Negative Predictive Value of Systematic Ultrasound-guided Prostate Biopsy: Which Tumours Do We Miss?

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Abstract. *Background: The aim of the study was the determination of the negative predictive value of sextant core prostate biopsy. Patients and Methods: Prostate cancer was diagnosed in 126 patients by systematic ultrasound-guided sextant biopsy and was subsequently treated with radical prostatectomy. The prostatectomy specimens were examined histopathologically using the whole-mount section technique. Results: 81 patients were diagnosed with unilateral and 45 with bilateral prostate cancer after biopsy. In 15/81 patients, the diagnosis of unilateral disease was confirmed by the whole-mount sections; 66 patients turned out to have bilateral disease. In 14/66 cases, the missed tumour foci were diminutive. In the remaining 52 patients, an erroneous diagnosis of unilateral prostate cancer had been made after biopsy, although the missed tumour foci were not diminutive. The negative predictive value of sextant core biopsy with respect to unilateral disease was 36%. Conclusion: An unexpectedly high number of tumour foci are missed by systematic ultrasound-guided sextant prostate biopsy.*

Systematic sextant core biopsies were introduced in 1989 (1). In the last decade, a number of improvements have been suggested in an attempt to make the procedure more sensitive. Stamey (2) postulated that cancer detection rates were higher if the biopsies were taken more laterally so as to ensure a better representation of the peripheral zone as described by McNeal (3). In the following years, different biopsy strategies with increasing numbers of biopsy cores were introduced to further improve the sensitivity of prostate biopsies (4-14).

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Some authors advocate limiting a nerve-sparing prostatectomy approach to the side on which biopsy is negative (17, 18). Yet this proposal again raises the question of the negative predictive value of a negative unilateral biopsy.

The present study addresses the question of the negative predictive value of a negative unilateral biopsy by analysing the particular sextant prostate biopsy procedure. For this purpose, the standardized sectioning protocol of radical prostatectomy specimens originally described by McNeal (3) was applied in a slightly modified form as described elsewhere (16), and then correlated with the biopsy results.

Patients and Methods

Between 1999 and 2003, 126 patients underwent both ultrasound-guided prostate biopsy and radical prostatectomy at the University Clinic, Münster, Germany. The standard ultrasound-guided sextant biopsy procedure consisted of one core each from the base, the middle and the apex of both prostate lobes. All biopsy cores were positioned laterally as described by Stamey (2). A Kretz ultrasonic unit (Combison 311) with a 7.5 MHz transducer was used. Patients who had received androgen therapy before surgery or had undergone transurethral resection of the prostate were not included in the study. The clinical characteristics of all 126 patients are shown in Table I. After radical prostatectomy, the specimens were examined histopathologically in a standardized manner as described elsewhere (3, 16).

After fixation, the urethral margin was removed as a 3-5 mm thick section. This tissue block was subsectioned at 2 mm intervals in parasagittal planes. The apical margin was removed and sectioned in the same fashion. The remaining portion of the prostate was serially blocked at 3-5 mm intervals rectangular to the urethra and embedded separately for each side. The location and extension of each single tumour focus was documented on a standard prostate card summarizing the histopathological findings based on the 6 slices from the apex to the base of each prostate (Figure 1).

Afterwards, the prostate cards were transferred to Excel cards (Microsoft Corporation; Redmond, WA, USA) with 6 similarly arranged sections (Figure 2) summarizing the prostate anatomy in a total of 6 planes with 474 pixels. Pixels containing carcinoma were labeled with "1"; benign tissue with "0" in the corresponding pixel. In this way, the operative specimens were reconstructed in

Table I. *Descriptive analysis of the 126 patients investigated.*

Variable	No. (%)
Patients	126 (100)
Age (years)	
≤54	5 (4)
55-59	17 (13)
60-64	41 (33)
65-69	40 (32)
≥70	23 (18)
Total PSA before therapy (ng/ml)	
0.56-4.0	6 (5)
4.1-10.0	69 (55)
10.1-20	38 (30)
>20	13 (10)
Tumour stage TNM 1992*	
pT2a	11 (9)
pT2b	3 (2)
pT2c	53 (42)
pT3a	34 (27)
pT3b	6 (5)
pT3c	16 (13)
pT4	3 (2)
Gleason sum in prostatectomy	
4	1 (1)
5-6	49 (39)
7	62 (49)
8-10	14 (11)

*Tumour stage according to the TNM classification system from 1992 (20).

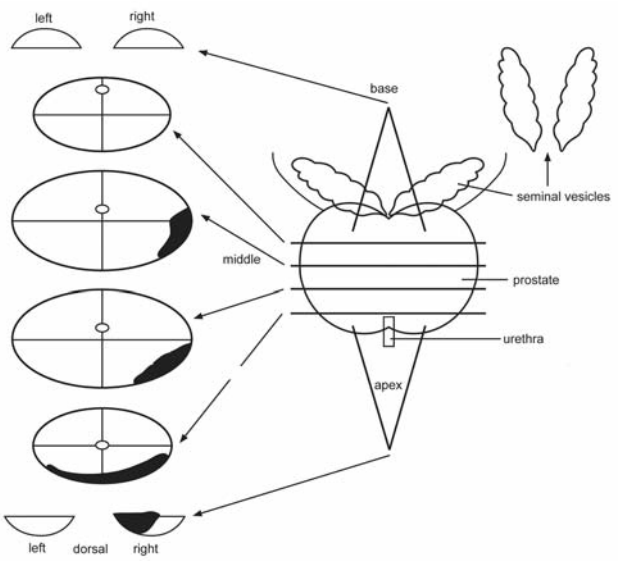

Figure 1. *Example of a prostate card from the prostatectomy specimen produced by the pathologist. The black areas represent prostate cancer.*

digitised form. In each case, the tumour volume was estimated according to the proportion of positive pixels and the weight of the prostatectomy specimen without seminal vesicles. The Excel cards were superposed so that a summary of prostate cancer distribution could be calculated for every pixel. Using Axum6-Graphics (MathSoft, Corporate Holdings, MA, USA) the frequency of prostate cancer for each pixel was visualised in a color-coded plot.

To retrieve information about the location of tumours that were missed during the sextant biopsy procedure, those cases in which prostatectomy specimens revealed bilateral cancer were analysed, although the biopsy cores had only been positive for prostate carcinoma unilaterally. Cases with missed tumour foci of less than 4 pixels (*i.e.* <1% of the prostate volume) were considered separately. For all the tumour foci missed by biopsy, the frequency of capsular infiltration, penetration or positive surgical margins was also recorded.

Results

Prostate cancer was diagnosed in 126 patients by first time systematic ultrasound-guided sextant prostate biopsy at the local university clinic. A total of 45 patients had prostate cancer in biopsy cores obtained from both prostatic lobes. The median age was 65 (range 55 to 75) years and the median total PSA concentration before biopsy was 9.2 (range 7.3 to 10.3) ng/ml. Eighty-one patients were diagnosed with unilateral prostate cancer on biopsy. The median age in this group was 65 (range 48 to 76) years and the median total PSA concentration before biopsy was 7.9 (range 3.4 to 41.9) ng/ml. There was no statistically significant difference between the two groups with respect to age (p=0.7) or PSA (p=0.4; Wilcoxon test).

For all the 45 patients who had been diagnosed with bilateral disease after prostate biopsy, this diagnosis was confirmed by the whole-mount sections. Analysis of the 81 patients who had initially been diagnosed with unilateral prostate cancer after biopsy revealed that an elevated number, namely 66 out of 81 patients (81%), did indeed suffer from bilateral prostate cancer as confirmed by prostatectomy specimens.

In 14 cases, the missed tumour foci were diminutive (less than 4 pixels, *i.e.* <1% of the prostate volume), the remaining 52 cases showed a side distribution of 21 positive biopsy results only in the right lobe and 31 only in the left. Nevertheless, the whole-mount sections of these 52 prostatectomy specimens revealed bilateral disease, although the biopsy result indicated unilateral disease. Consequently, the negative predictive value of sextant core prostate biopsy was 19% before and 36% after exclusion of cases with diminutive foci.

The volumes of the missed tumours ranged from 0.3 to 15.6 cm^3 after exclusion of the foci smaller than 4 pixels (<1% of the prostate volume). The mean tumour volume of the missed foci after exclusion of the diminutive tumour foci was 2.5 cm^3 (±2.7 standard deviation SD). The median tumour volume was 1.3 cm^3. The tumour volume of the contralateral lobe in which prostate cancer was diagnosed by

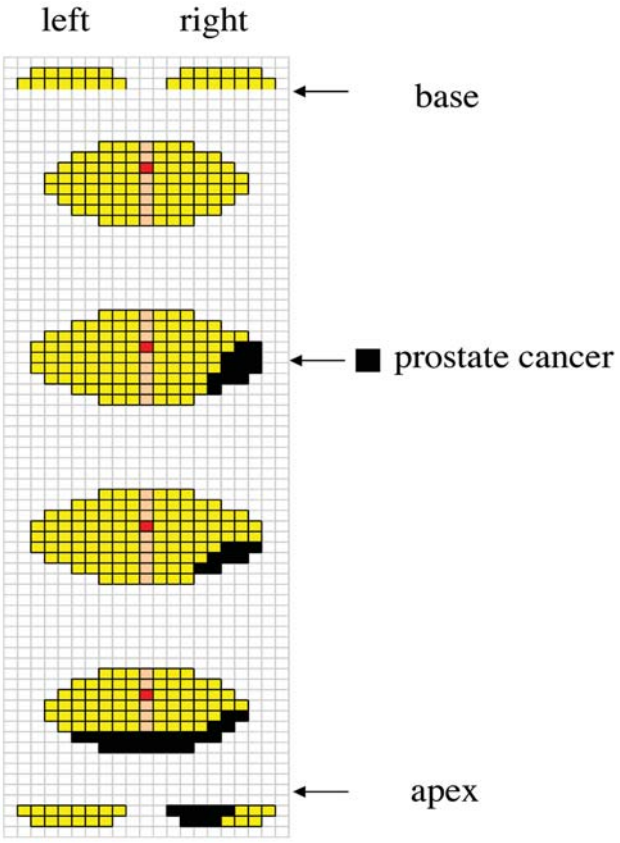

Figure 2. *Transformation of the cancer areas shown in Figure 1 into a digitized Excel®-card. Black pixels contain a "1" and represent prostate cancer. Yellow pixels contain a "0" and represent benign tissue.*

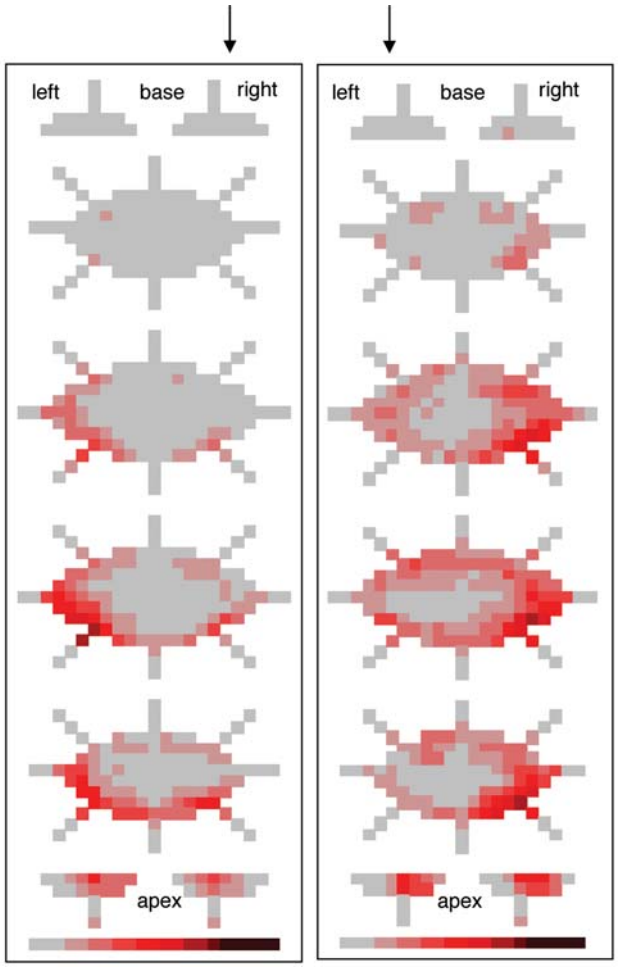

Figure 3. *Summary card of 31 (a) and 21 (b) patients with bilateral prostate cancer in the prostatectomy specimen although the biopsy result suggested only contralateral prostate cancer. The lobe which was diagnosed as cancer-free by biopsy is marked by an arrow. The figures show an accumulation of missed tumour in ventral basal areas of the gland, in medial apical dorsal areas close to the rectal mucous membrane and in apical lateral locations.*

biopsy ranged from 0.1 cm^3 to 17.0 cm^3. The mean tumour volume in this lobe was 4.4 cm^3 (±4.1 SD) and the median tumour volume was 3.4 cm^3. The volume of the missed tumours was significantly smaller than the contralateral tumour volume (p=0.01, Wilcoxon test).

The missed tumour foci were associated with capsular invasion in 19 out of 52 (37%) patients, capsular penetration in 7 out of 52 (13%) and a positive surgical margin in 8 out of 52 (15%), while patients with diminutive tumour volume showed none of these characteristics.

Figures 3a and 3b take into account all those cases with bilateral disease where biopsy had suggested unilateral tumour only. They reveal that most of the tumour burden is localized in the biopsy-positive prostatic lobe. The contralateral lobe shows the tumours missed by biopsy. An accumulation of missed carcinoma can be observed in the gland's ventral basal areas, in medial apical dorsal areas close to the rectal mucous membrane and in apical lateral locations. Closer to the base, prostate cancer manifests itself more laterally within the peripheral zone. At the apex, prostate cancer mostly appears laterally close to the neurovascular bundle and medially close to the rectal mucous membrane. Closer to the prostatic base, missed cancer is often located in the transition zone that is not examined in the routine sextant biopsy procedure.

Discussion

Some authors advocate limiting the nerve-sparing surgery approach to the side of the prostate in which biopsy is negative (17, 18). This suggestion raises the question of the negative predictive value of unilateral negative biopsy.

In this study, 66 out of 81 patients (81%) who had been diagnosed with unilateral prostate cancer after biopsy actually had bilateral prostate cancer, as confirmed by the

prostatectomy specimens. Even excluding cases with diminutive tumour volume, manifestations of cancer were still found in 64% (52 out of 81) of those prostatic lobes that biopsy procedure had incorrectly classified as benign. This proportion is unexpectedly high. This study confirms those results of previously published studies (15, 17-19). Huland *et al*. (17) and Daniels *et al*. (18) reported rates of bilateral carcinoma that amounted to 85 and 78%, respectively, in cases where biopsy had been positive in only one lobe. Öbek *et al*. (15) found bilateral prostate cancer in as many as 69% of patients in whom a diagnosis of unilateral disease had been made after biopsy. In 5 patients (5%), cancer was confined to the contralateral lobe. Öbek *et al*. observed a lack of histological evidence of bilateral cancer in 9 out of 55 patients (16%) with a positive bilateral biopsy. These results differ from those of Huland *et al*. (17), Daniels *et al*. (18), and those found in the present study, in which it was possible to demonstrate bilateral prostate cancer in all the whole-mount sections whenever biopsy had previously revealed tumour in both prostatic lobes. Complete removal of a minute focus of tumour by biopsy may occur in individual cases, but is unlikely to account for a total of 14 cases reported (15). Of these 14 patients, 8 had received hormonal induction treatment preoperatively, which may have affected the final pathological interpretation. To avoid such distortions, patients with preoperative hormonal treatment were not included in this study.

In 1994, Huland *et al*. (17) analysed a cohort of 39 patients that had unilateral cancer on biopsy. In 33 (85%) of these patients, the diagnosis had to be changed to bilateral cancer after prostatectomy. Huland *et al*. reported capsular penetration in 2 (5%) out of the 39 patients, yet none of them showed a positive surgical margin in the biopsy negative lobe.

Daniels (18) reported on 57 patients who were digitally diagnosed with tumour confinement to one prostatic lobe and subsequently underwent radical prostatectomy. Twenty-five patients had positive biopsies bilaterally and 32 unilaterally. Twenty-five patients (74%) had bilateral tumours in the final histopathological examination although the biopsy had suggested unilateral disease only. Twenty patients had small contralateral tumours averaging a volume of 0.4 cm^3. The largest tumour missed on biopsy was 1.9 cm^3. None of the patients had a positive surgical margin at the contralateral lobe.

Huland *et al*. (17) limited their analysis to clinical stage T2 tumours. Details concerning the PSA levels prior to biopsy were not included in this study. In the study of Daniels *et al*. (18), all patients were digitally diagnosed with tumours confined to one prostatic lobe. The preoperative selection bias may to some extend explain the varying results.

Modifications of the prostate biopsy procedure have been discussed by a number of authors. Some resorted to computer-based reconstructions in an attempt to optimize biopsy results (5-11). Others tested real biopsy modifications in addition to the sextant biopsy protocol and analysed different combinations of needle positioning and their impact on the detection rate (4, 12-14).

Nearly all authors demonstrated that additional lateral biopsies improve cancer detection rates. The coloured summaries in Figure 3a and 3b confirm the high prevalence of lateral location in this study.

Chen *et al*. (8) describe an 11-core multisided scheme consisting of a standard sextant, two transition zone, one midline, and two anterior horn biopsies. This scheme resulted from a computer-based digital visualization of 180 radical prostatectomy specimens. The location and extension of tumour foci were noted on a prostate paradigm comparable to our prostate cards. Afterwards the tumour probability for each region within the prostate was visualized by a pseudocolour-based plot. In their computerized reconstruction the authors described an accumulation of cancer foci probably missed on biopsy in lateral basal and more medial areas closer to the apex. Unfortunately, they did not provide any information on the biopsy procedure applied prior to prostatectomy.

In contrast, this study visualized the tumour foci missed on biopsy in a subanalysis of cases with bilateral tumour after prostatectomy, in whom an erroneous diagnosis of unilateral disease had been found in biopsy. The summary cards shown in Figure 3a an 3b do not outline those locations where tumour foci are more likely to be missed as clearly as in the study of Chen *et al*. This may be attributed to an extended biopsy protocol applied before prostatectomy in the study of Chen *et al*. In order to render the results obtained with the help of the summary cards more meaningful, the biopsy protocol has been adjusted to comprise six biopsy needles taken laterally from the base, middle and apex and two additional cores taken from the medial apex and two taken from the transition zone. The modified protocol thus takes into account those regions of the prostate where prostate cancer is most likely to manifest itself and, unfortunately, most likely to be missed by sextant biopsy procedures.

Conclusion

An unexpectedly large number of patients had prostate cancer bilaterally, although biopsy had been negative unilaterally and the missed tumour foci were not diminutive. The negative predictive value of sextant core prostate biopsy for unilateral disease was 19% before and 36% after exclusion of diminutive tumour foci. This means that in 4 out of 5 cases with unilateral prostate cancer suggested by biopsy, the disease was actually bilateral, as revealed in the prostatectomy specimens. In 4 out of 10 patients the missed tumour foci were not diminutive.

Relying on sextant biopsy results alone in making a decision of when to perform nerve-sparing surgery may not be a safe option for some patients.

To reduce false-negative biopsy results the model in this study suggests a good tradeoff between a high cancer detection rate and a minimal number of cores taken by means of a more lateral needle positioning closer to the base and by including cores from the transition zone and the medial dorsal apex of the prostate close to the rectal mucous membrane.

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