by directed biopsy and median biopsy. Therefore, the gain in detection rate of the 10-core biopsy group compared to the sextant biopsy group is 4% (4/100 patients). The binominal distribution was used for the 10+X group to look for the statistical difference for the additional 4 median biopsies and this test confirms a statistically significant difference of 4% with a 95% confidence interval from 1.1 to 9.9%.

**Table 1.** Detection rate of prostatic carcinoma stratified for standard sextant biopsy group (6+X), 10-core biopsy group (10+X) for different prostatic regions of core sampling

| Region of prostatic biopsy | 6+X | | 10+X | |
|---|---|---|---|---|
| | n | % | n | % |
| Sextant bpx. positive | 31 | 96.9 | 34 | 85.0 |
| Median bpx. positive | nd | nd | 27 | 67.5 |
| Median bpx. only positive | nd | nd | 4 | 10.0 |
| Directed bpx. positive | 15 | 46.9 | 8 | 20.0 |
| Directed bpx. only positive | 1 | 3.1 | 1 | 2.5 |
| Directed and median bpx. only pos. | nd | nd | 1 | 2.5 |

*Clinical Significance of Prostatic Cancer*

Two of 4 patients who were detected by median prostatic biopsies only underwent radical prostatectomy. The histology report revealed clinically significant tumors: Gleason score 6 and 7, both pT2b, according to the TNM classification [10].

*Morbidity*

Morbidity and pain was assessed by a self-administered questionnaire 1 week and 1 month after biopsy. The return rate of questionnaires was 89.9%. There was no statistical difference in morbidity or pain, but there was a trend towards an increased rate in the 10+X group. There was no difference in the severity or duration of side effects.

Gross hematuria was seen in 55.0% (6+X) and in 65.5% (10+X, fig. 2). Only 1 patient of the 10+X group was treated for gross hematuria. Mean duration of gross hematuria was 1.9 days (6+X) and 2.4 (10+X, fig. 2). These data suggest a similar intensity and duration of gross hematuria in both groups, but a trend to an increased rate without statistical difference (p = 0.11). Similar results were obtained for rectal bleeding, fever and chills.

An important aspect of prostatic biopsy is pain during and after biopsy evaluated 1 week and 1 month after biopsy. There was no statistical difference, but a trend towards more pain in the 10+X group (fig. 2). The rate of pain-free or nearly pain-free patients was 68.2% 6+X and 67.0% 10+X respectively. However, there is a subset of patients who experienced significant pain (7.1% in the 6+X group and 18.1% in the 10+X group). The mean du-

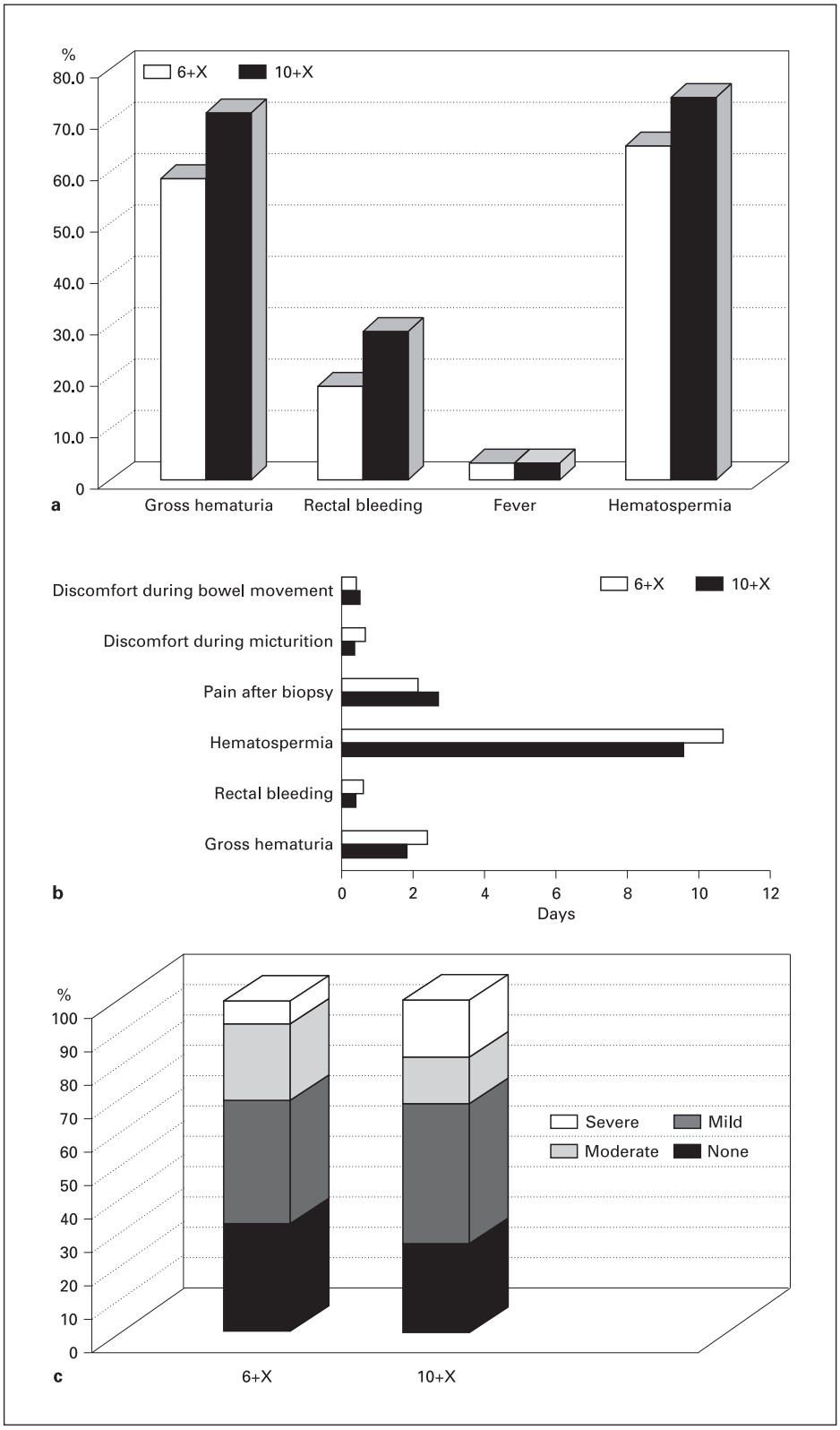


**Fig. 2.** Morbidity after biopsy stratified for modified sextant biopsy group (6+X) and 10-core biopsy group (10+X) demonstrating (**a**) overall rate and (**b**) mean duration of side effects and (**c**) pain during biopsy.

ration of pain after biopsy was 2.7 days (6+X) and 2.1 days (10+X). Discomfort during micturition was reported in 0.4 vs. 0.7 days and discomfort during bowel movements over 0.5 vs. 0.4 days (fig. 2). Again, no statistical difference was noted.

We also asked patients if they would be willing to repeat prostatic biopsy if their urologists would recommend it: 90.5% (6+X) would agree to repeat biopsy compared to 98.8% (10+X). This difference reached statistical significance ($p = 0.03$).

There was no difference if the questionnaire was evaluated 1 week or 1 month after biopsy regarding pain experience (data not shown).

## Discussion

Random systematic sextant biopsy is a widely used and accepted protocol. In 1989, Hodge et al. [2] reported that this procedure is superior compared to directed biopsies to hypoechoic lesions on TRUS. This 'standard' protocol is described by Hodge et al. [2] as sampling of 3 biopsies of the center of each lateral lobe of the prostate by using a 45° angle to the rectum. The real detection rate of random systematic biopsy is only 60% at the first biopsy [3]. Therefore, new biopsy strategies are under investigation with two different strategies. The first strategy is increasing core numbers, which seems to be intuitive that the more core biopsies are obtained the higher the detection rate will be. The second strategy is to direct the biopsy cores to distinct areas of the prostate like the lateral p-zone to enhance prostate cancer detection.

There are controversies regarding the usefulness of increased core numbers. Levine et al. [11] reported that an increase from 6 to 12 cores by taking two sets of sextant biopsies enhanced the detection rate by 37%. Interestingly the first set of sextant biopsy detected only 70% (30 out of 43 cancers) but the second set detected 93%, suggesting that the second set may have been directed to a different area of the prostate. Naughton et al. [8] reported that increasing the number of cores to 12 cores does not translate into a higher detection rate in their prospective randomized trial. Eskew et al. [7] noted a 35% increase in the detection rate by increasing the number but directing them to distinct areas – the five-region biopsy. Chen et al. [4, 6] reported of a computer model to optimize the core number and region of sampling. The highest detection rate was not achieved with the highest number of core biopsies, suggesting that the area of sampling is more important than increasing the core number. In this model [4] the highest yield was achieved with an 11-core strategy including the standard sextant biopsy and additional 4 lateral biopsies of the anterior horn of the p-zone and median biopsy.

In our institution we are performing a modified systematic sextant biopsy and are using a multiplanar ultrasound probe which enables us to biopsy in the transverse section. We are directing our biopsies to the most lateral region of the p-zone, according to the anterior horn. This strategy is based on the observation by Stamey [12] who reported that sampling in the lateral aspect of the peripheral zone increases the detection rate. The presented study should determine if additional biopsies medially to our modified sextant series will increase the detection rate, because the observed gain of detection rate by Chen et al. [4] and Eskew et al. [7] are due to sampling in the area where we are placing our standard sextant cores. The gain of prostate cancer detection rate was high in both studies ranging from 21% [4] and 35% [7]. This gain in prostate cancer detection rate favors our hypothesis that sampling in the lateral aspect of the prostate is most important. The question raised by this study is if there is a need to sample the more medially located cores at all.

Ravery et al. [15] evaluated an extensive biopsy protocol by using a 12-core biopsy with a standard sextant biopsy and additional 6 lateral biopsy cores. The gain in the prostate cancer detection rate was only 6.6%. Chang et al. [13] also investigated the benefit of 4 additional biopsies, which were sampled at the most lateral edge of the p- zone at the central and basal part of the prostate. They noted a significant but moderate increase in the detection rate of 14%. In the recent trial they stated [14] that an 8-core biopsy strategy would be best, in this strategy the 2 median biopsies at the prostatic base can be omitted demonstrating the importance of the most lateral biopsy. Therefore, we designed our study to elucidate the effect of additional medial biopsies compared to our modified sextant biopsy with sampling in the areas of highest prostate cancer detection rate.

The gain of prostate cancer detection rate in our investigation was also significant but only 4% (95% confidence interval 1.1–9.9%) by adding for median biopsies (fig. 1), confirming that sampling in the very lateral portion of the p-zone is most important. On the other hand, the detection rate in the 10-core biopsy group was 40% and in the sextant biopsy group 32%, although both groups demonstrated equal distribution by randomization. This increase of 8% detection rate is achieved in 50% by median biopsies and in 50% by improved detection of lateral biopsy cores, therefore 15% of cancers would have been

missed using our modified sextant biopsy only. A possible explanation may be that the lateral sextant biopsy series is sampled even more laterally if additional median biopsies are taken thus sampling in the region of interest is improved. The differences in the detection rate reported in different studies may be explained by different study populations and most probably because of subtle differences in technique and sampling. In this regard we are favoring sampling in the transverse section of the prostate by using a multiplanar probe, because directing the needle to the most lateral part of the peripheral zone is facilitated by this technique.

Our results demonstrate that the prostatic cancers detected by median biopsies only are clinically significant tumors. This finding is in concordance with the literature, there also tumors detected with extended biopsy protocols are considered as clinically significant cancers [14].

Although increasing the number of cores may increase the cancer detection rate, concerns exist regarding a potentially increased morbidity. The standard sextant biopsy scheme is a procedure with rare major complications but common minor morbidities [16]. In the prospective randomized study from Naughton et al. [17] there was no statistical significant difference in morbidity and pain between the 6- and 12-core biopsy, but a trend towards a higher rate in the 12-core group. Our findings are conclusive with the study from Naughton et al. [17], we noted no statistical significant difference between our 6- and 10-core biopsy, but a trend towards a higher rate – but not severity of morbidity – in the extensive biopsy group. Our results confirm that an extensive prostatic biopsy with 10 or 12 cores can be safely performed. Patient acceptance is therefore high in both groups. Over 90% of all patients would agree to undergo a second prostatic biopsy if necessary.

## Conclusion

There is a minor but statistically significant gain of about 4% in prostate cancer detection rate by increasing the standard sextant biopsy scheme, with sampling of the most lateral aspect of the peripheral zone, compared to a 10-core biopsy program by adding 4 median biopsy cores. The prostatic carcinomas detected by median biopsy cores only were clinically significant tumors. The observed morbidity demonstrated no statistical difference between the sextant biopsy group and the 10-core biopsy group, but there was a trend towards a higher rate of pain and side effects in the 10-core biopsy group, but not in the severity and duration of symptoms. Taking these data into account, we favor the 10-core biopsy strategy because additionally detected patients with prostatic carcinoma will benefit from curative therapy even if the additional gain may be low, but acceptance of a 10-core biopsy strategy is very high in patients.

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